COST-EFFECTIVENESS ANALYSIS OF RADIOFREQUENCY ABLATION VERSUS DRUGS FOR THE TREATMENT OF ATRIAL FIBRILLATION IN THE SOUTH AFRICAN POPULATION

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Declaration

I, Heather Lynn Henry, declare that the entire body of work contained in this research assignment is my own, original work; that I am the sole author thereof (save to the extent explicitly otherwise stated), that reproduction and publication thereof by Stellenbosch University will not infringe any third party rights and that I have not previously in its entirety or in part submitted it for obtaining any qualification.

H L Henry-Lines

March 2021

Dedication

This piece of work is dedicated to Liam Mark Edwards and my late father Andrew John Henry.

To Liam, who at age five, lost his mother, after she died suddenly from a haemorrhagic stroke, and to my wonderful father Andrew John Henry, you were my hero in my life. Thank you for loving me, encouraging me and for always believing in me. Sadly, you passed away only months before I completed this.

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Abstract

Atrial fibrillation is the most commonly found and sustained arrhythmia. It affects about 1% of the total population and is found in more than one in ten in the elderly. The prevalence is increasing with the aging population. Patients with atrial fibrillation are at an increased risk of heart failure and all-cause mortality, and have a fivefold increased risk of stroke. Atrial fibrillation is associated with debilitating symptoms and an impaired quality of life. The restoration and maintenance of sinus rhythm is favourable and the current guidelines recommend the use of both rate and rhythm control strategies, which involve the prescription of anti-arrhythmic drug therapy. These anti-arrhythmic drugs are frequently ineffective, with large studies showing that atrial fibrillation returns in as many as 85% of patients within one year. These drugs are also associated with adverse events, occasionally serious, which may lead to hospitalisation.

Catheter ablation (a minimally invasive procedure), has over the past decade revolutionised the treatment of atrial fibrillation. The 2010 European Society of Cardiology guidelines recommend catheter ablation for paroxysmal atrial fibrillation as a class IIa recommendation with level of evidence “A”. Current literature indicates that patients with atrial fibrillation who undergo pulmonary vein ablation have a significantly lower risk of death, stroke and dementia compared to patients with atrial fibrillation who are not treated with ablation, while stroke and dementia is similar to that of the general population.

This study used a decision tree analysis, a Markov model and Monte Carlo simulation to calculate the cost-effectiveness of catheter ablation versus commonly used anti-arrhythmic drugs for the treatment of paroxysmal atrial fibrillation. Input into the model was founded on an extensive literature review, interviews with local electrophysiologists and a sample of real patient data, which examined the costs associated with among others, the length of hospital stay and the cost of the procedure.

The model simulated 1 000 patients receiving either pulmonary vein isolation through radiofrequency ablation or anti-arrhythmic drugs and the following variables were measured, QALYs, average cost, incremental costs, average effectiveness, incremental effectiveness, average length of stay in hospital for complications, relative risk of death for radiofrequency catheter ablation versus anti-arrhythmic drugs and also the net monetary benefits.

A total of fourteen variables were tested and sensitivity analyses were performed on each. It was found that in all but two cases, pulmonary vein isolation with radiofrequency catheter ablation dominated over anti-arrhythmic drug therapy as being more cost-effective for the management of paroxysmal atrial fibrillation. Finally, it was determined that pulmonary vein isolation with radiofrequency catheter ablation should be considered as a first line therapy for patients with paroxysmal atrial fibrillation in South Africa.

Key words: paroxysmal atrial fibrillation, cost-effectiveness analysis, pulmonary vein isolation, radiofrequency ablation.

Opsomming

Atriale fibrillasie is die mees algemene en volgehoue aritmie. Dit raak ongeveer 1% van die bevolking. Onder bejaardes is die voorkoms egter soveel as 10%, wat beteken dat die toestand toeneem in verhouding met die verouderende bevolking. Atriale fibrillasie verhoog ’n pasiënt se risiko vir beroerte vyfvoudig, tesame met hartversaking en alle-oorsake mortaliteit. Die toestand se uitmergelende simptome verlaag ook lewenskwaliteit. Die kanse vir die herstel en instandhouding van sinusritme is positief. Bestaande riglyne beveel dus die gebruik van ritme- of spoed-beheer medikasie aan, wat beteken dat anti-aritmie medikasie voorgeskryf word. Dit is egter dikwels oneffektief en verskeie omvattende studies het bewys dat tot 85% van die pasiënte binne een jaar weer ‘n ritmestoornis ervaar. Hierdie middels word ook dikwels verbind met newe-effekte wat ernstig mag wees en tot hospitalisasie mag lei.

Kateterablasie (’n minimaal-ingrypende prosedure) het oor die afgelope dekade die behandeling van atriale fibrillasie onherkenbaar verander. Vir pasiënte wat hoogs simptomaties, of paroksismaal, is ten spyte van optimale terapie, beveel die Europese Vereniging van Kardiologie se 2010 riglyne ablasie aan as ‘n klas IIa aanbeveling. Huidige literatuur dui op ‘n laer koers van sterftes, beroerte en demensie onder atriale fibrillasie pasiënte wat atriale fibrillasie ablasie ondergaan, in vergelyking met pasiënte wat met medikasie behandel word. Eersgenoemde het inteendeel dieselfde risikoprofiel as die algemene bevolking.

Hierdie studie gebruik ’n keuse-boom analisemodel en ’n waarskynlikheid-Markov model met Monte Carlo-simulasie om die koste-effektiwiteit van kateterablasie met anti-aritmiese medikasie te vergelyk in die behandeling van pasiënte met paroksismale atriale fibrillasie. Die data wat in die model gebruik word, is gebaseer op ’n uitgebreide literatuurstudie, onderhoude met elektrofisioloë, en ’n steekproef van pasiëntdata, en ondersoek, onder andere, die duur van hopitaalverblyf en die koste verbonde aan die prosedure.

Die studie maak gebruik van ’n simulasiemodel waar 1 000 pasiënte óf ablasie óf medikasie ontvang het. Die volgende veranderlikes is gemeet: QALYs, gemiddelde koste, toenemende koste, gemiddelde doeltreffendheid, toenemende doeltreffendheid, gemiddelde hospitaalverblyf tydens komplikasies, die relatiewe riskio van sterfte en monetêre voordele.

Veertien veranderlikes is getoets en aan sensitiwiteitsanalises onderwerp. In dertien uit die viertien analises was kateterablasie meer koste-effektief as anti-aritmiese medikasie in die behandeling en bestuur van anti-aritmiese medikasie. Die studie kom dus tot die gevolgtrekking dat kateterablasie oorweeg moet word as voorkeurterapie vir pasiënte met paroksismale atriale fibrillasie in Suid-Afrika.

Sleutel woorde: paroksismale atriale fibrillasie, kateterablasie, koste-effektiwiteit

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List of acronyms and abbreviations

AF	atrial fibrillation
AADs	anti-arrhythmic drugs
AAI mode	single chamber atrial pacing mode
ACC	American College of Cardiology
ACE	angiotensin converting enzyme
ADT	anti-arrhythmic drugs therapy
AF	atrial fibrillation
AFFIRM	atrial fibrillation follow-up investigation of rhythm management
AHA	American Heart Association
AIDS	acquired immunodeficiency disease syndrome
AMI	acute myocardial infarction
AP	anterior-posterior position
APAF	ablation for paroxysmal atrial fibrillation
ARBs	angiotensin receptor blockers
ARV	anti-retroviral therapy
ASDs	atrial septal defects
ASSA	Actuarial Society of South Africa
AT	atrial tachycardia
ATP	anti-tachycardia pacing therapy
AV	atrioventricular
AV conduction	atrial to ventricular conduction
AV Node	atrioventricular node
AVNRT	atrioventricular nodal re-entrant tachycardia
BCR	benefit to cost ratio
BMJ	British Medical Journal
BMS	bare metal stent
BVP	bi-ventricular pacemaker
C	consumption
CABG	coronary artery bypass graft
CAD	coronary artery disease
CARAF	Canadian Registry of Atrial Fibrillation
CASSA	Cardiac Arrhythmia Society of South Africa
CBA	cost benefit analysis
CCF	congestive cardiac failure
CCU	coronary care unit

CRT-D	cardiac resynchronisation therapy - defibrillation
C-E	cost-effectiveness
CEA	cost effectiveness analysis
CFAE	complex fractionated atrial electrograms
$CHADS_2$	CHADS score acronym
CHD	coronary heart disease
CHF	congestive heart failure
CI	confidence interval
CIA	Central Intelligence Agency
CMA	cost minimization analysis
CMM	Colour M Mode
CMS	Council for Medical Schemes
COMET Trial	Carvedilol or Metoprolol European Trial
CPI	consumer price index
CRT	cardiac resynchronisation therapy
CT	computerised tomography
CT scan	computed tomography scan
CUA	cost utility analysis
CVD	coronary vascular disease
DALY	disability adjusted life year
DES	drug eluting stent
DC	*direct current*
EBM	evidence-based medicine
ECG	electrocardiogram
ECHO	echocardiogram
EP study	electrophysiology study
ESC	European Society of Cardiology
EU	European Union
ExtHE	external resources
FBC	full blood count
GDP	gross domestic product
GGHE	general government health expenditure
GNI	gross national income
GP	general practitioner
H	health
HCM	hypertrophic cardiomyopathy
HCU	high care unit

HDI	Human Development Index
HF	heart failure
HIV	human immunodeficiency virus
HIV/AIDS	human immunodeficiency virus/acquired
HOT CAFE	how to treat chronic atrial fibrillation
HR	hazard ratio
HRS	Heart Rhythm Society
HTA	health technology assessment
ICD	implantable cardioverter defibrillators
ICE	intracardiac echocardiography
ICER	incremental cost-effectiveness ratio
INR	therapeutic international normalized ratio
ICD	implantable cardioverter defibrillator
ICE	intracardiac echo
ICER	incremental cost effectiveness ratio
INR	international normalised ratio
J	joules
JACC	Journal American College of Cardiology
JAMA	Journal of American Medical Association
KZN	KwaZulu-Natal
LA	left atrium
LAA	left atrial appendage
LAF	lone atrial fibrillation
LFT	liver function tests
LV	left ventricle
LVEF	left ventricular ejection fraction
LVH	left ventricular hypertrophy
MCS	mental component summary
Min	minutes
MN	Minnesota
MR	mitral regurgitation
MRC	Medical Research Council
mmHg	millimetres of mercury
NGOs	non-government organisation
NHA	national health accounts
NHI	national health insurance
NHS	national health system

NICE	National Institute for Clinical Excellence
NMB	net monetary benefits
NPV	net present value
NSR	normal sinus rhythm
NYHA	New York Heart Association Functional Class
OAT	oral anti-coagulants
OOPS	out-of-pocket spending
ORT	orthodromic reciprocating tachycardia
PAF	paroxysmal atrial fibrillation
PCS	physical component summary
PIAF	pharmacological intervention in atrial fibrillation
PMBs	prescribed minimum benefits
PPP	purchasing power parity
PR	PR-interval
PrepaidHE	prepaid plans & risk-pooling arrangements
ProBNP	pro brain naturetic peptide
PTCA	percutaneous transluminal coronary angioplasty
PV	pulmonary veins
PVAC	pulmonary vein ablation catheter
PVB	present value of benefits
PVC	present value of costs
PVI	pulmonary vein isolation
PvtHE	private health expenditure
QALY	quality adjusted life year
QoL	quality of life
RA	right atrium
RACE	rate control vs. electrical cardioversion for persistent atrial fibrillation
RCT	randomised controlled trials
REF	risk equalisation fund
RF	radiofrequency
RFA	radio frequency ablation
RFCA	radiofrequency catheter ablation
rrADT	relative risk of dying from ADT
RV	right ventricle
RVR	rapid ventricular response
SA	wino atrial node
SAIRR	South African Institute for Race Relations

SARS	South African Revenue Services
SEC	spontaneous echo-contrast
SF-36	short form-36 for QoL
SG	standard gamble
SHI	social health insurance
SPAF	stroke prevention in atrial fibrillation III
SR	sinus rhythm
SSHE	social security health expenditure
STAF	strategies for treatment of atrial fibrillation
STOP-AF	North American Arctic Front (STOP AF) pivotal trial
SVC	superior vena cavae
SVT	supra-ventricular tachycardia
2D	two dimensional
T_4	tetraiodothyronine
TB	tuberculosis
TDI	tissue Doppler imaging
TEE	trans-oesophageal echo
THE	total healthcare expenditure
TIA	transient ischaemic attack
TSH	thyroid stimulating hormone
TT	thrombin time
TTE	transthoracic echo
TTO	time-trade-off
U&E	urea and electrolytes
UCT	University of Cape Town
UK	United Kingdom
USA	United States of America
V	volts
VA conduction	ventricle to atrial conduction
Val-HeFT	valsartan heart failure trial
VAS	visual analogue scale
VVI	single chamber ventricular pacemaker
VVI mode	single chamber ventricular pacing mode
WC	Western Cape
WHO	World Health Organization
WPW	Wolff-Parkinson-White syndrome
WTP	willingness to pay

YLD	years of life lost due to disability
YLL	years of life lost due to premature mortality
ZAR	South African Rands (currency)

PREFACE

The intention of this preface is as follows:

1. To provide elucidatory background on the development of this dissertation;
2. To delineate the structure of the dissertation;
3. To provide an overview on atrial fibrillation (AF);
4. To provide an update on changes in the literature over the past decade; and
5. To confirm the relevance of the study area.

Background to dissertation

The first version of this dissertation was lodged for review in 2013. Two further reviews were undertaken in 2015 and 2019. On each occasion, I have received valuable feedback that has shaped the scope and structure of the finalised dissertation that is contained here. Changes made in response to the various reviews have been integrated into the dissertation to allow for a seamless review thereof.

This document provides a summary of structural and content changes and additions that have been made to the dissertation to support this finalised version thereof.

Dissertation structure

It was agreed by the Dean's Office in the Faculty of Economic and Management Sciences at Stellenbosch University in 2019 that the structure of this dissertation be as follows:

- A preface that serves to provide an introductory statement on the dissertation topic and further background to locate this work within a broader context; and
- The original dissertation, revised in accordance with examiner feedback and containing two major content additions:
    - Annexure A is a manuscript containing wholly new content reviewing available systematic reviews. Since initial completion of the dissertation in 2013, one of the most significant changes has been the introduction and use of Cryoballoon technology for atrial fibrillation ablation. At present there are some centres that only use Cryoablation when doing the first AF ablation on patients and reserve radiofrequency ablation (RFA) with 3D mapping for re-do ablations, while others routinely use RFA with 3D mapping for all paroxysmal atrial fibrillation (PAF) ablations. There is debate about which technology has better patient outcomes with fewer adverse events and shorter procedural and fluoroscopy time. This new manuscript addresses this debate. It is titled 'Radiofrequency versus cryoablation for treating patients with paroxysmal atrial fibrillation: An overview of systematic

reviews'. Eleven systematic reviews, all published between 2015 and 2018, were used for the overview. This manuscript has been prepared for submission to *EP Europace*.

- Annexure B is a second manuscript in the form of a journal article based on Chapters 6 and 7 of the dissertation, and written in response to a recommendation of the examiners since, in spite of the rapid growth in electrophysiology, this study remains unique in South Africa. This manuscript is titled 'The Cost-Effectiveness of RF-Ablation vs. Anti-Arrhythmic Drug Therapy for Paroxysmal Atrial Fibrillation in the South African Private Sector'. It has been prepared for the *Cardiovascular Journal of Africa*, which focuses on research done in Africa for Africans.

These two annexures are positioned following all other documentation relating to the dissertation. As a result, they have been included on the Table of Contents for the dissertation as the final two items.

Since the intention is that these manuscripts will be submitted for publication following completion of the dissertation examination process, the structure, style and referencing of the manuscripts follows the stylistic requirements of the respective journals to which they will be submitted. For ease of reference, a summaryof the relevant journal's style guide outlining its requirements for journal submissions has been included as an appendix on each of the annexures.

Background on atrial fibrillation

Atrial fibrillation (AF) is the most commonly found and sustained cardiac arrhythmia of clinical significance and was recognised by physicians in ancient China, Egypt and Greece. In 1628 William Harvey (1578-1657), first described fibrillation of the auricles in animals and Jean Baptist de Sénac (1693-1770), a French "clinical pathologist" pondered on a possible correlation between "rebellious palpitation" and mitral valve stenosis (Munger, Wu & Shen, 2014). The discovery in 1785 of the digitalis leaf by William Withering (1741-1799) brought relief to patients with AF and congestive heart failure by reducing the ventricular rate.

The first human electrocardiograph (ECG) depicting AF was published in 1906 by Willem Einthoven (1860-1927). Sir Thomas Lewis (1881-1945), a pioneering cardiologist and clinical scientist, was the first to study electrophysiological characteristics of AF. The major discoveries in the 20th century relating to the pathophysiology and clinical features of atrial fibrillation were led by, among others, Karel Frederick Wenckebach (1864-1940). But it was the Framingham Heart Study, which started in 1948 and is now in its 72nd year, that provided substantial insight into the epidemiology of cardiovascular disease and its risk factors, including AF and stroke. With the data from the Framingham Heart Study and subsequent research into AF, physicians have sought ways to treat patients with AF and to prevent stroke. Up until the late 1990s, the gold standard treatment of atrial

fibrillation was drugs. Anti-arrhythmic drugs are still prescribed as a first-line therapy for patients with AF but the awareness of transcatheter radiofrequency and cryoablation of non-valvular AF has increased and is now accepted in the American and European guidelines for the management of AF. The most recent 2019 European Society of Cardiology (ESC) guidelines for the management of supra-ventricular tachycardia (SVTs) now also include the use of robotic magnetic navigation to perform ablation.

Estimates suggest that the prevalence of AF in patients 20 years and older is approximately 3%, increasing as patients age. It is expected that 25% of all middle-aged adults in Europe and the USA will develop AF in their lifetime. Atrial fibrillation is associated with debilitating symptoms, an impaired quality of life and a 1.5-fold to two-fold increase in all-cause mortality, including heart failure and stroke. In 2010 the worldwide estimate for AF was 33.5 million people. When applying the estimated incidence rates of 2010, the estimated number of new AF cases per year is 2.7 million for men and 2.0 million for women.

Atrial fibrillation is associated with other cardiac diseases such as coronary artery disease, valvular-heart disease, cardiomyopathy, hypertension, heart failure and stroke. Diabetes, chronic obstructive pulmonary disease, and renal failure are among the most frequent co-morbidities. Higher incidence and prevalence rates are found in developed countries; however, the World Health Organisation (WHO) data shows that, of the estimated 17.9 million deaths in 2016 as a result of cardiovascular disease, myocardial infarction and stroke accounted for 85% of all these deaths, and more than three quarters of these deaths were in low- and middle-income countries.

The mainstay of treatment for AF has been drugs. Electrophysiology (EP), a super-specialty within cardiology, is a discipline that focuses on the electrical conduction in the heart, from which arrhythmia arises. Prior to the introduction of ablation for atrial fibrillation, only a relatively small number of cardiologists pursued the field of electrophysiology when compared with their colleagues in interventional cardiology. Technology was limited and, while patients suffered from arrhythmia, only a limited number of patients found their way to an EP lab to have the arrhythmia ablated.

In the late 1990s and 2000s, the number of electrophysiologists being trained globally increased to meet the demand for treatment, especially for atrial fibrillation. At the same time, the number of electrophysiologists in South Africa declined through emigration or death. Training centres like those affiliated with Wits University closed; and, for many years, no new electrophysiologists were trained in electrophysiology in South Africa. With little or no exposure to EP during their cardiology fellowship, only a few cardiologists went on to further specialize in EP. (The average time to train as an electrophysiologist from start of undergraduate studies to completion of electrophysiology is around 18 years).

When catheter-based radiofrequency ablation started to achieve international acceptance in the late 1990s, South Africa could not keep up with the growth. In 2010, there were only 10 practicing

electrophysiologists in South Africa who could perform ablation for atrial fibrillation across a population of close to 50 million people.

Key stakeholders in South Africa who are in a position to help or frustrate the process for patients with AF to receive ablation, are the following: medical doctors (both referring and treating), funders (medical aids and government), and the multinational companies who developed and supplied the technology. When planning this research in 2010, I did so with these stakeholders in mind. At the time, the situation in relation to each was as follows:

- The treating doctors in South Africa - many of them being world-renowned experts in their fields - were frustrated by the lack of willingness of the funders to reimburse AF ablation, while themselves not fully understanding (or perhaps interested in) the complexities of funding models, principles of rationing and cost-effectiveness. Most of them only wanted to be responsible for treating patients.
- On the other hand, those responsible for funding these procedures understood the dynamics of our economy, healthcare structure and even health economics, but had little grasp of the complexities of atrial fibrillation and ablation and were often not willing to fund “expensive therapies”, taking a short- rather than long-term outlook on patient outcomes and often citing “churning” as a reason for doing so. There was simply no data to convince them that this treatment should be funded. Sadly, this is often still the case almost a decade later.
- Large multi-national suppliers had little understanding of the complexities of South Africa and its healthcare system. To them a population of more than 50 million people meant a large market to tap into. They set unrealistic expectations for the growth of the market locally and lacked understanding that, in order to get growth, investment in training would first be required.

From the outset, my aim was to conduct research that would be relevant to all these stakeholders and effect change for the patient in particular. With this in mind, I embarked on research that would address the gaps in knowledge and understanding of these stakeholders.

Changes in literature over past decade

- **Definition of AF**

The 2001 AHA/ACC/ESC Guidelines for the management of patients with atrial fibrillation defined atrial fibrillation as either first detected, paroxysmal (self-terminating), persistent (not self-terminating) or permanent. The 2016 guidelines add an extra classification, namely long-standing persistent atrial fibrillation.

- **Guidelines for the management of AF**

The 2001 AHA/ACC/ESC Guidelines for the management of patients with atrial fibrillation introduced the concept of ablation for atrial fibrillation. The data showed that ablation reduced the frequency of recurrent AF in more than 60% of patients, with recurrent AF of 30% to 50% in the first year. Their recommendation was that these procedures produced promising results but were not widely applied.

The 2006 *AHA/ACC/ESC Guidelines* updated in 2011 introduced an updated section that, for the first time, discussed catheter ablation for atrial fibrillation in some detail and reported that the available studies did not provide convincing evidence of optimum catheter positioning or absolute rates of treatment success, and that more evidence was needed. However, in 2012, the ESC published an update of the *2010 Guidelines for the management of atrial fibrillation* and, for the first time, catheter ablation was recommended as a possible alternative to anti-arrhythmic drug therapy for patients with symptomatic recurrent paroxysmal AF on anti-arrhythmic drug therapy, provided the procedure was performed by an experienced operator.

The *European Society of Cardiology (ESC)* (2016) and the *American Heart Association/American College of Cardiology/Heart Rhythm Society Guidelines* (2014) now both recommend catheter ablation in patients with symptomatic recurrences of atrial fibrillation on anti-arrhythmic drugs as a I A level of evidence for PAF and IIa level C evidence for persistent atrial fibrillation, with clinical data supporting catheter ablation as a first-line rhythm control strategy before the use anti-arrhythmic drugs.

The advent of catheter ablation in the 1990s resulted in the proliferation of ablation for atrial fibrillation that continues to grow, both in South African and around the world. There has also been another very positive spin-off related to the growth in AF ablation technologies: the increased number of other cardiac arrhythmia that are now treated, allowing patients to lead normal lives without palpitations. This has also paved the way for the more controllable and safer procedures for cardiac ablation, including in children with congenital heart defects.

Since the submission of this thesis in 2019, there have not been any major changes in the way that paroxysmal atrial fibrillation is treated. The drugs used in the modelling in this dissertation therefore remain the same as recommended in the latest guidelines.

Changes in South Africa

Ablation for atrial fibrillation has grown significantly in numbers since the initial submission of this dissertation. Patients being treated in South Africa has grown from a few hundred patients a year, to a few thousand a year. At the time of submission there were 10 electrophysiologists practicing in South Africa. These services were limited to 10 hospitals in the major centres like Johannesburg,

(three electrophysiologists) Pretoria (one electrophysiologist), and Cape Town (five electrophysiologists) and a single centre in KZN (one electrophysiologists).

Only one academic centre (Groote Schuur Hospital) offered full time electrophysiology service with occasional cases being performed at Inkhosi Albert Luthuli Hospital in Durban by a visiting professor from Cape Town until his untimely death.

Since 2010 there has been a 90% increase in the number of electrophysiologists in South Africa. The demographics of the electrophysiologists has also changed and reflects the transformation within South Africa. In 2010 of the 10 practicing electrophysiologists, seven were white males and the others males were from previously disadvantaged communities. These 10 electrophysiologists serviced communities by working in 10 EP labs around South Africa. In 2019 there are 34 hospitals where EP services are offered, with 19 electrophysiologists with new hospital starting these services each year. (2019 has seen three new labs being opened and two academic hospitals starting EP services). The demographics have changed to show further transformation in healthcare with 47% of electrophysiologists now coming from previously disadvantaged backgrounds and 16% of all electrophysiologists are women. Limited electrophysiology services are now offered in six government sector hospitals, compared with only two in 2010. These electrophysiology services have expanded to Namibia, with two South African doctors preforming cases in Namibia every six to eight weeks. There are plans to expand the electrophysiology services to Botswana and perhaps Angola at a later stage. There are currently two black female cardiologists undergoing electrophysiology training in Europe and America who are expected to return to South African in mid-to end 2020 and one recently qualified black male cardiologist who is working under the direction of a local electrophysiologist, who will, when funds are available, enter into a formal training program in either the northern America or Europe. Approximately 300 ablations were performed in South Africa in 2010 and in 2017 alone there were three EP centres who performed between 350-400 procedures each per year, this has increased to a conservative estimate of 2500-3000 procedures per year and increasing year on year with some electrophysiologists reportedly performing 600 cases a year in a single EP lab.

Changes in patient costs

When comparing the average cost of treating patients with atrial fibrillation with either ablation or anti- arrhythmic drugs in 2011 and again in 2019, it was found that outpatient costs had grown by 127% over this period. Based on cost data over a one-year period from the same hospital where previous data was received, the costs associated with pulmonary vein isolation (PVI) have also grown by an average of 78%, with the professional fees accounting for most of this growth while the costs of radiofrequency ablation disposables having only grown by an average of 38% in the same period. The anti-arrhythmic drugs used in the 2011 model are still recommended in the 2016 guidelines for the management of atrial fibrillation. Their price has also grown between 67-74% since

2011. The Novel Oral Anti-coagulant drugs (NOACS) are more frequently prescribed and the reimbursement thereof has improved, but as these would be used by both the patients treated with drugs and those who had ablation, this addition would not affect the outcome of the model. As the main cost driver in our model for the ADT group was re-hospitalisation, there is no reason to expect a change in the result of cost-effectiveness of RFA vs. ADT for paroxysmal atrial fibrillation as the cost of hospitalisation has also increased.

The introduction of national health insurance (NHI)

The South African government is at present pushing the NHI Bill to be passed through Parliament. While driven in political circles, there is still a great deal of uncertainty among the general population, hospitals, medical insurance and healthcare providers. Affordability will become more of a driving issue in decision-making for treatment options. This makes the understanding of cost-effectiveness of catheter ablation for atrial fibrillation important. The NHI will no doubt be an extra tax burden. While not a disease of only the elite, we do know that from the age of 55, the risk of developing atrial fibrillation increases, as does the risk of stroke. It is interesting to note that in the 2016 tax year, of the approximately 4.8 million tax payers, 21.8% were over 55 years of age and a further 22.3% of the tax payers were between 45-54 years old and fast approaching the age where they are at risk of developing atrial fibrillation and stroke. Having cost-effective healthcare solutions like AF ablation may help to reduce the already burdened healthcare sector by keeping the economically active population active.

Medical aid insurance

In spite of the volumes of literature available on ablation for atrial fibrillation, there are still a number of insurance companies that won't fund AF ablation, still citing it as expensive technology. Arrhythmia forms part of the group of diseases known as prescribed minimum benefits (PMBs), meaning that treatment must be funded. However, some of the insurers continue to decline reimbursement of AF ablation, using the excuse that only life-threatening arrhythmia forms part of the PMBs. Atrial fibrillation itself does not cause patients to die but, as demonstrated in this study, it is associated with increased mortality and morbidity. Understanding the value and cost-effectiveness of ablation for atrial fibrillation would make access to this treatment available to more South Africans in the private sector.

Public sector patients

Growth in the private sector often translates into more investment being available for training in the public sector, which then leads to more public sector patients being treated. While AF ablation is not likely to be available for the general population for some time, the investment and growth in EP has made cardiac ablation available to public sector patients with other symptomatic or disabling cardiac arrhythmia, many of them young active people, including children.

Relevance of study area

Within this thesis, the chapters on atrial fibrillation are very complex, even for physicians who are not in the field of cardiology. Other chapters are not unique, yet were deliberately included as part of the study design to address the gaps in the knowledge of the various stakeholders and to answer my research question:

> *Is radiofrequency ablation cost-effective compared to anti-arrhythmic drug therapy for treating atrial fibrillation in South Africa?*

With the re-submission of this dissertation, a further question is raised:

> *Is this dissertation still relevant today?*

The answer is yes. In fact, with proposed changes in our healthcare system, an economy that is sluggish, and national health insurance looming, I believe that it is more relevant now than it was before.

In summary, in spite of the many challenges in the process of completing this PhD, I have been part of a journey where we have almost doubled the number of electrophysiologists practising in South Africa. Rather than training only one electrophysiologist every few years, South Africa has a pipeline of young cardiologists interested and being trained in electrophysiology. The demographics of the electrophysiologists has transformed, with more previously disadvantaged groups and women being trained as electrophysiologists. We have regular electrophysiology workshops being held in the public sector/academic hospitals with a focus on training of hospital staff at various levels. We now also have one paediatric cardiologist and electrophysiologist who is able to treat patients with congenital cardiac disorders with ablation, both in the public sector and the private sector. We have developed and trained people who have had opportunities to work in prestigious international hospitals. In answering the question as to whether this study is still relevant in South Africa, I believe it is more relevant than ever. Each day we move closer to achieving my end goal, to make AF ablation more accessible to more patients.

CHAPTER 1: INTRODUCTION

1.1 BACKGROUND

1.1.1 The rise in cardiovascular disease

An estimated 17.9 million people died as result of cardiovascular disease in 2016. This represented 31% of all deaths globally (see Figure 1.1). Myocardial infarction and stroke accounted for 85% of all the cardiovascular deaths (WHO, 2017). More than three quarters of the cardiovascular deaths were in low- and middle-income countries. Of all the 17 million premature deaths in 2015 (persons under the age of 70 years), 82% were due to non-communicable diseases with 82% in low-and middle-income countries, while 37% were due to CVD.

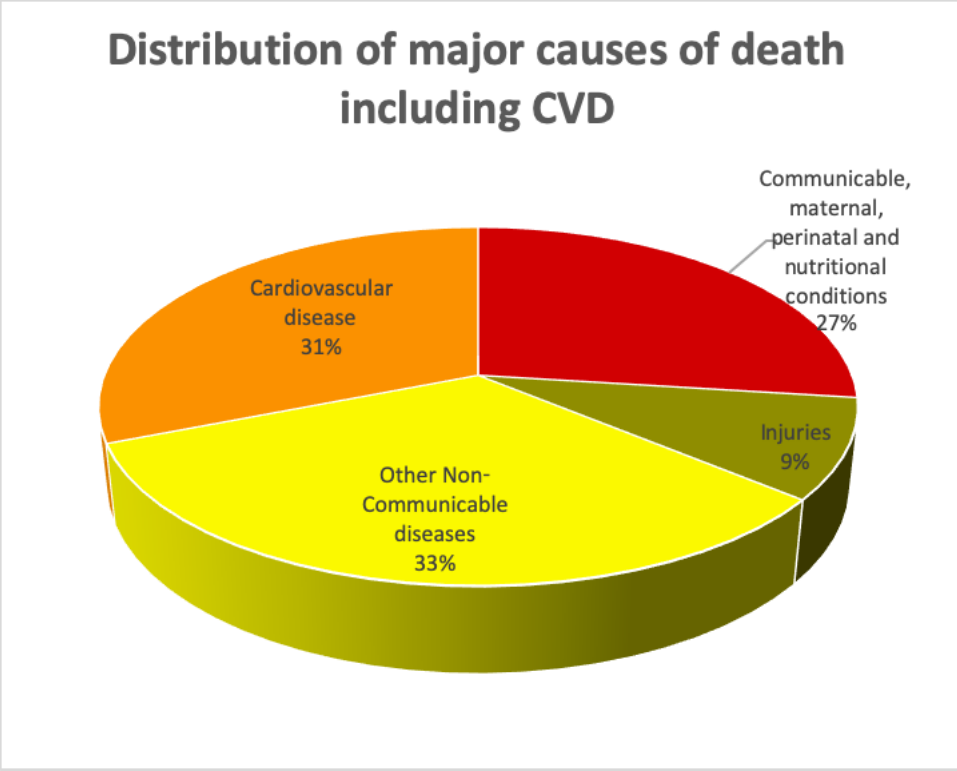

Figure 1.1: WHO reported deaths in 2016

Source: WHO, 2017.

These data are important for this study, as the population of patients who are being measured are those with atrial fibrillation (AF). People with AF have a significantly increased risk of stroke, possibly as much as seven times that of the general population (Dressing & Schweikert, 1985).

A common misconception exists that cardiovascular diseases are diseases of affluent societies or developed nations and that developing nations are plagued with infectious diseases. However, WHO reports show that, in 2001, cardiovascular disease (CVD) accounted for nearly one-third of all deaths globally and, in 2008, more than 80% of deaths from CVD were in low- to middle-income countries.

These statistics raise concerns as the number of deaths from CVD in low- to middle-income countries has doubled in recent years, and these deaths are occurring at an earlier age in these countries as compared to similar deaths in developed countries (The World Health Report, 2003: 85; WHO, 2011).

The WHO 2003 report estimated that, by 2010, death from CVD would be the leading cause of death in developing countries. The WHO 2011 report estimated that, by 2025, CVD disease would claim the lives of 25 million people globally each year. Coronary heart disease, heart failure and other cardiovascular diseases are chronic in nature, leading the Institute for International Health to project that, by 2020, 71% of deaths in the developing world would be directly related to ischaemic heart disease and 75% related to stroke (WHO, 2003: 86).

People in low- and middle-income countries are also more exposed to risk factors, such as tobacco, which is a leading cause of CVDs, as well as other non-communicable diseases. Moreover, people in low- and middle-income countries often do not have the benefit of prevention programmes that are available to people in high-income countries. They may also have less access to effective and equitable health care services that respond to their needs, including prevention and early detection (WHO, 2012).

Table 1.1 illustrates the cardiovascular-related deaths by cause and by region in the world for 2008 as found in the WHO Health Report of 2011.

Table 1.1: Cardiovascular related deaths in 2008 by cause and WHO regions (thousands)

Cause	WORLD		AFR D	AFR E	AMR A	AMR B	AMR D	EMR B	EMR D
Population (000)	6,737,480		376,474	428,391	356,130	478,058	81,242	158,778	421430
	(000)	% of total	(000)	(000)	(000)	(000)	(000)	(000)	(000)
Cardiovascular Disease	17,327	30.5	566	688	985	867	91	315	879
Rheumatic Heart Disease	220	0.4	6	5	4	5	-	3	19
Hypertensive Heart Disease	1,153	2	35	51	67	102	16	37	59
Ischaemic Heart Disease	7,254	12.8	170	204	506	345	29	156	432
Cerebrovascular Disease	6,152	10.8	204	245	172	240	26	71	221
Inflammatory Heart Disease	402	0.7	25	31	36	29	1	6	27

Cause	Eur A	Eur B	Eur C	SEAR B	SEAR D	WPR A	WPR B
Population (000)	429,625	226,391	233,154	413,792	1,445,693	157,605	1,629,716
	(000)	(000)	(000)	(000)	(000)	(000)	(000)
Cardiovascular Disease	1,505	1,006	2,073	727	2,889	420	4,314
Rheumatic Heart Disease	10	7	8	15	41	3	93
Hypertensive Heart Disease	98	82	46	69	218	9	265
Ischaemic Heart Disease	594	420	1,182	312	1,522	141	1,242
Cerebrovascular Disease	361	283	634	220	972	151	2,354
Inflammatory Heart Disease	35	42	39	11	21	9	92

Note: The full description of WHO regions is given in Appendix A.

Source: WHO, 2011.

The British Heart Foundation estimates that more than 4 million deaths occur each year in Europe as a result of CVD, making this the leading cause of death in Europe and accounting for 49% of all deaths. The WHO reported in 1990 that CVD death was the leading cause of years lost due to an early death. Of all the CVD-related deaths, almost 50% are from coronary disease and a further one-third are from stroke. In a global context it should be noted that, of the estimated 32 million heart attacks and strokes that occur each year, about 12.5 million or 39% are fatal. Many of these CVD-related deaths were linked to tobacco and were preventable (Office of the Surgeon General (US) & Office on Smoking and Health (US), 2004).

Reports from the World Health Organisation (WHO) in 2005 showed a global increase in the incidence of disease entities such as heart disease, *diabetes mellitus* and congestive heart failure (WHO, 2001). *Diabetes mellitus*, hypertension and cigarette smoking are known risk factors for CVD and strokes (Rosamond, 2007: 69), and a combination of these factors means that heart disease and its contributing factors are high in both developed and developing nations. In 2003 the WHO stated that 13% of the disease burden in adults over 15 years of age was as result of cardiovascular diseases and that ischaemic heart disease and stroke were the two leading causes of mortality and disease burden among adults over the age 60. Up to 36% of deaths in all developed countries can be attributed to ischaemic heart disease and stroke. These death rates are higher in men than in women (The World Health Report, 2003).

The incidence of *diabetes mellitus* around the world has doubled in the past 30 years (Council for Medical Schemes Annual Report 2003-4, 2004:9). Other risk factors for heart disease, such as obesity, have grown by 27% in recent years. This worldwide increase in obesity, *diabetes mellitus* and cardiovascular disease (CVD) has resulted in heart disease killing more people in the world than any other single disease. In the United States of America (USA), 27% of the total population has one or more types of cardiovascular disease. Approximately 47% of these patients with CVD are over the age of 65 years (Rosamond, 2007: e117).

1.1.2 The economic burden of cardiovascular disease

Because the burden of disease is on the increase, there is also a growing economic burden. In 2006, the direct cost to the health care system of cardiovascular disease amounted to almost 110 billion Euros or 10% of the budget for healthcare in the European Union (EU). The greatest portion of this expenditure was allocated to hospitalisation costs for in-patient care (54%), while medication or drug therapy accounted for a further 28%. Of all the expenditure on CVD in 2006, 22% was related to ischaemic heart disease and 17% was related to stroke (24 billion Euro and 18 billion Euros respectively) (Allender *et al*., 2008: 105).

Loss of productivity due to death or illness in people of working age adds to non-healthcare related costs, resulting in an increase in the financial burden of CVD. In the EU in 2006, loss of productivity

due to mortality and morbidity from CVD was estimated to cost 41 billion Euros. Twenty-seven billion Euros or 65% was related to death and a further 35% or 14 billion Euros was due to illness. The cost of mortality and morbidity as the result of stroke was 26% of the total cost for CVD and accounted for eight billion Euros (Allender *et al*., 2008: 105).

An important consideration in low- and middle-income countries affected by CVDs and other non-communicable diseases is that the affected often die younger, which means that their most productive years are lost forever. This compounds the incidence and effects of poverty due to loss of family income, catastrophic health spending and high out-of-pocket expenditure at the household level. At a macro-economic level, the WHO (2012) estimates that premature death caused by non-communicable disease, including cardiovascular disease and diabetes, reduces the GDP by up to 6.77% in low- and middle-income countries.

Improved methods of diagnosis have enabled physicians to diagnose these conditions far earlier, exposing the seriousness of these conditions. New technologies have not only afforded the medical fraternity the ability to make a diagnosis earlier, but they have also offered a mechanism to safely and effectively treat patients who, in previous years, would have been considered either ‘too old’ or ‘too risky’ for conventional treatment.

1.1.3 New technologies vs traditional drug options

The costs associated with healthcare have attracted increasing attention in recent years. While some countries have seen a decline in general inflation during the last decade, many countries have seen a concomitant increase in medical inflation, at times recorded at levels double that of general inflation. Politicians label the increase in medical costs and medical inflation as excessive but continue to promise voters improved health services in a bid to gain political favour. Thus, the debate that has evolved around the issue of medical costs has served to unite global policy makers in their endeavour to reduce healthcare costs while improving the health of the world’s population (Drummond *et al*., 2006: 5).

Life expectancy around the globe has increased and healthcare has adopted an approach not unlike other commodities where patients shop around on the internet for information and services. Many patients approach healthcare in much the same way as any other form of consumerism, demanding better quality of life for longer periods, thereby contributing to significantly higher costs of healthcare, driving medical inflation beyond general inflation and undoubtedly placing extra financial burden on governments and policy makers alike (Gleckman & Carey, 2002: 123; Seifan & Shemer, 2005).

According to Gleckman and Carey (2002) the use of new health technologies may be one of the tools to control the acceleration in medical inflation (Gleckman & Carey, 2002: 123). Use of these new technologies in the United States has shown, in some instances, a reduction of overall costs as a result of reduced hospitalisation, decreased absenteeism and increased productivity. This has been

achieved through disease management programmes and the concurrent use of medical technology. While the initial cost of technology may be higher, there may also be significant cost savings in the long term.

In 2012/2013 the size of the medical technology market was estimated at US $ 270 billion globally. What appears to be driving growth in this market includes the demographic trends in both developed countries, where ageing populations are increasing, and developing countries, where there appears to be a change from communicable diseases to non-communicable diseases (KPMG, 2014). Figure 1.2 shows the growth in the global medical technology market from 2006 to 2015.

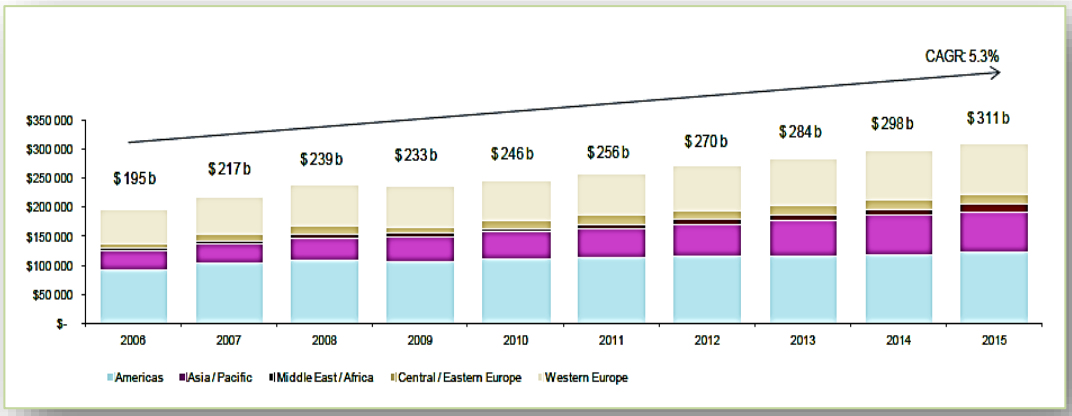

Figure 1.2: Growth in the global medical technology market from 2006 to 2015

Source: KPMG, 2014: 16.

Not only does the United States outspend other nations in health care, but U.S. health care costs are growing rapidly. From 1988 to 1993, U.S. health expenditures rose by 9.7% per year. Followed by a slowdown from 1993 to 2000, where the costs jumped by 8.5% in 2001, 9.3% in 2002, and 7.7% in 2003. The most rapid growth in the health care sectors were the cost of prescription drugs as well as administrative costs of private health insurance (each increasing at 11% to 16% in a 3 year period). Hospital and physician expenditures grew in average by 7% to 8% year on year over the same 3 years period.

High medical inflation rates are evident worldwide and the annual increase in healthcare costs have grown at historically high rates, with no signs of abating. Managed care has not appeared to slow medical inflation. From 1988 to 1993, U.S.A the health expenditure rose by 9.7% per year and medical insurance in the United States grew on average by 15% in 2003. This did slow down for the period of 2006 to 2011 when medical inflation in the USA ranged between 8.3% and 10.1% (Towers Watson, 2011: 3). At the time the federal government projected an average annual growth rate of 7.2% through 2013, with health expenditures rising from $1.6 trillion in 2002 (14.9% of GDP) to 17.9% of GDP in 2011 and again to $3.6 trillion by 2013 (18.4% of GDP). (Wayne, 2012). Health

Inflation News (2004) showed that this was particularly high when considering that medical inflation in February 2004 was 4.2%, an increase from November 2003 when it registered 3.5%. Both these rates were significantly higher than the growth in the Consumer Price Index (CPI) of 1.8% and 1.7% respectively. One of the biggest contributors to this was in-patient hospital care (Health Inflation News, 2004: 3).

Fong (2003: 9) found that after nearly a decade of managed healthcare in the United States, which was meant to revolutionise the marketplace, hospital and physician expenditure showed increase of between 7% to 8% year in year. (Smith *et al*., 2005)

Similarly, managed private healthcare costs in South Africa increased by 14.2% in 2003, totalling around R5.5 billion, without any apparent concomitant improvement in healthcare delivery. The USA is among those countries where controlling medical inflation has become of paramount importance, and various methods are adopted in order to achieve this. In 2003 the USA started recruiting medically trained doctors from developing countries as nurses. Many of these doctors were unable to gain a licence to practice in the USA as a medical doctor, owing to a complex registration process. For the USA, at least in the short term, this meant that, in addition to addressing the problem of the shortage of nurses, they gained the expertise of a higher level of competency and training, paying 'physician-nurses' nursing salaries and wages and saving the costs involved in recruiting and training of nurses themselves (Clemente, 2003: 1). One may question what real long-term impact this type of practice will have on costs.

Business Day (2003) refers to the fact that more and more South Africans have been funding part of their medical bills out-of-pocket, with this phenomenon unlikely to improve any time soon. This seems particularly true in the area of health technology, where the device industry has been increasingly expected to discount devices that offer lifesaving technologies in order to meet the growing out-of-pocket expenditure of patients in the private health sector.

According to Miot (2005), there is a lack of clarity on managing costs associated with new technology, added to which is the lack of a legislative body to control the quality of health technology in South Africa. The onus rests with each individual medical scheme to assess whether new treatments and technology provided offer any added benefit to their patient, taking into consideration total cost and perceived value for money.

With limited healthcare resources and incentives for certain insurers to save costs, policy makers for healthcare provision often focus only on immediate costs and prefer to spread their risk over many years instead of paying the sometimes-substantial upfront cost of these new technologies. One of the greatest challenges facing health economists is the identification and valuation of the benefits from healthcare interventions. This has resulted in an international trend towards evidence-based medicine (EBM) decision-making in healthcare which, in turn, has led to an increased demand for economic evaluation studies in recent years (Sculpher *et al*., 2004). Today, a number of healthcare

systems use economic evaluations to make system level decisions regarding which interventions they fund from collective resources (Drummond *et al.*, 2006), thus using economic evidence in reimbursement decisions for healthcare technologies.

1.1.4 The South African reality

After peaking in the mid-1980s, inflation in South Africa declined to reach record low levels in the 1990s and the first half of the 2000s. This was as a result of solid and tight monetary policies and the introduction in 2000 of inflation-targeting policies (Henry, 2003: 128). Yet, in spite of the fact that general inflation declined in the 2000s, medical inflation continued to increase at a rate consistently and significantly higher than the general inflation rate; at times, it was more than double that of general inflation (Council for Medical Schemes, 2004:9; Twine, 2008). This has resulted in medical insurance companies; individuals and the government being forced to find solutions to curb medical expenditure.

This growing interest in and concern about healthcare costs in general has resulted in an upsurge in literature on the economic evaluation of healthcare by economists, medical researchers, clinicians and multi-disciplinary teams (Drummond *et al*., 2006: 1). Many of the problems associated with the rising costs of healthcare are not unique to South Africa, but South Africa has, in many instances, unique healthcare needs. The use of medical technology is often rejected in favour of traditional medical therapy as a means of treatment as new technologies are frequently considered too costly.

Studies investigating the impact of cost on healthcare systems, and particularly on medical technology and devices, are limited in the South African environment. This study, therefore, examines the rising costs of healthcare expenditure in South Africa and focuses in particular on arrhythmia and, more specifically, on non-rheumatic atrial fibrillation in the South African population and the costs associated with the disease. The justification for this delimitation of the research domain is explained in the next section.

Heart disease in the general South African population has also increased. This disease, identified in the 1970s as one that affected mainly white Afrikaans-speaking and Jewish men, is now prevalent in both males and females of all population groups and ages in South Africa. The epidemiological studies established at Chris Hani Baragwanath Hospital (Sliwa *et al.*, 2008: 916) reveal a high prevalence of modifiable risk factors for atherosclerotic disease and a combination of infectious and non-communicable forms of heart disease. Although advances in medical care have enabled people to live longer, they may still have residual disease or damage to their hearts, requiring major surgery and lifelong drug therapy with their potentially toxic or other debilitating side effects, or both.

The South African government remains concerned that more than 60% of the total health expenditure in South Africa is spent on only 15% of the population, while the remaining 85% of the population benefit from around 40% of the health expenditure - a trend which has not changed since

1996 (Schellack *et al*., 2011; KPMG, 2014; *The Economist*, 2010). The public sector appears to have insufficient capital to access “expensive” technologies. This is as a result of insufficient resources and poor management of these resources. Schellack *et al.* (2011) state that, in spite of an enabling legal and fiscal environment which exists to expedite government health goals, there is fragmentation and a lack of co-ordination in the various policy initiatives, many of which have not only been poorly managed but also lack transparency and the involvement of the public.

In a report prepared by KPMG for the South African Medical Device Association (SAMED) in 2014 it is argued that the South African public system has typically been characterised as suffering a lack of resources, especially human resources, medicine and medical technology. However, it is often the management challenges at both a provincial and district level that are most apparent to the press and the public. Furthermore, the public sector’s poor service delivery is severely affected by poor infrastructure and backlogs in capital projects (KPMG, 2014: 12).

The other side of the coin reflects that the medically insured population of South Africa has remained stagnant at around seven million lives since 1996. This industry is notorious for “churning” of members, i.e. members who change from one scheme to another (Council for Medical Schemes, 2004: 15). As a direct result of this, many policy makers have adopted what some might consider a short-sighted attitude of not paying for what may be considered expensive technologies. The reason for this appears to be that the insurers consider that they may not reap the benefit of any potential cost-saving which these new technologies may offer. In many instances a medical device or use of a new technology may ameliorate the need for certain medication. However, the cost of most devices (or therapy) is borne upfront while the cost of medication is carried over months or even years. A medical scheme that pays for these new technologies or devices could potentially save on treatment costs over the lifetime of the device, considering that the cost of medication is unlikely to decrease with time. Some devices and therapies are proven to decrease hospitalisation in patients with chronic diseases such as congestive heart failure, again potentially saving the medical schemes a significant amount of money. In spite of this, however, some medical aids choose to pay for medication only. Should the patient move to another medical scheme (as seen in churning) the financial outlay for that patient is, in essence, reduced. The result of this is that the patient may not benefit from the best treatment modality.

Unlike pharmaceutical agents, health technology in South Africa has no regulatory body that approves and monitors the introduction of new technology into the country’s healthcare system. This may result in not only inferior quality products entering the system but also technologies that are not backed up by good clinical evidence. Medical schemes are aware of the need to promote evidence-based medicine and, at present, Discovery healthcare leads the industry by evaluating the clinical evidence to support their decision either to fund or not fund a specific therapy. Many of the smaller medical aid schemes, which do not have the resources to offer the same evaluation, follow the lead

of Discovery Health. This has resulted in some therapies being accepted on a larger scale than might have been the case previously, but it does not provide an unbiased ruling as the medical scheme administrators are expected to conserve their financial reserves.

According to the KPMG report of 2014, the estimated value of the South African medical devices industry is in excess of R10 billion. This equates to about 0.4% of the total global technology market. However, it should be noted that while the global compound annual growth rate in the medical technology market is 5.3%, the growth rate in the medical technology in South Africa has grown by 19% since 2009 (KPMG, 2014: 18).

This highlights the need for a Health Technology Assessment body in South Africa similar to the National Institute for Clinical Evidence (NICE) in the United Kingdom (UK) where unbiased evaluations and recommendations are made on an assessment of what the best option is for the patient. In 2005 Brunner described how every 3.5 minutes a patient somewhere in the world who required an Implantable Cardiac Defibrillator died without receiving one. The value of health technology agencies can be seen by the change in funding policy, in particular in the UK, USA, Australia and the EU, and by the number of patients who now receive ICDs based on MADIT II criteria (Brunner, 2005).

Discovery Health, the largest private health insurer in South Africa, uses a concept known as a financial filter in their health technology assessment. This filter enables Discovery Health to evaluate the contribution impact known as “premium life per month”. This premium determines the amount per capita needed to fund a new therapy or technology. Unfortunately, the spread of risk is skewed among the insured population as many young healthy employed people are not subscribing to medical schemes because of the costs of these schemes, and contributions are increasing at a rate that exceeds general inflation, despite a range of cheaper products being available from medical schemes. This phenomenon is not unique to South Africa. In *Business Insurance* (Wojcik, 2004: 6), Bill Sharon of Aon Consulting, as quoted by Wojcik, stated that medical insurance premiums were expected to increase between 15% and 25% annually. This may be the trend as described by Brady (2003: 101) who showed that Aetna Inc. (a medical insurance firm in the USA, with a customer base of 19 million members) increased their annual rates by 16% in 2003 to keep ahead of medical inflation.

In South Africa some medical aid schemes have a higher percentage of pensioners who often require more medical treatment than the younger population, while other schemes tend to attract younger, healthier members. This issue has been addressed by the Council for Medical Schemes (CMS) who proposed the introduction of the Risk Equalisation Fund (REF) and the ruling that schemes were no longer permitted to turn applicants away, i.e. no “cherry picking.” The REF was to be implemented in 2007 but, at the time of writing this (2012), it had still not been implemented.

This study examines rising costs in healthcare expenditure in South Africa and, in particular, costs related to various treatment methodologies for paroxysmal atrial fibrillation in the South African

population. The preceding discussion points to the need to take a closer look at the factors underlying the increase in the cost of medical treatments.

1.2 RESEARCH PROBLEM AND OBJECTIVES

Billions of USA dollars are spent annually by large corporations and governments on research and development of new drugs and technologies and, at some point, it becomes necessary to evaluate whether any of these new drugs and technologies actually improve patient outcome, what the degree of improvement is and, finally, at what cost. The primary objective of this study is to measure the cost-effectiveness of radiofrequency catheter ablation compared to anti-arrhythmic drugs for the treatment of paroxysmal atrial fibrillation. The secondary objectives of this study are to explore the various aspects of healthcare expenditure in South Africa and to understand how health technology is defined. Together with this the review of available literature indicates the need to analyse the rising costs in South African healthcare expenditure, and, in particular, costs related to the treatment of various cardiac and cardiovascular diseases.

To achieve these objectives, the study will introduce the principles of health economics, evaluate the healthcare sector in South Africa and compare it to other developed and developing nations. The study will examine the concept of “willingness to pay” in the South African context and will then explore paroxysmal atrial fibrillation as a disease, its growing incidence, as well as the current treatment options available for its management, and the costs and, more importantly, the cost-effectiveness associated with these treatment options.

Finally, a summation will be presented of the author’s findings and recommendations offered both in terms of the utilisation of the various treatment options from the viewpoint of what is cost-effective in South Africa at a given date and also in terms of areas that would benefit from further research.

1.3 THE VALUE OF THE STUDY

Through the investigations proposed in this study, the author will attempt to answer important questions associated not only with the private health sector, but also with Government and the Department of Health on the behaviour of cost and trends in health technology in South Africa. There are various stakeholders who are affected by the apparent lack of knowledge associated with aspects of health technology in South Africa, namely Government, medical schemes, the Council for Medical Schemes, industry, physicians, potential investors and, more importantly perhaps, the patient, who is an unwilling or reluctant consumer.

To attempt to establish how this type of research could improve current management practices, it may be argued that improvement could be introduced at various levels. It would be hoped that, as with the introduction of policies like prescribed minimum benefits (PMB), there would be better provision for those patients within the medical schemes, perhaps resulting in fewer co-payments by

patients and ensuring that they receive not just any form of treatment but rather the appropriate technology based on evidence-based medicine. The information derived from such a study could potentially highlight, at an academic level, the critical need for an independent organisation to monitor health technology in South Africa.

Unlike the pharmaceutical industry, which is regulated in South Africa, an exploration of this nature could help highlight one aspect within the basket of goods compounding medical inflation. The medical devices industry could benefit from increased exposure to and utilisation of technology which, in turn, could drive the provision of better expertise in the field, as well as improve potential investment in the country, in particular with regard to investment in the training of physicians and nurses. In 2012/13 it was estimated that medical technology companies in South Africa spent in the region of R31.7 million on the training of healthcare professionals and a further R 23.7 million on sponsorships to educational meetings. This is illustrated in Figure 1.3. In this regard it may be noted that this investment accompanies job creation and skills development, particularly in the industry that supports these technologies, such as hospitals.

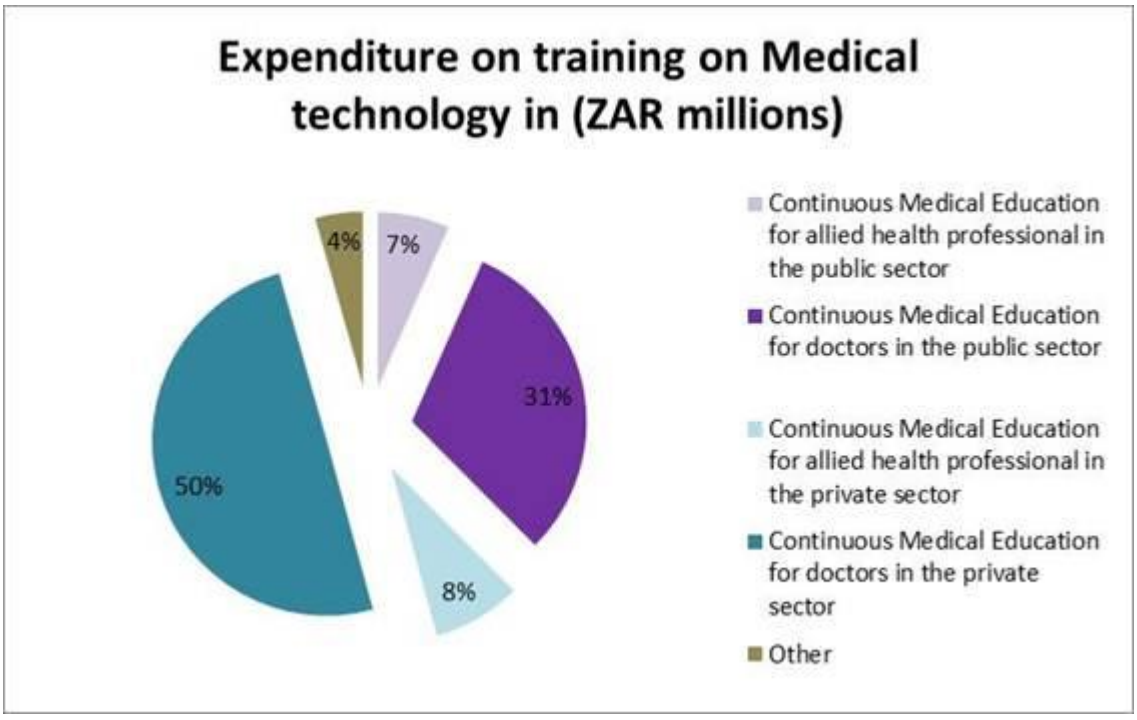

Figure 1.3: Expenditure on training on medical technology in (ZAR millions)

Source: KPMG, 2014: 27.

In the same period, the general contribution to the national economy by the medical technology industry was about R3.88 billion per year. The authors of the KPMG report suggest that when the associated economic multiplier is calculated at 1.25, it means that for every additional R1 spent in the national economy by the medical technology industry, an additional 25 cents is generated in economic activity.

The report further states that the capital and operational expenditure by the medical technology industry has allowed a total of 20 901 jobs to be supported, while the tax generated by the medical technology industry during the same period under review was estimated at R1.86 billion.

It is important to note that there are other positive spin-offs besides the obvious economic impact, but also that medical technology adds value to patients, healthcare professionals and, more generally, the health system.

It may be argued that incentives could be put in place by the South African government to create an environment in which it is more attractive for all medical technology companies, both multinationals and local manufacturers. These incentives could be put forward by the Department of Trade and Industry (DTI) who could potentially play a role in prioritising the medical technology sector as was done previously by this Department for the pharmaceuticals market. As such, the DTI could also create awareness of what the industry means for the country's economy.

There are at least three groups of people for whom this research may be important. The first comprises the medical aid societies in South Africa, who are required to make decisions about what new procedures they will fund. This group understands the concepts of health economics as well as the complexities of healthcare in South Africa. However, they are unlikely to be fully conversant in the topic of atrial fibrillation and all the treatment options that are available to the patients. With this in mind, Chapters 4-8 would be of value to the medical aid societies.

The second group for whom this study will have value are the physicians. The physicians and, in particular, cardiologists and electrophysiologists have a very good understanding of atrial fibrillation, the diagnosis thereof and most of the treatment options that are available. They would all be conversant with the major drug trials relating to the treatment of atrial fibrillation. Some may not, however, have been exposed to the literature on the use of implantable intra-atrial cardioverters. While this group will have an understanding of the healthcare sector, they may not have an in-depth understanding of the financing of healthcare. Many would also have limited knowledge of healthcare economics and the criteria needed for a cost effectiveness or cost-benefit analysis. Therefore, Chapters 2, 3, 5, 6, 7 and 8 would be of value to this group.

The final group who would be interested in this study are the potential investors. These are often large multinational companies who look for opportunities for their products and services in developing markets. Based on the type of products these companies have, it can be assumed that they would have good knowledge of health economics and atrial fibrillation. However, these investors often do not understand the complexities of the South African healthcare system. For this group, Chapters 2, 6, 7 and 8 would be of value.

1.4 THE RESEARCH QUESTION

As pointed out above, billions of US dollars are spent on research into and the development of new drugs and technologies. At some point, therefore, it becomes necessary to evaluate whether any of these new drugs and technologies improve the outcome for patients, what the degree of improvement is and finally, at what cost. The research question will focus on the domain in which the author is working at present, namely cardiovascular diseases. The research domain is narrowed down to the analysis of the question:

> *Is it more cost-effective to treat South African patients suffering from paroxysmal atrial fibrillation with radiofrequency catheter ablation rather than the current standard of care which is anti-arrhythmic drugs?*

Historical records from many ancient civilizations contain accounts of various ways of treating patients with diseases. These have varied from bleeding patients in the Middle Ages to modern day surgery or pharmaceutical treatment. The latter two have proven to be the mainstay of healthcare for most of the last century. While drug therapy and surgery have well-defined and specific roles in treating patients, these two interventions are at times unable to compensate for the mechanical failure of the body or its organs.

Pharmaceutical substances have been available in various forms for thousands of years and often evolved from herbal remedies, traditions and even folklore. Health technology and medical devices, on the other hand, are still relatively new and poorly defined. The terms ‘health technology’ and, more specifically, ‘medical devices’, refer to almost all forms of apparatus and appliances that are not pharmaceutical in nature, although they may include some chemical element (Medical Device Directive, 2007).

1.5 HYPOTHESIS

Treating patients in South Africa who are diagnosed with paroxysmal atrial fibrillation with radio-frequency ablation by means of pulmonary vein isolation is more cost-effective than treating them with the anti-arrhythmic drugs as recommended in the current guidelines.

1.6 RESEARCH PHILOSOPHY

The research philosophy that underpins this study is centred in positivism, where positivism is believed to hold the notion that the goal of knowledge is simply to describe the phenomena and to evaluate what can be observed and measured (Crossan & Schindler, 2001: 48).

The approach of this study is deductive, as the process begins with theory about healthcare costs. It next states a hypothesis and this is followed by a process of observation and finally a conclusion or confirmation of the theories (Cooper & Schindler, 2001). This process is represented

schematically in Figure 1.4. The end point of this research is determined by an evaluation of cost-effectiveness between the traditional approach (ADT) and new treatment options (PVI) and is measured in South African Rand (ZAR).

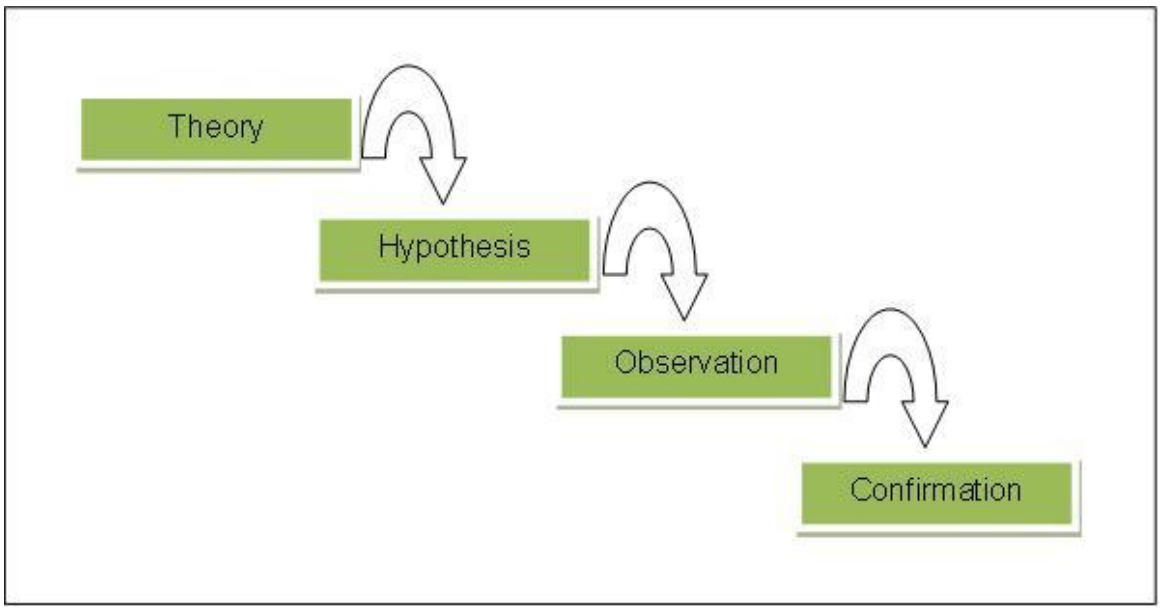

Figure 1.4: A schematic representation of deductive reasoning

Source: Trochim, 2006.

As clinical decisions are made based on the data available in clinical trials and may have an impact on millions of people's lives, it is of utmost importance that the paradigm of this type of research be objective and scientific. Therefore, the nature and philosophy of clinical trials employed by healthcare workers around the world reflect a formal structure. Axiological assumptions are free from value and are unbiased, while the epistemology is determined from peer-reviewed clinical data established as landmark clinical trials for treatment of patients with related diseases. The ontological characteristic of the study is determined by the current situation in the South African healthcare environment.

1.7 METHODOLOGY

The methodology is triangulated, which in this study refers to the use of more than one method for gathering data. In this case, both qualitative and quantitative data are used (Hussein, 2009).

Atrial fibrillation is investigated within a descriptive and interpretive philosophy, while the cost calculations are founded in a positivistic philosophy which takes the approach of deduction. This approach is followed to calculate the cost-effectiveness of treating paroxysmal atrial fibrillation with catheter ablation rather than anti-arrhythmic drugs. The study is structured into eight chapters with distinct topics that follow the research process and progress table, as shown on Figure 1.5.

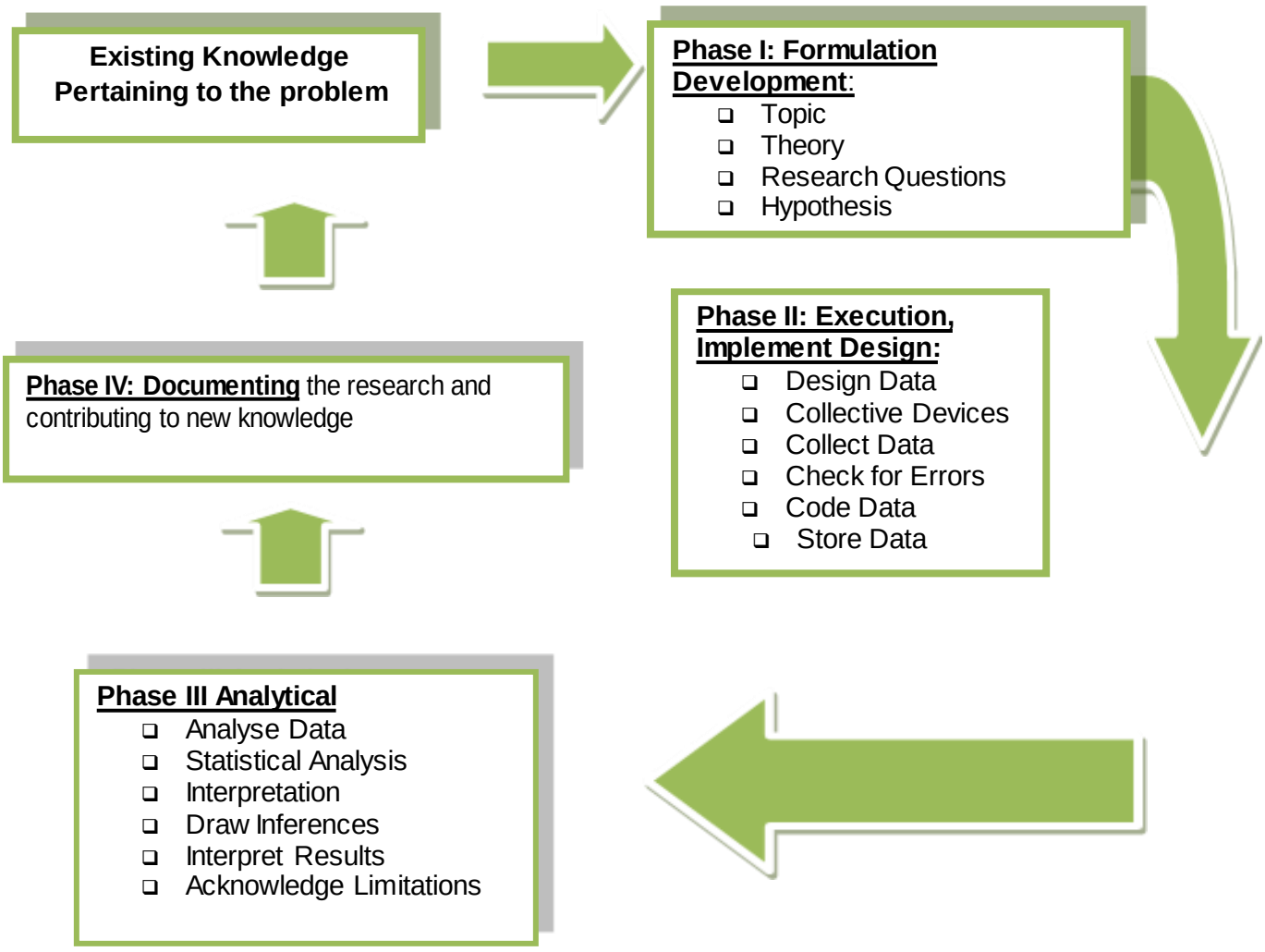

Figure 1.5: The research process and progress report

Source: Adapted from McCombes, 2019.

As seen in Phase I on Figure 1.5, the topic is introduced and defined. An evaluation is performed on the existing body of knowledge about the topic. The theory that underpins the topic is explored, a research question is formulated, and a hypothesis is stated. Finally, the study design is described.

Chapter 2 introduces concepts within health economics and attempts to summarise some of these while establishing the need for each of these evaluations. This chapter evaluates the positivistic nature of the study and will also defend the choice of cost-effectiveness as the method of evaluation.

Chapter 3 is a descriptive, interpretive exploration of South Africa and investigates the demographics of the country as compared to other countries in order to gain a better understanding of the healthcare needs of the South African population. The chapter gives an overview of the healthcare sector in South Africa and compares it to other developing and developed nations, with regard to size, healthcare expenditure as a percentage of GDP and the expenditure per capita. It also examines some of the trends in healthcare expenditure.

Chapter 4 is an introduction to the condition known as atrial fibrillation. This chapter is descriptive and defines the characteristics and nature of the disease and describes the disease in detail, from signs and symptoms to the diagnosis of the disease. This is of value to readers for whom the topic of atrial fibrillation is unfamiliar.

Chapter 5 investigates the types of treatment currently available and employed to treat or manage patients with atrial fibrillation.

Chapter 6 contains an extensive literature review of studies pertaining to the treatment of AF with either catheter ablation, referred to as pulmonary vein isolation (PVI) or anti-arrhythmic drugs therapy (ADT). It explores the concepts and data which underpin the model developed in Chapter 7 to measure cost-effectiveness of PVI versus ADT in South Africa. It also seeks to establish the rate of mortality and morbidity associated with both treatment modalities as well as studies that have been performed to assess the impact on the quality of life (QoL) for patients with AF.

Chapter 7 is founded in the positivistic philosophy and uses a decision tree analysis and a Markov model with Monte Carlo simulation as a quantitative approach to assess the relative value of different decision options. This conceptual model is used to perform a cost-effectiveness analysis. The decision analysis is an estimation of quality adjusted life years and involves a measurement in utilities, in this case “No AF” and “quality of life” at two years. Sensitivity analysis is used to examine the cost of the treatment with anti-arrhythmic drugs and compares it to the cost of treatment with catheter ablation therapy. This chapter includes processes from both phase II and III as illustrated in Figure 1.5, where devices for collection of data are designed, the data are collected and checked for errors (Phase II of Figure 1.5). As seen in phase III the data are then analysed statistically and interpreted. Inferences are drawn from the data and the results are interpreted.

Finally, in Chapter 8, a conclusion is reached with regard to the cost-effectiveness of radiofrequency catheter ablation for paroxysmal AF compared to anti-arrhythmic drugs within the South African context; the limitations of the study are explored and discussed; and recommendations are offered for further research (Phase III of Figure 1.5).

1.8 RESEARCH DESIGN

Table 1.2 describes the method of data collection through a process of literature review, questionnaires and interviews with local electrophysiologists, and finally the exploration of patient data. The dimension is longitudinal, and the final Markov model uses statistical data and simulation to establish cost-effectiveness of PVI versus ADT in paroxysmal AF.

Table 1.2: Research design

Type of Study	Formal
Method of data collection	Literature review/Interrogation
Researches control of variables	Ex Post Facto
Purpose of the study	Causal
Time dimension	Longitudinal
The topical scope	Statistical
The research environment	Simulation

Source: Own compilation.

1.9 PLAN OF THE STUDY

Chapter 2 introduces relevant concepts within health economics, discusses various methods of evaluating cost impact and attempts to summarise some of the important concepts in health economics while establishing the need for each of these evaluations. This chapter introduces rationing in healthcare, continues to discuss the quality adjusted life years (QALY) and disability adjusted life years (DALY). Both the QALY and the DALY are measures of the disease burden. In addition, the economic measure of willingness to pay is discussed and a comparison is made within healthcare as opposed to consumerism. Finally, the theory of 'cost-effectiveness analysis' is introduced. This forms the basis of the analysis in Chapter 7. This chapter is of particular interest to physicians who may be unfamiliar with the concepts of healthcare financing and health economic measurement tools.

Chapter 3 introduces South Africa from an historical, economics and demographic point of view. It then provides an overview of the healthcare sector in South Africa and compares it to that of other developing and developed nations with regard to size, healthcare expenditure as a percentage of GDP and expenditure per capita. It also explores trends in healthcare expenditure and examines the differences in the private and public healthcare sector, before discussing the proposed National Health Insurance model. This chapter is of particular interest to potential investors and multi-national companies who often have limited knowledge of the complexities of the healthcare system within South Africa. Often multi-national companies liken the size of the population with the opportunity within the country and for this reason it is important to highlight the issues such as the demographics, economics and healthcare structure of the country.

Chapter 4 examines atrial fibrillation (AF) as a medical disorder. The signs and symptoms are explored as well as how a definitive diagnosis is made. The next stage is to identify those patients who are at risk of developing AF. It then defines the various characteristics of the disease from paroxysmal episodes to a chronic condition. The risk of stroke and congestive heart failure associated with AF are also described. The focus of this chapter is of particular relevance to medical

aid societies and other funding decision makers like hospital administration, who would have knowledge of the healthcare structure and possibly health economics but would have a limited understanding of the particular disease entity.

Chapter 5 describes the many treatment modalities that are available to the patient suffering from AF and offers insight into the effectiveness and limitations of each. These treatment modalities include surgery, pacemakers, defibrillators, medical therapy and finally radiofrequency ablation. As with Chapter 4, this chapter is intended for medical aid societies and other policy makers.

Chapter 6 examines the literature which underpins the basis of the cost-effectiveness model with regard to the efficacy of treating patients with paroxysmal AF (PAF) with anti-arrhythmic drugs and catheter ablation. It also reviews the literature on mortality and morbidity data associated with both treatment modalities as well as studies that have been performed to assess the impact on the quality of life (QoL) for patients with AF. Data from interviews performed with practicing South African electrophysiologists are reviewed to establish commonality between the studies, which have been completed internationally, and current clinical practice in South Africa. Chapter 6 would be of interest to all the stakeholders although most physicians would be familiar with this information.

In Chapter 7 using a decision tree analysis, a Markov model and simulations is developed to establish the cost-effectiveness of radiofrequency catheter ablation for PAF compared with commonly prescribed anti-arrhythmic drugs. This chapter would be of interest to all the stakeholders as it presents the model and all the data collected. It also includes the results.

Finally, in Chapter 8 a conclusion is reached with regard to the cost-effectiveness within the South African context. The limitations of the study are discussed, and recommendations are offered for further research. This chapter would be of interest to all the stakeholders.

CHAPTER 2: ECONOMIC EVALUATION OF HEALTHCARE COSTS

2.1 INTRODUCTION

Globally, an ever-increasing volume of resources is being allocated to healthcare. Moreover, in many developed nations where the healthcare sector is well established, a significant percentage of the population may live to be in their eighties. This begs the question as to whether people are living healthier lives. The evidence suggests not; a large proportion of the world's population is affected by lifestyle diseases such as diabetes and hypertension (WHO, 2011). Health economics or medical economics refers to that branch of economic theory that is applied to the healthcare sector. The aim of this discipline is to allocate scarce medical resources to those who need them. In extended terms, health economics is a study of the healthcare system, its functioning and efficiency, as well as the private and social impact of individuals' behaviour. This study utilises information from biostatistics and epidemiology and, by means of mathematical models, supports or rejects policies that may affect both the individual and a wider health policy (Culyer, 1989: 216).

Sawert and the WHO Task Force on Health Economics (1996) defined the study of healthcare economics as follows:

> *The study of how the scarce resources are allocated among alternative uses for the care of sickness and the promotion, maintenance and improvement of health, including the study of how healthcare and health related services, their costs and benefits, and health itself are distributed among individuals and groups in society.*

This chapter explores the nature of healthcare financing, delves into the terminology that is particular to healthcare expenditure and compares South Africa with both emerging and developed economies with regard to healthcare expenditure.

This chapter also introduces various principles of economics that relate not only to the study of macro- and microeconomics but also directly to the principles related to the attainment of health. The emotive and financial issues related to rationing in healthcare are investigated as well as the various methods employed to ration healthcare.

Finally, the various methodologies used in health economics are scrutinised in order to evaluate the most appropriate method of analysis for this study. These include concepts such as the QALY, DALY, cost-utility analysis, cost-benefit analysis and cost-effectiveness analysis.

2.2 FINANCING IN HEALTHCARE

In many societies the effective use of scarce resources, particularly healthcare resources, is considered a priority (Jordan *et al*., 1998: 83). This section introduces important concepts related to financing for healthcare. It may be argued that the most critical part of any healthcare system relates to the structure of the financing for that system. Large databases like those of the World Health Organisation (WHO), the World Health Report, national health accounts (NHA) and domestic country specific data are examined in the hope of providing indicators based on the expenditure information within an internationally recognised framework. NHAs are a combination of recorded budgets and costs for the operation of any healthcare system and include information across geographical, demographic, socio-economic and epidemiological dimensions. Some important concepts in healthcare financing are discussed below.

Gross domestic product (GDP) refers to the value of all goods and services produced in a country by both its residents and non-residents. GDP relates to the total sum of expenditure, consumption and investment by government and the private sector in the economy in a given year.

A hypothetical unit of currency with the same purchasing power as the US dollar has in the United States at a given point in time is known as the international dollar. The international dollar utilises the concepts of both purchasing power parities (PPP) and international average prices of commodities. The PPP calculates the rate between two countries at which the currency of Country A is converted into that of Country B in order to guarantee that the same amount of goods and services can be purchased in both Country A and B (World Bank, 2010c; IMF, 2010).

Total expenditure on health (THE) refers to the total expenditure in a given year on healthcare by both the government and the private sector and is computed in the national currency units in current prices. THE includes all costs used for the maintenance, restoration or enhancement of the health status of the population. As seen in Table 2.1, THE is often stated in international dollars as a percentage of GDP, or per capita expenditure. THE includes all social and private health insurance as well as the burden placed on households as result of out-of-pocket spending (OOPS) and the reliance on external resources in financing health.

The sum of all the expenditure by government entities in purchasing healthcare services and goods is known as general government expenditure on health (GGHE). Included in this are all expenses on health made by all levels of government, including social security agencies, and the direct expenditure by parastatals and public firms.

Social security expenditure on health (SSHE) represents expenditure for purchases of health goods and services by schemes that are mandatory and controlled by government.

External resources (ExtHE) incorporate all grants and loans for healthcare goods or services in cash or kind, regardless of whether they originate from governments or private entities.

Private health expenditure (PvtHE) is characterised by the sum of all expenditures on health by the bodies listed below.

- Prepaid plans and risk-pooling arrangements (PrepaidHE): the outlays of private insurance schemes and private social insurance schemes. This is typical of the medical aid schemes in South Africa where there is no government control over payment rates or participating providers. There may, however, be broad guidelines from government as seen in the case of the Council for Medical Schemes in South Africa.
- The financial outlays by private enterprises for medical care or services or benefits other than payments to social security or other pre-paid schemes is known as firms' expenditure on health. These would include clinics at the workplace.
- Non-profit institutions or non-government organisations (NGOs) are entities whose status does not permit them to be a source of financial gain for the units that establish, control or finance them. These NGOs may be either internally or externally funded.
- Household out-of-pocket spending (OOPS) refers to all direct expenditure incurred by households, including, but not limited to, gratuities and in-kind payments made to health practitioners, suppliers of pharmaceuticals, therapeutic appliances and other goods and services, direct payments to public and private providers of healthcare services, non-profit institutions, and non-reimbursable cost sharing, such as deductibles, co-payments and fees for services.

Table 2.1 illustrates the total health expenditure in a selection of countries as a percentage of the GDP in 2000 and in 2005, as well as the change in total healthcare expenditure over this period. This offers insight into the expenditure of South Africa, its neighbours, and various developing countries and developed countries such as the UK, USA and Canada, which have well developed medical systems. With an expenditure of GDP on health of more than 8%, South Africa's expenditure is the highest of all cited African countries, except Malawi, which experienced a growth in healthcare expenditure of 100% between 2000 and 2005. The expenditure of 8.8% is also in line with that of many developed countries like Australia (8.8%), Italy (8.9%) Netherlands (9.2%) but is lower than Germany (10.7%), Switzerland (11.4%) and the USA at 15.2% (WHO, 2005).

Table 2.1: Total healthcare expenditure (THE) as a percentage of GDP

Year	2000	2005	Percentage change 2000–2005
Angola	2.4	1.8	(25)
Australia	8.3	8.8	6.0
Botswana	4.8	8.3	72.9
Canada	8.8	9.7	10.2
Egypt	5.6	6.1	8.9
France	9.6	11.2	16.6
Germany	10.3	10.7	3.8
Ireland	6.3	8.2	30.1
Israel	8.0	7.8	(2.5)
Italy	8.1	8.9	9.8
Lesotho	6.2	5.5	(11.2)
Malawi	6.1	12.2	100
Namibia	7.0	5.3	(24.2)
Netherlands	8.0	9.2	15
Portugal	8.8	10.2	15.9
South Africa	8.1	8.8	8.6
Switzerland	10.3	11.4	10.6
United Kingdom	7.2	8.2	13.8
United States of America	13.2	15.2	15.1

Note: Figures in parenthesis () indicate reduction in expenditure.

Source: WHO, 2005.

Table 2.2 highlights the fact that the South African healthcare system is mainly funded privately, with 58.3% of expenditure coming from fully private investment. This is second only to Egypt with 62% of their expenditure coming from private healthcare, and more than the USA, which also has a highly developed private healthcare market accounting for close to 55% of all healthcare expenditure.

Table 2.2: General government expenditure and private expenditure on health as a percentage of THE

	GGE		PvtHE	
Year	**2000**	**2005**	**2000**	**2005**
Angola	79.9	81.5	20.1	18.5
Australia	67.0	67.0	33	33
Botswana	63.7	78.4	36.3	21.6
Canada	70.4	70.3	29.6	29.7
Egypt	40.1	38	59.9	62
France	78.3	79.9	21.7	20.1
Germany	79.7	76.9	20.3	23.1
Ireland	73.5	79.5	26.5	20.5
Israel	69.5	66.5	30.6	33.5
Italy	72.5	76.6	27.5	23.4
Lesotho	51.0	56.1	49	43.9
Malawi	43.8	71.3	47.6	28.7
Namibia	68.9	65.2	31.1	34.8
Netherlands	63.1	64.9	36.9	35.1
Portugal	72.5	72.3	27.5	27.7
South Africa	42.4	41.7	57.6	58.3
Switzerland	55.6	59.7	44.4	40.3
United Kingdom	80.9	87.1	19.1	12.9
United States of America	43.7	45.1	56.3	54.9

Source: WHO, 2005.

2.3 HEALTH ECONOMICS

The discipline of health economics has grown significantly over the past 30 to 40 years, mainly as a result of the explosive growth in available medical treatment options. The field of health economics was born out of two main foundations or theories which date back to the 1960s / early-1970s and include applied economics. On the one hand, there are theories of human capital where the investment in health is one of the forms of human capital. The second foundation acknowledges the unique nature of the health care market. Grossman, in his pivotal work, *On the Concept of Health Capital and the Demand for Health*, published in 1972, developed the concept of health as an important element of human capital. Grossman (1972) suggested that the demand for healthcare is unlike most other markets or goods as each individual is simultaneously a producer and consumer of health. In this 1972 model, Grossman viewed health as a stock. Thus, if there is insufficient investment to replenish the stock, it would degrade over time. The model compared health at a basic level to a capital item (Grossman, 1972: 1).

The Grossman model remains one of the most original and fruitful contributions to health economics, particularly because it has proved to be a highly useful tool for analysis and explanation of differences in levels of health and the demand for health services by individuals.

However, the birth of health economics is often associated with the seminal paper by K.J. Arrow (1963), *Uncertainty and the Welfare Economics of Medical Care*. This is due in part to the fact that it deals with a more profound set of problems more directly rooted in neo-classical economic theory, and in part to the fact that there are a greater number of subsequent applications and ramifications. Arrow examined the differences between health and mainstream economic goals and found that, in principle, the dilemma in healthcare was subject to the fact of relative scarcity of resources and his work defends the thesis that the functioning of the medical services market is affected by special economic problems that can keep that market from attaining efficiency. These problems are caused basically by the existence of uncertainty, which concerns both the incidence of illnesses, giving rise to, among other factors, worries about financial risk and the efficacy of the treatment option. There is also the non-commercial nature of many of the risks arising from that uncertainty, for which there is no insurance. The lack of markets for those risks implies loss of well-being, since there are individuals who would be willing to transfer their risk (at a cost) and individuals for whom it would be profitable to acquire those risks at that cost. It is forbidden, or at least frowned upon, for a person who requires a kidney transplant to trade a kidney and agree to a price with a donor. On the other hand, one cannot insure oneself against the risk of falling ill as, even where insurance is available, it is, as a rule, incomplete and does not operate under the ideal conditions for competitive markets. No one can insure oneself against the risk of an incomplete cure. It is in the presence of uncertainty that information and knowledge become goods, which are not distributed symmetrically among doctors and patients. Since an individual cannot try out the product before consuming it, the exchange of health services is based mainly on trust. Given these circumstances, it is difficult to conceptualise the demand for health services as one might under the conditions of perfect information in a competitive market. On the supply side, Arrow points out other specificities, such as restrictions on entry into the medical profession and the lack of diversity in the quality and prices of medical services.

In the 40 years that have passed since then, the study of health economics has undergone extensive development. According to two highly respected authors, T. Culyer and J. Newhouse, editors of *The Journal of Health Economics* and *The Handbook of Health Economics*, the study of health economics has flourished because it has shown that it can provide practical answers to practical problems and has been able to develop its own theoretical models which contribute to the main current of economics. The fields where those contributions (or “mutual inspirations”) have been made include, as mentioned above, human capital theory, but also product measurement and assessment in the case of services such as health service, which are traditionally difficult to quantify and measure. Further to this, areas of contribution include, but are not limited to, cost-effectiveness analysis

methodology, the fundamentals of the economics of well-being, the economics of insurance, principal-agent models, economics of information, the theory of incomplete markets, and the theory of regulation.

Health economists may argue that healthcare financing is different as a result of the intrinsic uncertainties in health, but this argument is often refuted by mainstream economists who point out that life is full of uncertainties and countries may be affected by natural disasters that can also have an impact on budgeting for government (Suvanto & Vartianen, 2007: 112).

The importance of this discipline lies in the fact that the growth in healthcare development is almost unprecedented. The continued innovation in healthcare can be seen by the fact that that it was only around the turn of the 20th century that the impact of hygiene and clean running water was realised, and the importance of sterilisation or at least surgically clean instruments was accepted. By 1930, further improvements in sanitation and hygiene in the West saw the life expectancy at birth reach 59.7. As recently as during World War II, the use of penicillin on a wide scale significantly reduced the number of lives lost due to infection (Faria, 2002: 122).

Treatment options for diseases such tuberculosis, pneumonia, syphilis, typhoid fever, and diphtheria were hailed as major breakthroughs and spurred the pharmaceutical industry to invest large amounts of money into research and development. Today, an internet search on any medical topic reveals a myriad of treatment options. The availability of information in the public domain has stimulated a demand for healthcare options from patients driving the healthcare industry towards what may now be regarded as consumerism.

Burden of disease studies highlight the rapid increase in lifestyle-related diseases such as obesity, diabetes mellitus, and cardiac diseases, while at the same time there is a drive to increase longevity and decrease morbidity. This all comes at a cost and as healthcare in many countries is the responsibility of governments, the control of this cost is also the responsibility of the government. It may be stated that the responsibility to provide healthcare services, stimulate health and support and promote improved productivity of its members, lies with government. As with all other government departments the annual healthcare budget is set and is measured as a percentage of GDP. To set these budgets, a good understanding of the demand for healthcare is required and this must be matched by the ability to supply these services.

It is important to acknowledge that, with the ever-increasing costs of healthcare interventions, it is the responsibility of the payer to ensure that the limited resources available are utilised in an appropriate manner. To ensure that there are sufficient resources available to cover medical costs, many insurers create what are known as risk pools. The concept of risk pooling is that young, healthy members subsidise the health of the aged and infirm. It is impossible to predict fully the potential medical expenses of members and adverse selection can have a very negative impact on the risk pool. In South Africa, the risk equalisation fund established by the Council for Medical Schemes, but

not yet implemented (at the time of writing), is one method which is employed to ensure that such adverse selection does not destroy any particular fund. Another method employed in South Africa is to ensure that insurers do not only accept young, healthy members. This is referred to by medical insurers in South African as “cherry picking”. One way to protect insurers from the effects of adverse selection is to make use of exclusions for pre-existing conditions.

While healthcare funding entails a component of consumerism, the reality is that the competition which defines a free market system is not available in most healthcare systems. This is because healthcare in most countries is often heavily regulated by the government, which is often the largest purchaser of healthcare services. In addition, other factors that distinguish healthcare economics from mainstream areas of economic interest include the asymmetry of information, and intractable uncertainties. The consumer or patient in this context experiences an unbalanced relationship with the real demand for medical care and the real cost. This is typically the case because most medical services are not purchased directly by the consumer, but are acquired through insurance, either social or private, and therefore any out-of-pocket expense is typically at a value much lower than the real market value. As a result, the effective demand differs in price and quantity from the real demand or marginal benefit curve (Grossman, 1972: 240).

Uncertainty in terms of patient outcomes and financial obligation is intrinsic to healthcare. The principle of asymmetrical information refers to the knowledge gap created between the treating physician and the patient, who may be at a distinct disadvantage.

These concepts are important within the South African context to expose the reader to concepts such as scarcity of resources, financing of healthcare, considering the patient as a consumer and, finally, to expose the reader to concepts such as cost-effectiveness analysis.

However, in spite of these arguments many people have difficulty in making the connection between health and economics, as most would argue that health is a “priceless” commodity. But does “priceless” refer to something that is invaluable in an ethical sense or does it refer to something that is very costly in an economic sense? Either way, expenditure on healthcare since the 1960s and 1970s in many Western countries, measured as a percentage of GDP, has more than doubled, as seen in Table 2.3. This has resulted in many countries implementing legislative measures to curb the rate of increase in public healthcare expenditure.

Table 2.3: Healthcare expenditure as a percentage of the GDP from 1960 to 2008 in selected countries

Year	1960	1970	1980	1990	2000	2008
Canada	5.5	7.1	7.4	9.0	8.8	10.1
Germany	4.7	5.9	8.4	8.1	10.3	10.5
France	4.2	5.8	7.6	8.9	10.1	11.2
Italy	3.3	5.2	6.8	7.6	8.1	9.1
Japan	2.9	4.4	6.4	6.5	7.7	8.1
Netherlands	3.9	6.0	8.0	8.1	8.0	9.0
Sweden	4.7	7.2	9.4	8.7	8.2	9.4
Switzerland	3.3	5.2	7.3	7.4	10.2	10.7
United Kingdom	3.9	4.5	5.6	6.1	7.0	8.7
USA	5.3	7.4	9.3	12.4	13.4	16.0

Sources: Adapted from Zweifel & Breyer, 1997; OECD, 2010.

Figure 2.1, which illustrates the growth in expenditure in healthcare as a percentage of GDP between 1960 and 2008, shows the share in the USA trebling between 1960 and 2010 (Zweifel & Breyer, 1997; OECD, 2010).

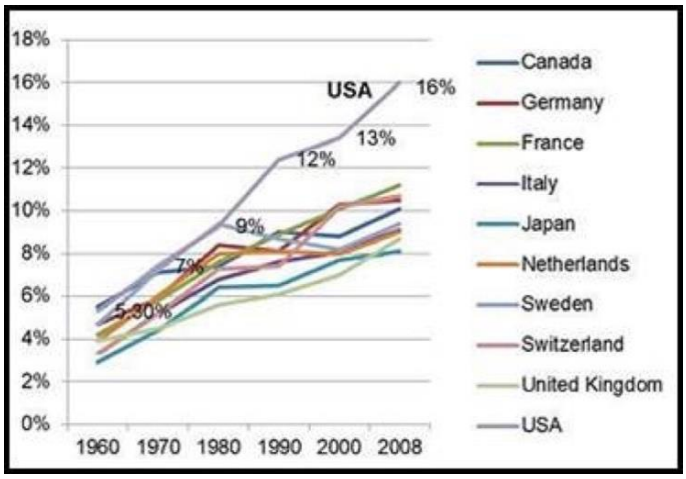

Figure 2.1: Growth in healthcare expenditure as a percentage of GDP 1960-2008

Sources: Adapted from Zweifel & Breyer, 1997; OECD, 2010.

While it is accepted that healthcare costs are not the only costs that have experienced this "explosion", healthcare has perhaps eluded stringent evaluation for much longer, as certain idiosyncrasies exist in healthcare that may have prevented such comparisons being made. What remains important is that there is a high degree of similarity between the principles of economics and health economics. In health economics, as in mainstream economics, the same features exist, that is, wants, needs and demands (Zweifel & Breyer, 1997: 382).

It is not unusual for societies to experience unlimited wants and desire for goods and services where each individual is prone to want better goods or improved services. The concept of “wants” differs vastly from “needs,” where needs may be thought of as necessities, or things that are essential for survival. Wants or desires on the other hand may be limitless and, as such, difficult to measure. The concept of demand differs from both needs and wants by virtue of the fact that demands for goods or services are usually made by those who are able to pay for them (Mohr & Fourie, 2000).

The same situation arises in healthcare. Health may be considered a want for certain individuals who, for example, “want” cosmetic surgery. But health can also be defined as a need where certain aspects are considered necessities, for example fresh air, sanitation and clean drinking water. Finally, as healthcare is funded globally by contributions of individuals either through a system of taxation or through health insurance, these same individuals may demand both goods and services.

Thus, it is of great importance that the question is again posed: “Is health a priceless commodity?” As previously stated, there are two possible interpretations of this. One, the ethical stance, is that health is priceless as it is invaluable; no price can be placed on health or life. The second, a pure economics interpretation, is that health may be expensive.

Society can determine the basic needs for survival. An example of this is represented by research conducted by the Bureau for Market Research (UNISA, 2007) of the University of South Africa, which evaluated the basic goods and services required by a household to sustain a minimum standard of living. What are the minimum requirements to sustain health? Should this measure be on pure economic levels or based on ethical values, or perhaps both? A second and perhaps more pertinent question is who makes the decision?

A well-known way of calculating poverty lines as a statistical measure is to estimate the cost of a minimum basket of goods that would offer the daily energy requirement per person needed over a period of one month. This was defined by the South African Medical Research Council (MRC), as 2 261 kilocalories per person. Based on data from the 2000 Income and Expenditure Survey from Statistics South Africa and evaluating the type of food sources generally available to low-income South Africans, the cost was determined at R211 per person every month at 2000 prices. However, it needs to be considered that households require other goods and services, beyond food, to meet basic needs. These include housing, electricity, clothing, schooling, transport and medical services. The cost of these essential non-food items was calculated at R111 per person each month. This means that, in 2000 prices, the minimum cost of essential food and non-food consumption per person per month is R322. Based on 2006 prices, the per capita poverty line was R431 (Woolard & Leibbrand, 2006: 8).

Economic principles generally require that a level of satisfaction is achieved while consuming the minimum amount of a scarce resource. Each country, province, hospital, family and individual will, at some stage, be faced with the reality of the cost of healthcare, and each of these entities will be

required in some way to evaluate a budget available for these needs. This means that each such entity, at some stage, will be required to make certain choices with regard to allocating resources to health.

Other factors of importance when discussing healthcare delivery and health economics include, but are not limited to, the following:

- Public regulation of the health services

  Government involvement in healthcare costs is found in all nations, with the result that, in many instances, the more involved the government is in healthcare, the more regulated the healthcare system is. Examples of these healthcare systems are the National Health System in the UK and Italy, where, as noted in Table 2.2, in 2005 the government contribution to healthcare was 87% and 77% respectively. In these systems, most of the services are carried out by civil servants. South Africa and the USA, on the other hand, have most healthcare dependent on health insurance policies, with 58% and 54% respectively of total health expenditure being private. These insurance policies or medical aids typically result in a fixing of fee schedules for medical services rendered. What is important to note is that both of these models deviate from true market forces and elicit the question as to whether it is possible to achieve an optimal allocation of scarce resources in such circumstances.

- Emotional significance

  The subject of health, or lack thereof, is an emotional one. It is not unusual for politicians campaigning for leadership to use promises of healthcare policies to attract votes. Often these promises cannot be fulfilled as governments and insurance agencies are forced to evaluate the resource available and develop policies to ensure the best use of these scarce resources. All too often conflict surfaces between the economic allocation of these resources on the one hand and the ethical allocation on the other, and, if left unchecked, emotive choices are made as life is deemed to be invaluable. The study of health economics is aimed at developing methods to structure the expenditure on a group of goods that change over time, in an appropriate way, avoiding many of the emotive issues through the analysis of statistical lives as opposed to real ones (Zweifel & Breyer, 1997: 2).

- The size of the healthcare sector

  As illustrated in Table 2.3, most western, industrialised countries spend close to 10% of their GDP on health. This ratio has grown significantly over the past three decades and has also had an impact on the number of people who are employed in the healthcare sector.

  Table 2.4 illustrates the percentage of the population who were employed in the healthcare sector in 1970 and 1989 as a percentage of total employment. This shows a significant increase in the

number of healthcare workers of up to 168% with an average change in healthcare employment of 92% or 3.1% per annum.

Table 2.4: Employment in healthcare as a share of total employment (in percentages)

Year	1970	1980	1989	Change 1970-1989
Germany	2.9	4.5	5.5	90
United Kingdom	3.1	4.6	4.7	52
Italy	1.6	3.9	4.3	168
Netherlands	4.0	6.4	7.1	78
Switzerland	2.8	4.6	n.a	64**
United States of America	3.7	5.3	6.3	70

*Note: ** Percentage change from 1970 to 1980.*

Source: Huber and Orosz, 2003.

In 2011 Miliard stated that, in the USA, the proportion of those employed only in the private sector of healthcare had grown to 10.7%. Considering that only 60% of healthcare expenditure in the USA is in the private sector, it infers that considerably more than 10.7% of people in the USA are employed in the healthcare sector (Miliard, 2011). This is an interesting phenomenon, as it appears that employment growth in healthcare is dissimilar to the economy at large. Miliard (2011) reports that between December 2007 and January 2011 employment in the healthcare sector grew by 6.3%, while non-healthcare employment fell by 6.8%.

As discussed above, there has also been a substantial increase across the globe in the total healthcare expenditure as a percentage of GDP. The average increase in total healthcare expenditure (THE) for the period 2000 to 2005 was roughly 2.1% per annum.

These measures may give some perspective to the allocation of total resources within a specific country. This may also help to evaluate the similarities or difference between various countries by measuring the percentage of GDP that is spent on total healthcare, but it does not offer sufficient information to form a true perspective of the impact of this percentage on the country. Other important factors to be considered include the size of the GDP, as a high percentage of a low GDP may look impressive but does not offer the individual much in the form of resources. It is also important to examine factors such as GDP per capita, how far the resource must stretch, and the healthy life expectancy of the country, as well as child mortality rates.

2.3.1 The macro- and micro-economic view of healthcare

All individuals seek to be healthy, in the sense that they do not desire the opposite, which is to be unhealthy or diseased. However, to be always totally free of disease is unlikely. Simple lifestyle choices like diet, exercise or stress introduce elements of life that are contradictory to health. Thus,

in real terms ‘health’ may be traded off against all other targets (Zweifel & Breyer, 1997). In economic terms, ‘health’ is traded off against any other aim.

Two important factors to consider with regard to health are that:

1. The consumptive benefit that a person can gain from his/her income is dependent on his/her state of health.
2. There is an assumption that only a person in good health can earn an income in the labour market. Thus Zweifel and Breyer (1997) state that disposable income is dependent on the state of health. They further argue that, if income were not dependent on health, then budget constraints would be linear.

Therefore, it may be hypothesised that, as health improves, one is able to consume more.

2.4 MEASURING UNCERTAINTY IN COST AND EFFECTIVENESS

2.4.1 Uncertainty in measuring costs

Where there is uncertainty in the estimations of cost-effectiveness, this could lead to a situation where an incorrect set of interventions is financed. It is therefore vital to understand that the manner in which the available evidence is interpreted and then applied when calculating the costs and outcomes are dependent on uncertainty. The impact of this could be that the target population’s healthcare is not maximised, resulting in an opportunity cost to uncertainty in terms of health.

Most economic evaluation studies tackle the issue of uncertainty surrounding the estimates associated with the measuring costs and effectiveness. Within economic evaluations, uncertainty is likely to occur in three situations, namely, uncertainty in measuring costs, uncertainty in measuring effectiveness, and uncertainty in the choice of the discount rate.

Uncertainty in measuring costs may occur in the following:

- The identification of the range and resources to be included.
- The valuation of the unit costs.
- The measurement of the volume of the resource used.

Uncertainty in measuring effectiveness is often associated with imprecision in the process used and may be associated with the following:

- The choice of the outcome being measured.
- Where and how the required effectiveness data was acquired.

Uncertainty could occur with the choice of the discount rate used:

- In general, a baseline discount rate should be used. In this study, a discount rate of 3.5% per annum was applied for both costs and outcome, which is consistent with the lower range of the inflation target set for South Africa. However, economic evaluation studies may use discount rates with a range which could, for example, be between 0% and 15%

It should also be noted that uncertainty regarding the true value of an estimate could occur for a number of reasons, which may include the following:

- Inadequate data sources.
- Situations where an investigator uses the results of a specific region and generalises them.
- Situations where the estimates are specific to a precise time.
- Analytical techniques used in the study that are open to debate.

Sensitivity analysis is the traditional method used in economic evaluation studies to test for uncertainty.

2.4.2 Sensitivity analysis

Sensitivity analysis is a useful method of exploring how sensitive the results of an economic evaluation are when the cost and effectiveness values are changed. To do so the investigator may vary these values of the cost parameter by halving, doubling or even trebling the values. This allows the investigator to assess the significance of this factor in reaching the final result. Sensitivity analysis can be useful for a range of reasons, which include, but are not limited to, the following:

- To test the robustness of the results in a model where uncertainty exists.
- To increase the understanding of the relationships between input variables and the output variables in a model.
- To recognise inputs in the model which may result in considerable uncertainty in the output of the model.
- To explore possible errors in the model.

2.5 RATIONING IN HEALTHCARE

The healthcare market does not behave the same way as traditional demand-supply markets. The demand is ever increasing, creating a disparity between the demand and the ability to supply. Unlike traditional markets where the consumers' understanding of their purchase precipitates the correct working of market forces, in healthcare there is an unbalanced understanding (Seifan & Shemer, 2005: 68).

It has been noted that the two most important factors to the individual are the state of health (H) and consumption (C). Attempts to direct healthcare start with these two concepts. The subject of healthcare provision remains an emotive one, and one that brings in votes for political figures, but the fact remains that each country has a limited amount of available resources for healthcare and there is a continual drive to stabilise the extent of healthcare expenditure as a percentage of GDP as well as limiting the increase of contribution to healthcare expenditure as a portion of wages. This has resulted in increased amounts of out-of-pocket expenditure in many societies (Zweifel & Breyer, 1997: 7, 8, 64, 151).

Rationing in healthcare is difficult as it may, in effect, divert resources from one area of healthcare expenditure to another and thereby possibly prevent some individuals from receiving therapies which may be deemed beneficial or necessary. In reality, the increased demand for healthcare services and the cost associated with providing them indicates that rationing manifests itself in all medical systems. Rationing has traditionally occurred through location, the availability of practitioners and services, as well as the ability of the population to pay (Mechanic, 1995: 1665).

Interest in the subject of healthcare rationing has intensified over the past few years. This has been a focus not only of governments but also of academia, industry, the media and, through them, the public at large. Globally, the life expectancy of the population is increasing and, as new technologies burgeon, the topic of healthcare rationing ascends on the political arena (Jagsi *et al.,* 2004: 2249).

Rationing occurs at many levels. The first level may be at the level of government, the local authorities, and insurance plans. Another level of rationing is seen at hospital level, where long waiting lists are a crude but real form of rationing. Rationing at a clinical level occurs when the clinician makes decisions about certain treatment schedules (Mechanic, 1997: 83). An unpopular form of rationing occurs when centres of excellence are set up for the performance of certain procedures. This principle tries to ensure that services will only be reimbursed if specific centres or physicians are used. While this opens itself up to political bargaining, there may be merit in it. Data from the 1999 Dartmouth Atlas showed that there was a relationship between the volume of procedures at centres and outcome for most surgical procedures.

Figures 2.2 and 2.3 indicate the 30-day mortality rate in low volume centres compared with high volume centres for four different procedures, namely coronary artery bypass grafting, mitral valve replacement, oesophagectomy and pancreatic resection, as documented in a study by Birkmeyer *et al.* (2002). The results from this study revealed significantly lower mortality rates in the high volume centres. This fact has been disputed in other studies, but it remains a consideration among payers who may elect to use this as a form of rationing.

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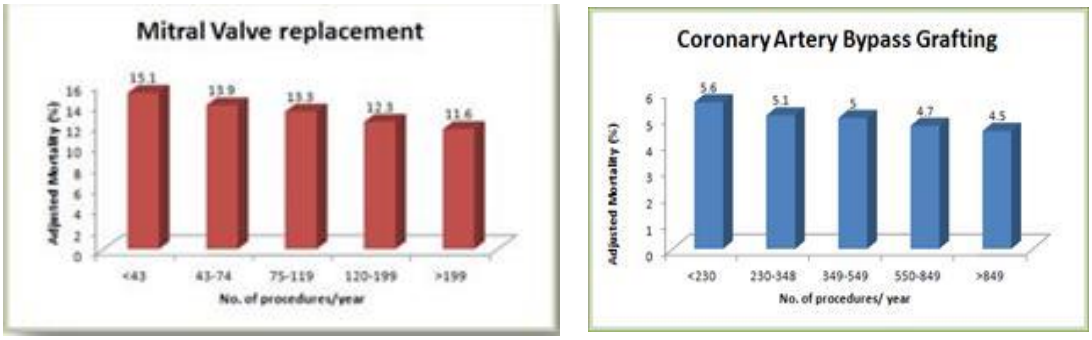
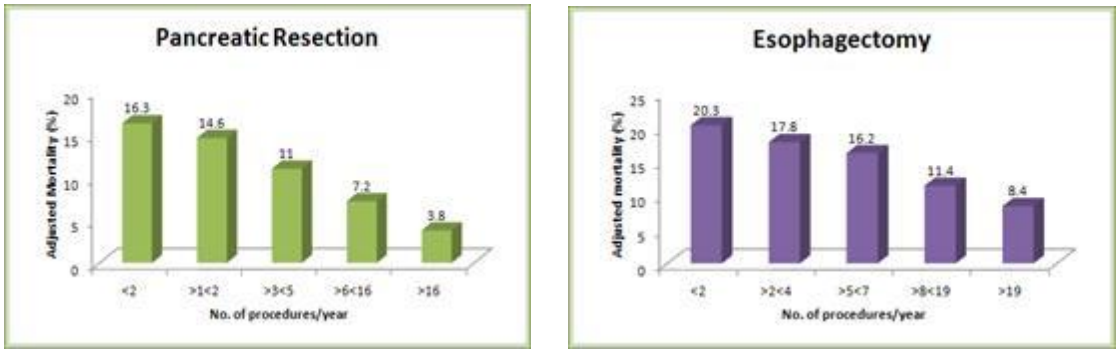


Note: Values above bars in each graph are the percentage of mortality (P<0.001 for all procedures).

Figure 2.2: Adjusted in-hospital or 30-day mortality among Medicare patients (1994-1999) according to quintile of total hospital for cardiac procedures

Source: Adapted from Birkmeyer et al., 2002: 1135.



Note: Values above bars are the percentage of mortality (P<0.001 for all procedures).

Figure 2.3: Adjusted in hospital or 30-day mortality among Medicare patients (1994-1999) according to quintile of total hospital for resections for gastrointestinal cancer

Source: Adapted from Birkmeyer et al., 2002: 1136.

Rationing may be classified as either explicit or implicit. Explicit rationing refers to an open process which is codified and written down or expressed. It is transparent, and the outcome is stated (Mechanic, 1997: 84). On the other hand, implicit rationing refers to the discretionary decisions made at a clinical level or by managers within a fixed budgetary allowance. Examples of these different approaches may be seen in the public sector in South Africa where a combination of both implicit and explicit rationing occurs. Services might be said to be implicitly rationed if a patient with HIV/AIDS is not admitted to an ICU, or where a 93-year old patient may not get an aortic valve replacement.

An example of explicit rationing in the public sector is the medicine formularies that are available. The private healthcare sector in South Africa typically exercises explicit rationing where defined benefits are given to the members at the start of each year.

2.5.1 Explicit rationing

The benefits of explicit decisions in healthcare are that they establish the framework for medical practice. Governments can ascertain the level of expenditure and the type of resources that are available to the population. Explicit rationing occurs in both public and private healthcare and is impacted on by the facilities and types of technologies that are available. Explicit rationing is under question in the UK. Brown and Calnan (2010) describe the rationing of healthcare in the UK as having transformed from a system where healthcare budgets were rationed through the discretionary decisions and where general practitioners and specialists effectively were the gatekeepers, to a modern, world-renowned body using evidence-based medicine. This new body, the National Institute for Clinical Excellence (NICE), espoused a framework of systematic decisions which were made in a transparent way, offering polices based on meticulous reviews of scientific evidence for treatments that are both cost-effective and affordable (Brown & Calnan, 2010: 65).

Some of the problems inherent in explicit rationing include the fact that these types of policies are laborious to develop, which means there may be a degree of resistance to change once established. It takes NICE, on average, fourteen months to perform a full appraisal of a new therapy (although there are some therapies which may be fast-tracked over a six-month period). This results in lags between policy approval and changing realities and NICE, in particular, is trying to compensate for this by scanning the horizon of new technologies and therapies. These long processes can be problematic, particularly in the case of medical devices where technology evolves at a fast rate and the product life cycle is very short and product changes are made continuously to improve efficiencies of the procedure.

Mechanic (1997) describes medical care as a process of discovery and negotiation between physician and patient, where the relationship between patient and physician is iterative and the course of action for each patient is not commonly known beforehand.

A third important factor is the difference between patients' needs and values. Patients, given a choice, may have varying views about treatment options as well as the trade-off between longevity and quality of life.

A further consideration for explicit rationing is the potential for political or emotional manipulation. An example of this is cited by Brown and Calnan (2010: 66), who question the public legitimacy of NICE in the UK. Brown and Calnan (2010) describe NICE as "engaged in ongoing, complex and interdependent relationships with interested parties". Mechanic (1997: 86), in his debate about the balance between explicit and implicit rationing, states that explicit rationing may result in medical decisions being debated in public forums with conflicting needs, preferences and political mobilisation and even political manipulation. He asserts that once the decision is taken out of the arena of patient and physician and into the public, key decisions become a battle ground where

social, moral and political battles are waged. Brown and Calnan (2010) define how these battles may be waged and use six examples of how the pharmaceutical industry is potentially able to influence NICE in its policy making process, namely:

- the development and presentation of its own evidence;
- lobbying NICE and the media;
- through funding of patient advocacy groups to lobby NICE;
- through government and the media;
- by liaising with government directly through cost sharing schemes; and
- by legally contesting decisions made by NICE.

2.5.2 Implicit rationing

Lauridsen *et al.* (2007) describe implicit rationing as a system where the range of choices available to the patients of potentially beneficial treatment options is limited. The only aim of setting these limits is to reduce costs and contain expenses. The limits which have been set are hidden from the patient, as is the rationale for setting the limits.

Mechanic (1997) argues that the strengths of implicit rationing include its discretion, flexibility and ability to take account of emotions, aspirations and preferences. Implicit rationing relies on the discretionary judgment of healthcare professionals and managers. A variety of strategies can be used. These include queuing, reducing the intensity of services, and substituting expensive services for less expensive ones. One of the values of implicit rationing is the fact that it can respond to complexities, diversity and any changes in information. This response is likely to be sensitive and timely. Implicit rationing should be underpinned by the understanding that there is a place for open public discussion and fair allocation of resources, and that rationing should never be done in secrecy. While implicit rationing builds on the strength of the doctor-patient relationship and addresses the needs and preferences of the patient, the characteristics of implicit rationing may have a contradictory role for potential violation of trust and abuse of discretion (Mechanic, 1997: 84).

Rationing in healthcare is inevitable and the literature supports arguments for both implicit and explicit rationing. Both these systems have positive and negative arguments. It is perhaps a combination of these two policies that best serves the needs of all the stakeholders, where guidelines are set through the interaction of professional bodies and the payers. The use of evidence-based medicine should not be overlooked, nor should the discretionary judgment of the clinician on a case-by-case level be ignored. All stakeholders need to understand that they share the same goal, which is to provide the patient with the best possible care with the available resources.

2.6 HEALTH ASSESSMENT

Some questions that remain unanswered in most countries are “How much healthcare do we need?” and “How many doctors should we train?” and “Is there a relationship between volume and outcome of procedures?” In the past two decades the number of cardiologists in the USA has doubled, while the number of radiologists has increased fivefold. In spite of managed care programmes, the costs in healthcare in the USA has shown the highest growth as a percentage of GDP from 1960 to 2008 (see Table 2.3). However, the healthcare status of Americans has shown no evidence of greater improvement than that of any other G7 country (Chapman, 2006). Data however show that the demand for physicians is driven by demographic changes. The U.S. Census Bureau projects that by 2030, 20% of the USA’s population will be over 65 years of age. An example of this is that during 2003 alone, an estimated 906 million visits were made in the USA to physician offices (Hing *et al.,* 2005), as shown on Table 2.5.

Table 2.5: Annual physician visits by patient age group in USA

Age group	<1 yr.	1-12 yrs.	13-21 yrs.	22-49 yrs.	50-65 yrs.	>65 yrs.
No. of annual visits	6.5	2	1.5	3	4	6.6

Source: Hing et al., 2005.

There were approximately 3.2 visits per person overall with infants aged <1 year and adults aged ≥65 years accounting for most of these visits, with approximately 6.6 visits per person in each of those age groups as seen in Table 2.5.

Chapman (2006) also claims that the diagnosis rate varies despite the constant prevalence of disease. Chapman cites Gan *et al.* (2000) and refers to studies that show gender bias in treatment between men and women. One study examined information from the charts of 138 956 Medicare beneficiaries (49% of them women) who, between 1994 and 1995, suffered acute myocardial infarction. Multivariate analysis was performed to measure differences between women and men with regard to the medications that were prescribed, the procedures performed, the assignment of “do-not-resuscitate” status and, finally, 30-day mortality. The results indicated that women in all age groups were less likely than men to undergo diagnostic cardiac catheterisation. The difference was more apparent among older women and, in particular, women over 85 years of age. The adjusted relative risk in this group was 0.75 (95% confidence interval, 0.68 to 0.83). The study found that women were less likely than their male counterparts to receive thrombolytic therapy within 60 minutes (adjusted relative risk, 0.93; 95 % confidence interval, 0.90 to 0.96) or to receive aspirin within 24 hours after hospital admission (adjusted relative risk, 0.96; 95% confidence interval, 0.95 to 0.97). Both men and women were equally likely to receive beta-blockers (adjusted relative risk, 0.99; 95% confidence interval, 0.95 to 1.03). Women were more likely than men to receive Angiotensin Converting Enzyme inhibitors (adjusted relative risk, 1.05; 95% CI, 1.02 to 1.08). Of

particular note was the fact that women were more likely to have a “do-not-resuscitate” order in their records (adjusted relative risk, 1.26; 95% confidence interval, 1.22 to 1.29). This was in spite of the fact that, after adjustment, women and men had similar 30-day mortality rates (hazard ratio, 1.02; 95% confidence interval, 0.99 to 1.04). The reason for highlighting these differences is to point out that the provision of healthcare services is dependent on good assessment, good clinical judgment and evidence-based medicine and, in spite of policies that may be in place, healthcare services are not necessarily equitable among all recipients.

Assessment of health needs is the systematic method of identifying the unmet health needs within a given population. This assessment must address economic, clinical and ethical issues and should include perspectives from patients (Jordan *et al*., 1998: 84). Both quantitative epidemiological data as well as qualitative data may be used to determine the priorities in the specific society being studied. The assessment of needs is fundamental to the success of any healthcare programme even as far as it addresses the needs of different geographical areas. Data are not easily transferable. For example, the unmet needs of the population in Bournemouth with an aged population, in the case of the care of those with dementia, differ significantly from those in Soweto, which has a relatively young population and a high incidence of HIV/AIDS and tuberculosis (TB).

2.7 HEALTH ECONOMIC EVALUATION

Economic evaluation in healthcare is important as there is a myriad of treatment options available, each with different features, benefits and medical claims. There is inequality in information and the end user or patient is an unwilling consumer, having choices made on their behalf. This inequality creates a possibility for exploitation by various parties in the medical profession. As illustrated in Figure 2.4, in most systems the need for economic evaluation at both a national and local level is to maximise scarce available resources and to provide a set of research methods and tools to support decision making (Chapman, 2006).

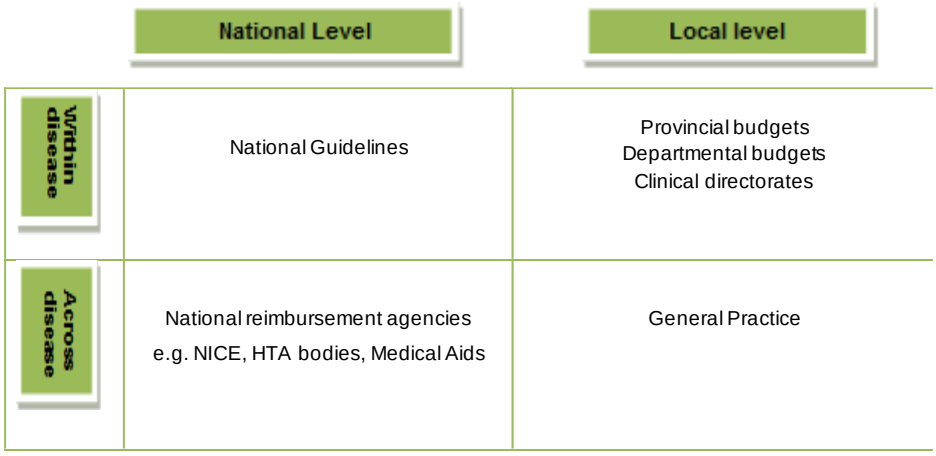


Figure 2.4: Economic evaluation as part of the healthcare system

Source: Chapman, 2006.

Economic evaluation is particularly useful when new technologies or treatment options, which are in competition with established treatment options, are introduced into the market. As such, economic evaluation focuses on the incremental or marginal cost of implementing a new therapy and the marginal outcomes suggested by the therapy (Seifan & Shemer, 2005: 68).

The economic evaluation of health may provide vital information for the decision makers and payers and it must be noted that it often only addresses one dimension of a healthcare programme. To ensure that the analysis is valuable to all stakeholders the following questions should be answered:

- Is the programme efficacious? To understand this, a simple question may be asked: Can the programme work? The answer needs to reflect that, by implementing the programme, procedure or service, it will ensure that more good is done than harm to those who are affected by such a programme or service. Efficaciousness is usually determined in a clinical study based on empirical data, produced under controlled conditions where the population is both limited and known. In many cases these studies are clinical trials designed for registration or licensing of products.
- What is the availability of the programme? To ensure that a programme has value it must be available to all those who need it and not restricted to only a few. This principle refers to equity, as priority may be given to certain groups, for example, patients with breast cancer. Other simple questions to be answered are: “Should this therapy be used and what will the cost or economic implications of this programme be or is there economic efficiency?” An example is developing a vaccine for a broad range of viral pneumonias that may be considered to be much more effective than a vaccine against a Hantavirus infection (Lopez *et al.,* 2001: 5).
- Is the programme effective? To evaluate effectiveness, the question to be asked is: “Does it work?” Effectiveness differs from efficacy in that it should be applied to the real world. While a treatment may prove to be efficacious in empirical data, one needs to question its application in the real world. Does it offer clinical value? (Chapman, 2006; Drummond *et al*., 2006: 8).

Drummond *et al.* (2006) describe the process of economic evaluation as a comparison of two or more possible treatment options in terms of both cost and consequences. The different types of evaluation are defined by the approach used to measure the outcome of a particular therapy. The methodology used should mirror the conclusion for which the evaluation is intended.

There are several different methods of doing health economic evaluation and the process usually involves one or more of the following:

- QALYs
- DALYs
- Cost-utility analysis
- Cost-benefit analysis
- Willingness to pay
- Cost minimisation
- Cost-effectiveness analysis
- Discounting
- Sensitivity analysis
- Programme budgeting and marginal analysis.

2.7.1 Quality adjusted life years (QALY)

Both quantity and quality of life are measures used when weighing the outcomes of healthcare provision. A quality adjusted life year (QALY) is a measure of both of these, combining morbidity and mortality into a single index (Chapman, 2006). A QALY is simply an arithmetic product of both life expectancy and the quality of the remaining life-years and is defined as a year of life free of all disabilities and symptoms (Chapman, 2006). NICE defines a QALY as a 'measure of a person's length of life weighted by a valuation of their health-related quality of life' (NICE, 2010). The QALY is used to assess the value for money of a medical intervention and requires independent utilities which are risk neutral and constant proportional trade-off behaviour (NICE, 2010). Therefore, the QALY may be thought of as providing a common currency for measuring the extent of health gain that results from healthcare interventions and, when combined with the costs associated with the interventions, can be used to assess their relative worth from an economic perspective.

Weinstein *et al*. (2009) agree that both the USA Panel on Cost-Effectiveness in Health and Medicine and the National Institute of Health and Clinical Excellence (NICE) in the UK endorse the conventional QALY as a standardised methodological approach to promote comparability in cost-effectiveness analyses of different healthcare interventions.

Life expectancy refers only to the quantity of life and, in these terms, it is accepted that a person is either dead or alive. When evaluating the quality of life, several factors need to be taken into consideration. Quality of life may include both physical and psychological attributes.

Health utilities are used to evaluate quality of life and these may include, among others, standard gamble, time trade-off and the use of rating scales.

Each health state is represented by a value on a continuum between 0 and 1, where 0 is equivalent to death and 1 to the best possible state in health. These measurements of health-related quality of life allow for states of health that are considered worse than death and these may be allocated a negative valuation, as seen in Figure 2.5 (Phillips, 2009: 2). Some people may, for example, consider being in a permanent vegetative state worse than death and so would give such a health state a negative utility (Garner, 2010).

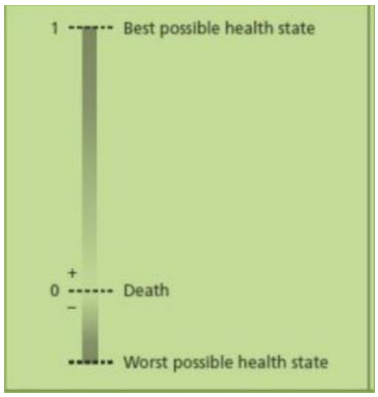


Figure 2.5: Valuation of health state where 1 is perfect health, 0 is death

Source: Phillips, 2009: 2.

Various rating scales are used to evaluate the preference for a treatment option. The preference should be representative of the patient, the practitioner or the public at large. There are a number of rating methods which can be used:

- **Time-trade-off (TTO).** As suggested by the name, this requires respondents to make a choice between remaining in a state of ill health for longer, and being restored to perfect health, but with a shorter life expectancy.
- **Visual analogue scale (VAS).** This is a method which is open to subjectivity, whereby respondents are asked to rate a state of ill health. The scale ranges from 0 to 100, where 0 represents death and 100 represents perfect health.
- **Standard gamble (SG).** This involves a choice between remaining in a state of ill health for a period of time or choosing a medical intervention which has a chance of either restoring them to perfect health or resulting in their death.
- **Willingness to pay (WTP).** This is a measure of what the individual is willing to pay to be cured or to prevent an incident.

Another instrument for the measurement and valuation of health-related quality of life appraisals is the EQ-5D. As seen in Table 2.6, the EQ-5D scoring system used to measure quality of health uses measures in five different dimensions, each at three levels.

Table 2.6: The EQ-5D scores as a measure of the individual's ability to function in five dimensions

Description	Scoring
Mobility	No problem walking around Some problems walking around Confined to bed
Pain or discomfort	No pain or discomfort Moderate pain or discomfort Extreme pain or discomfort
Self- care	No problem with self-care Some problems washing or dressing Unable to wash or dress oneself
Anxiety/ depression	Not anxious or depressed Moderately anxious or depressed Extremely anxious or depressed
Usual activities (work, study, housework, leisure activities)	No problems in performing usual activities Some problems in performing usual activities Unable to perform activities

Source: Phillips, 2009: 2.

Together with the states "unconscious" and "dead," there are 245 different possible health states. Table 2.7 provides some examples of selected possible EQ-5D health state valuations.

Table 2.7: Examples of selected possible EQ-5D health state valuations

Health state	Description	Valuation
1,1,1,1,1	No problems	1.0
1,1,2,2,1	No problem walking about, no problem with self-care, some problem performing activities, some pain/discomfort, not anxious or depressed	0.760
2,2,2,2,2	Some problem walking about, some problem with self-care, some problem with activities, moderate pain/discomfort, moderately anxious or depressed	0.516
1,2,3,2,1	No problem walking around, some problem with self-care, unable to perform activities, moderate pain/discomfort, not anxious or depressed	0.329
2,1,1,2,3	Some problem walking around, no problem with self-care, no problem with activities, moderate pain/discomfort, extremely depressed	0.222
2,3,3,2,2	Some problem walking around, unable to care for self, unable to perform activities, moderate pain/discomfort, moderately anxious/ depressed	0.079
3,3,3,3,2	Confined to bed, unable to wash or dress self, unable to perform activities, severe pain/discomfort, moderately anxious/depressed	-0.429

Source: Phillips, 2009: 3.

A QALY simply refers to the amount of time spent in a health state which is then weighted by using a utility score given to that health state. One year of perfect health equals one QALY (utility score of 1). On the other hand, one year in a health state valued at 0.5 is regarded as being equivalent to half a QALY. Therefore, when evaluating any medical intervention that produces four additional years in a health state valued at 0.5, two extra QALYs are generated. Similarly, an intervention that generates four additional years in a health state valued at 0.25, generates one extra QALY. It may be noted that when the QALY is combined with the cost associated with the medical intervention, it results in a cost-utility ratio. The cost-utility ratio denotes the cost required to produce a year of perfect health or one QALY. On this basis different therapy options can be compared and the best cost per QALY can be determined. An example of an application of a cost-utility ratio is given in Figure 2.6.

$$\text{Cost-utility ratio} = \frac{\text{Cost of intervention A - cost of intervention B}}{\text{Number of QALYs (A) - Number of QALYs (B)}}$$

Figure 2.6: An example of the calculation of cost-utility ratios

Source: Phillips, 2009.

QALYs may be calculated as follows: Therapy A offers the individual four years in the health state of 0.75, therefore they have 3 QALYs, while Therapy B results in four years in the health state of 0.5, or 2 QALYs. Note that Therapy A generates one additional QALY.

The measure of cost-effectiveness in relation to healthcare remains controversial. Agencies like NICE use incremental cost-effectiveness ratios or cost per quality life year, or cost per QALY as a means to shed light on the cost-effectiveness of a treatment option. There is much debate waged about the validity of this measure and despite its shortcomings the use of cost per QALY remains, in many instances the best measure available. The method of measuring cost per QALY is a complex measure that determines the cost for a group of people and not for individuals. The question is how, even by using the QALY, does one ascertain whether a therapy is cost-effective or not. Traditionally in the USA the threshold limit of US$50 000 is used for a QALY. The origin of this frequently cited benchmark seems to date back to at least 1992. There has been much speculation about the value and concept of the QALY in the US. Kaplan and Bush (1982) refer to renal dialysis as the standard for the acceptance of US$50 000 for a QALY but fail to comment on the empiricism of arriving at this value.

The theory connecting the QALY to renal dialysis is common among those in the field of health economics. The fact is that the value has remained in use with no adjustment for inflation for almost 20 years. Bridges *et al.* (2010) argue that the creation of the US$50 000 threshold is neither linked to dialysis nor the willingness to pay and is in fact not scientifically justifiable. Kaplan and Bush (1982)

suggest that no single threshold should be set but rather that a range of between US$20 000 to US$100 000 be used. The concept of a single threshold appeals to policy makers and is seen as being open and transparent. The application of a set threshold may be of value in societies like the UK, where the majority of the population access the NHS, and the single value threshold offers the opportunity to provide new technologies in a uniform fashion. This type of explicit threshold also gives manufacturers insight into what is required should they apply for their technology to be reimbursed. The downside of a single threshold it that it does not allow for shifts caused by normal supply and demands variations.

The cost per QALY in Canada is set at $40 000 while in the UK, NICE has accepted an incremental cost-effectiveness ratio of £20 000, but NICE generally accepts values that range from £20 000 to £30 000. The highest incremental cost per QALY that has been accepted by NICE was £49 000; the indication was for the blast phase of chronic myeloid leukaemia (Steinbrook, 2008: 1980). Whether one agrees or disagrees with the concept of a single fixed threshold for the QALY, most academics agree that at this stage it is still the most effective measure available.

2.7.2 Disability adjusted life year (DALY)

In 1992, the WHO worked together with Harvard University to start a study known as the Global Burden of Disease study. This was a systematic measure of more than 100 diseases over eight regions and 20 countries in the world. The result was a comprehensive and internally consistent estimate by age, sex and region of mortality and morbidity data (WHO, 2010: 1; Lopez *et al.,* 2001: 2).

An important outcome from the study was the introduction of a new metric known as the DALY. The DALY is a single measure of burden of disease, risk factors and injury. The premise underpinning the DALY is based on years of life lost from premature death and years of life lived in less than perfect health (WHO, 2011). The use of mortality data alone skews the picture of the burden of disease borne by individuals in different communities. When using DALY, for example in the case of death by drowning or measles, the burden of disease results only in early death but no disability, however, when compared to brain damage as result of near drowning or blindness as a complication of measles, where early death was averted, severe disability may remain.

One DALY therefore represents the loss of the one year of full health. In 2004, in all regions of the world, the global average burden of disease was 237 DALYs per 1 000 of the population. Close to 60% of these DALYs were due to premature death while the other 40% was due to non-fatal health outcomes. This report highlighted the usefulness of the DALY and showed that in 2004, 36% of the total disease and injury burden for the world involved children under the age of 15 years. Another 50% of total disease and injury burden involved adults between the age of 15 and 59 years (Mathers, Boerma & Fat*,* 2004).

One DALY is the sum of the years of life lost (YLL) due to premature mortality and years of life lost due to disability (YLD) or put more simply one lost year of "healthy" life. Currently life expectancy is measured at the most extreme, that of Japanese women at around 86 years of age.

Therefore, it can be stated that

DALY= **YLL**+**YLD**
YLL=**N** x **L** where

N = number of deaths and **L** = standard life expectancy at age of death in years

YLD = **I** x **DW** x **L** where

I = number of incident cases, **DW** = disability weight and **L** = average duration of the case until remission or death (measured in years) (Lopez *et al*., 2001: 3).

The major findings of the 2001 Global Burden of Disease were as follows: Of the 56 million deaths globally in 2001, 20% or 10.5 million were children under the age of five. Thirty three percent or 3.3 million stillbirths were recorded and almost 40% or 4 million children died before reaching the age of one month. Over 10.3 million of the 10.5 million deaths occurred in low to middle income countries.

In the age group 15 to 59, those who were deemed to be part of the productive society, only 15% of deaths were in high income countries, while twice as many (30%) of the deaths in the low to middle income countries were in this age group.

In 1990 and again in 2001 the number of deaths attributed to communicable diseases, maternal or peri-natal conditions or nutritional deficiencies remained almost unchanged at one out every three deaths. One major difference however was that in 1990 HIV/AIDS accounted for only 2% of all deaths, whereas in 2001, 14% of all deaths were attributed to HIV/AIDS.

An unexpected result of both the 1990 and 2001 global burden of disease report was that previously the burden of non-fatal illnesses and in particular neuropsychiatric disorders were not recognised. Neuropsychiatric disorders accounted for more than 37% of YLD among adults over the age of 15 in all regions of the world. Depression was the leading cause of disability for men and women with women having a 50% greater burden of depression than men. Disorders like migraine, senile dementia and anxiety disorders were more common in women than in men, but men were shown to have a six times higher predisposition for alcohol and drug disorders (Lopez *et al*., 2001: 7).

The Millennium Declaration in 2000 brought special global attention to HIV, tuberculosis, and malaria through the formulation of Millennium Development Goals. The high priority status of these three diseases was confirmed through the creation of the Global Fund to Fight AIDS, Tuberculosis and Malaria in 2002. The 2013 *Global burden of disease* found that the incidence of HIV was 1.8 million globally (1.7 million to 2.1 million with 95% uncertainty level), as seen in Figure 2.7.

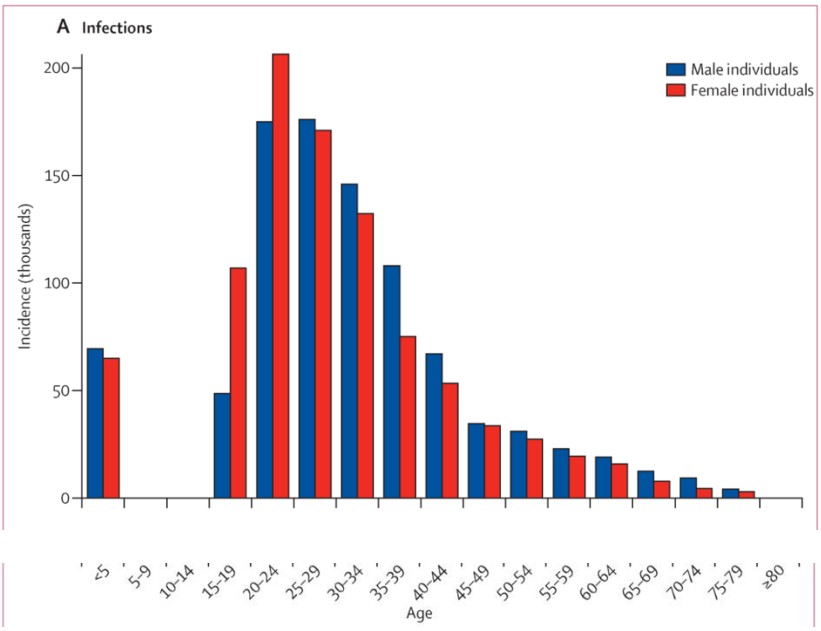


Figure 2.7: Global age-sex distribution of new HIV infections in 2013

Source: Murray et al., 2014: 9.

Figure 2.8 shows the age standardised incidence of HIV in 2013 for both sexes by region, with the highest prevalence per 100 000 of the population being in Southern sub-Saharan Africa. The 2013 prevalence of HIV was estimated at 29.2 million.

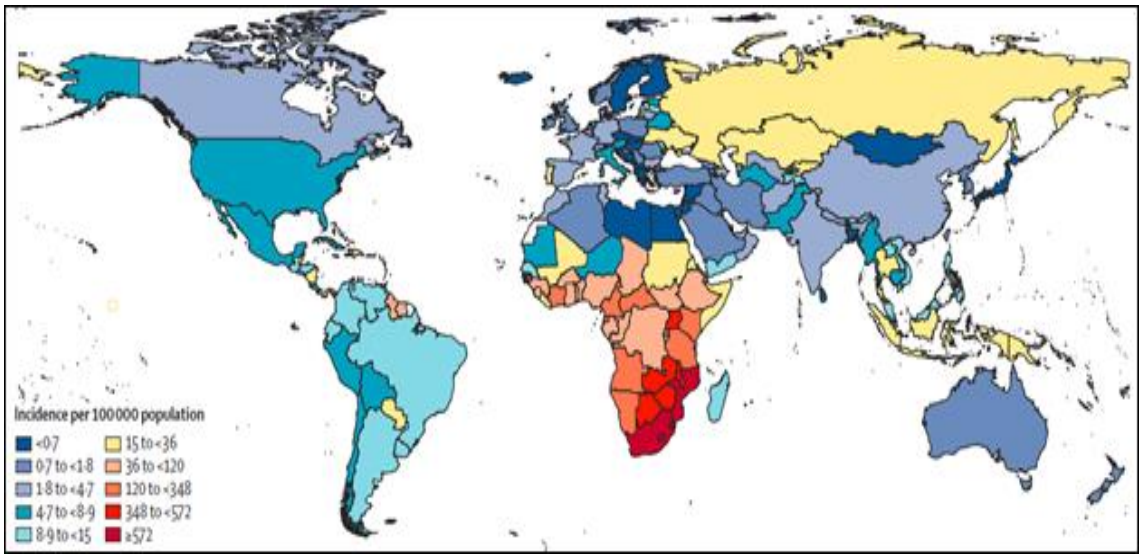


Figure 2.8: Age standardised incidence of HIV in 2013 for both sexes by region

Source: Murray et al., 2014: 9.

As illustrated in Figure 2.9 there were 1.3 million deaths attributed to HIV. This had declined from 1.7 million deaths in 2005 when the HIV epidemic was at its peak. Murray *et al.* (2014: 2) estimated that more than 19 million life-years have been saved through intervention.

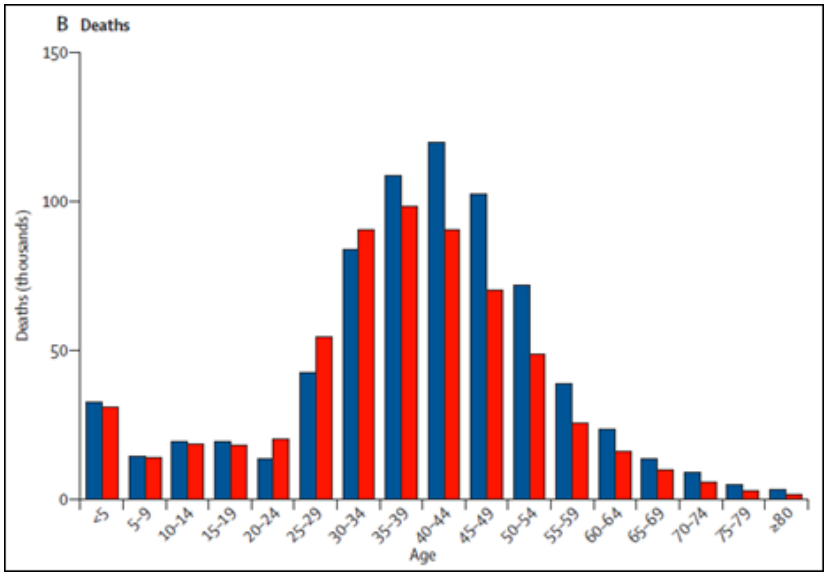


Figure 2.9: Global age-sex distribution of deaths related to HIV infections in 2013

Source: Murray *et al.,* 2014: 9.

The 2013 incidence of all forms of tuberculosis was estimated at 7.5 million. These included HIV-positive people. The prevalence of TB was 11.9 million and 1.4 million deaths were attributed to TB in 2013. Figure 2.10 shows the global age-sex distribution of the incidence of tuberculosis for 2013 in HIV-negative individuals, while Figure 2.11 shows the global age-sex distribution of deaths accredited to tuberculosis for 2013 in HIV-negative individuals.

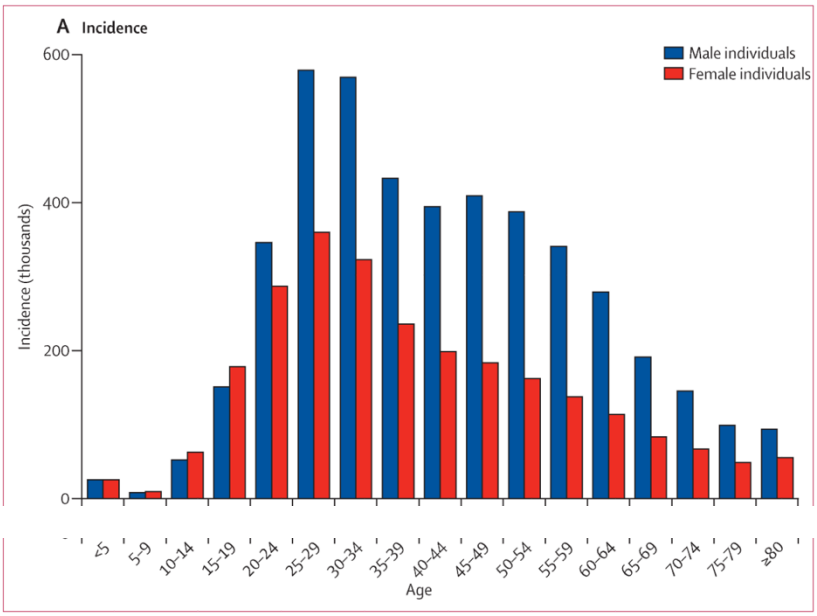


Figure 2.10: Global incidence of TB, by age/sex (2013). (HIV-negative individuals)

Source: Murray et al., 2014: 28.

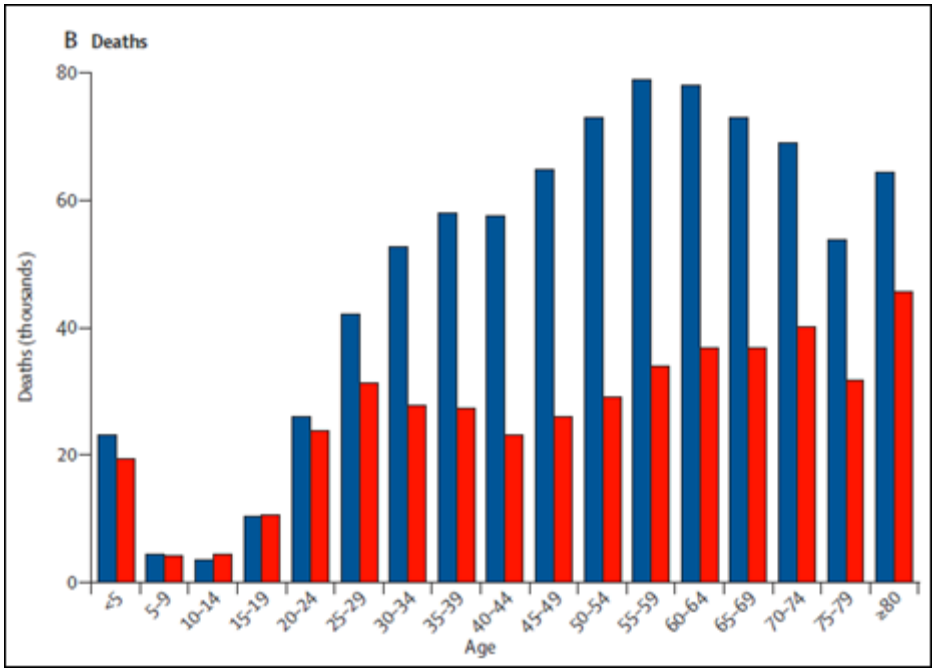


Figure 2.11: Global deaths accredited to TB by sex/age in HIV-negative individuals (2013)

Source: Murray *et al.,* 2014: 28.

Finally, the global number of malaria cases increased rapidly from 1990 reaching a peak in 2003 with an estimated 232 million cases (Figure 2.12). It should be noted that the highest incidence is in Africa, in particular Central and Western sub-Saharan Africa.

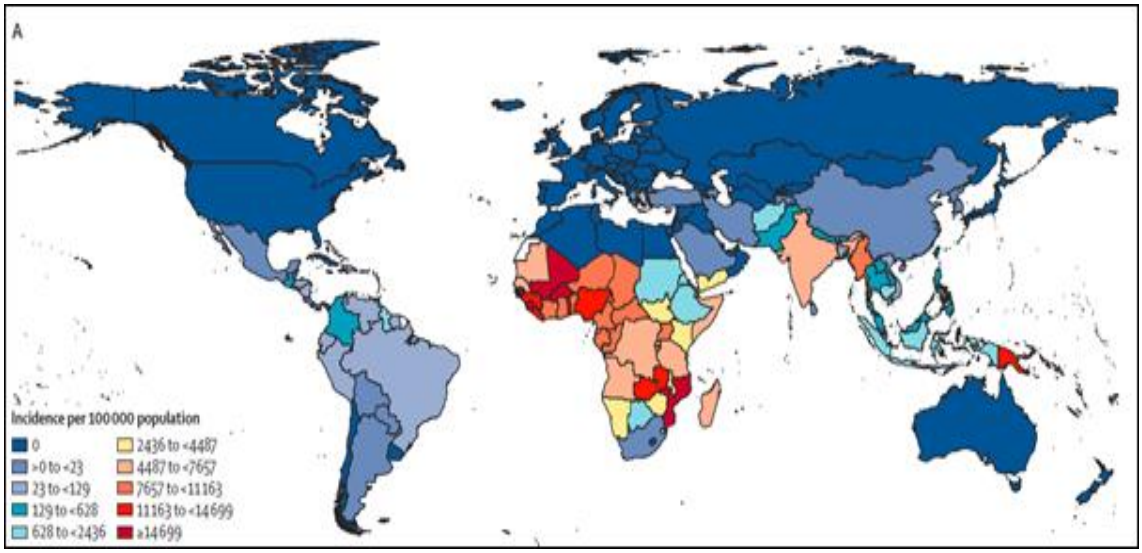


Figure 2.12: Age-standardised incidence of malaria for both sexes in 2013

Source: Murray *et al.,* 2014: 28.

Malaria resulted in 1.2 million deaths in 2013, as seen in Figure 2.13.

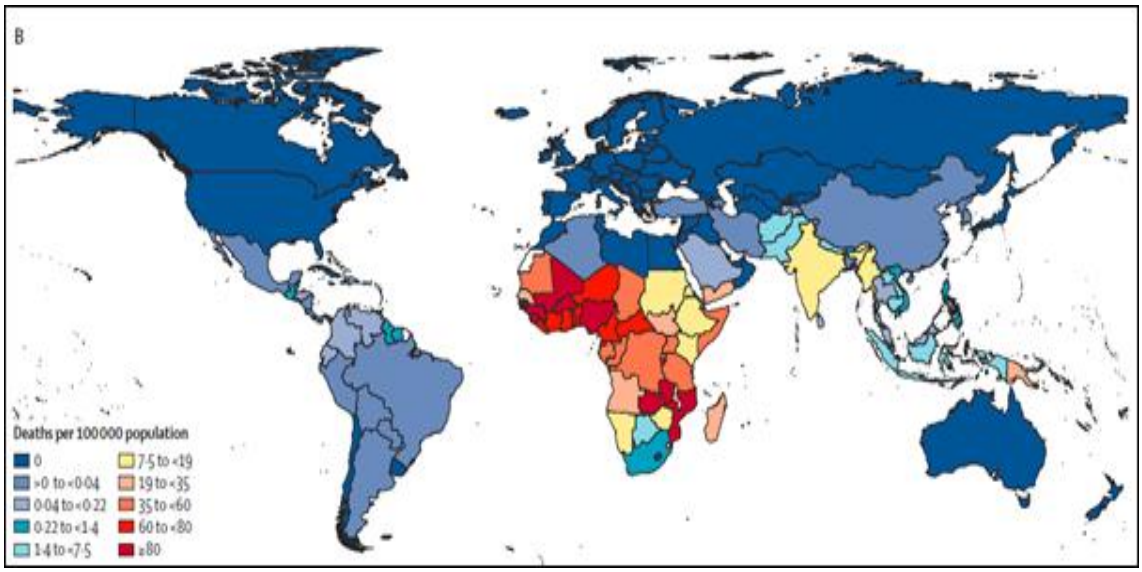


Figure 2.13: Age-standardised deaths as result of malaria for both sexes in 2013

Source: Murray *et al.,* 2014: 28.

The highest incidence occurs in the age groups below the age of 15 years (Figure 2.14) and the majority of the deaths from malaria occur in children under the age of 5 years old (Figure 2.15).

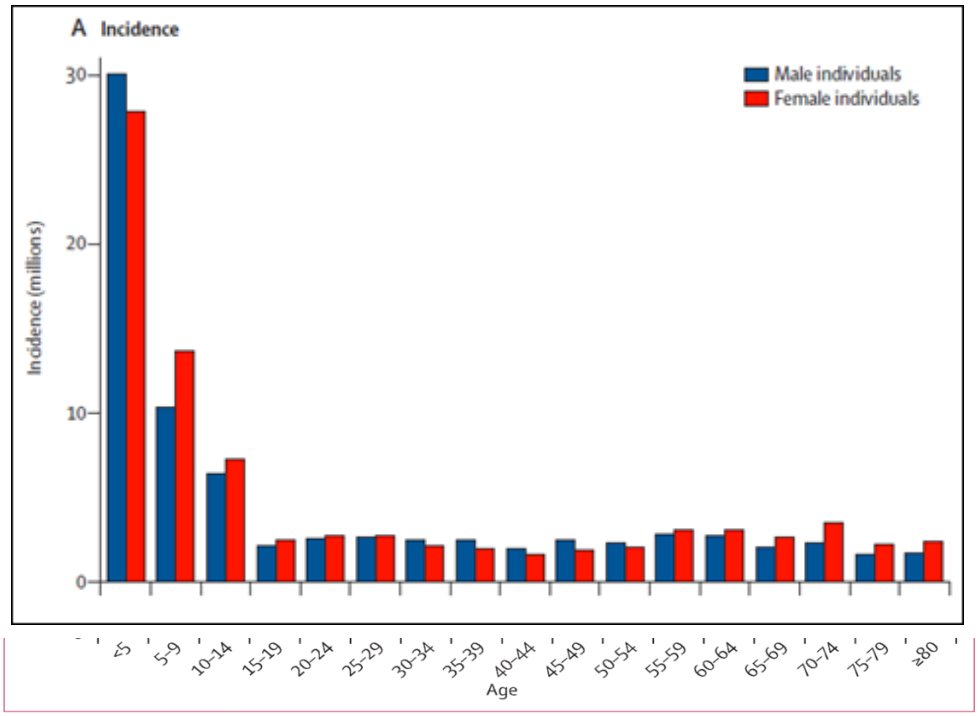


Figure 2.14: Global age-sex adjusted distribution of incidence of malaria in 2013

Source: Murray *et al.,* 2014: 28.

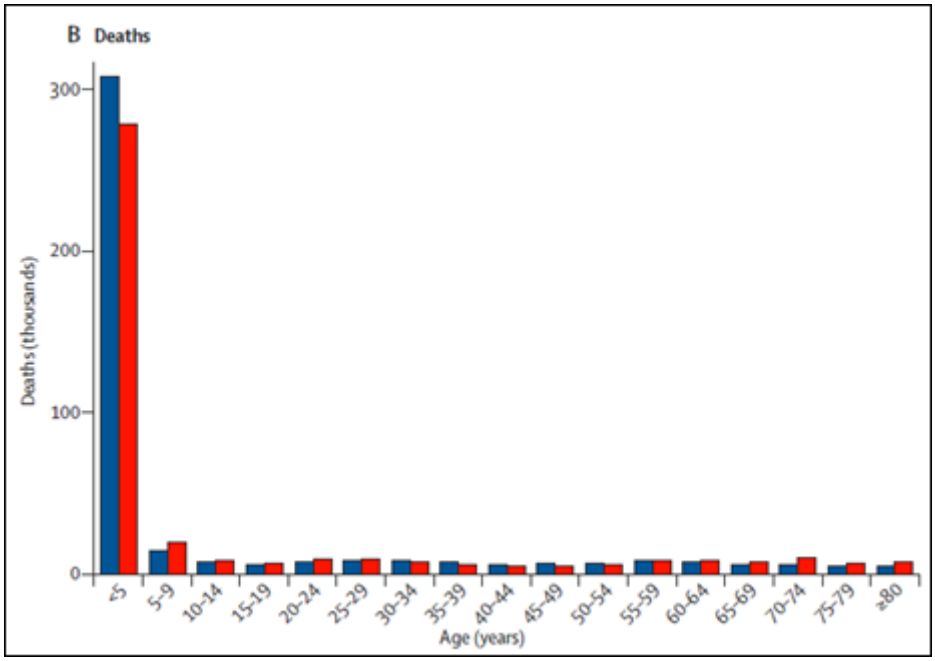


Figure 2.15: Global age-sex adjusted distribution of deaths from malaria in 2013

Source: Murray *et al.,* 2014: 28.

The use of the QALY may be advantageous in the short to medium term but the use of the DALY should force policy makers to consider the long-term implications for priority setting in health to ensure that sufficient funds are allocated for specific interventions to reduce the loss of health and to promote productivity.

2.7.3 Cost-utility analysis (CUA)

The use of cost-utility studies dates back to the early 1980s when this type of analysis was called this by the York group of health economists. Prior to 1980s this type of analysis was called generalised cost-effectiveness analysis (1971) and later utility maximisation (1972). In 1982 Kaplan and Bush described the use of CUA in their work. The concept of CUA has, however, not been adopted in all health economic centres and the USA does not use CUA but rather utilises cost-effectiveness analysis (CEA). CUA is used as an estimate of the ratio between the cost of a health-related intervention and the benefit it produces in terms of the number of years lived in full health by the beneficiaries. Hence it can be considered a special case of cost-effectiveness-analysis. In reality the two concepts are closely related. One of the main similarities between these two measures is the fact that the results are usually expressed in cost per unit effect, for example a QALY. The measure on the cost side is almost identical in both cost-effectiveness analysis and cost-utility analysis but differ in the outcome measure.

2.7.3.1 What are utilities?

As discussed in section 2.6.1 above, rating scales such as time trade-off and standard gamble are used as methods of asking individuals to trade off health status against life expectancy. The results of these exercises are known as utilities.

Utilities of a health state have been demonstrated to vary based on how the health state was described, who asked the question, and how the question was posed. This exposes the subjectivity of this type of measure.

Costs are measured in monetary units while benefits are expressed in a way that takes into account health states that are considered less preferable to full health. These are given quantitative values, in this case QALY. However, unlike cost-benefit analysis, the benefits are not necessarily stated in monetary terms.

The use of cost-effectiveness analysis is as a measure of a specific, single outcome while cost-utility analysis may have multiple, generic measures. An example of where cost-utility analysis could be used is a pancreatic resection colon procedure vs coronary artery bypass surgery. Cost-utility analysis has a major advantage in that it can be used to make comparisons across a broad spectrum of possible interventions. The York economists argue that cost-utility analysis was developed for this very reason (Drummond *et al.*, 2006: 138).

2.7.3.2 When should cost-utility analysis be used?

Cost-utility analysis was developed as a tool to enable decision makers to be able to compare the value of alternative interventions that have different benefits or outcomes. Cost-utility specifies a value assigned to a specific health state. This allows transparency in the process of allocating resources.

The primary outcome of the cost-utility analysis is the measure of cost per QALY. This is also referred to as the incremental cost-effectiveness ratio (ICER). The measurement of ICER is the calculated difference between the costs of two interventions divided by the difference in QALYs produced by such interventions. The ICER can be thought of as the ratio between the difference in costs and the difference between the benefits of two interventions.

An example of this is where intervention “A” enables a patient to live for three years longer than if no intervention had taken place, but with a quality of life weight of only 0.6, then the intervention presents 3 * 0.6 = 1.8 QALYs to the patient. If intervention “B” grants the patient two extra years of life at a quality of life weight of 0.75, then it presents an additional 1.5 QALYs to the patient. The net benefit of intervention “A” over intervention “B” is therefore 1.8-1.5 = 0.3 QALYs.

McCabe (2009) alludes to the fact that the early literature made the assumption that the results from cost-utility studies could be used to construct a cost-utility table, i.e. a ranking of ICERs, with the most efficient being noted at the top of the table and least efficient at the bottom. Such a league table would be most useful in determining which treatment options to choose as decision makers could, in theory, move down the league table until such time as resources had been exhausted. Sadly, the reality is far more complex than that and, in order to implement such a system, it would be necessary to have ICERs for all possible interventions, both old and new, at current prices.

The best way to utilise the ICER is by means of an ICER threshold. In most instances, ICERs below the ICER threshold are funded, while those above the threshold frequently are not. This, however, does not mean that an ICER with a high value will automatically be declined for funding, but it does mean that it might be under consideration for funding based on the severity of the condition, the availability of treatment and the burden of disease. The ICER may be thought of as the willingness to pay (McCabe, 2009: 3).

Since January 2005, the National Institute of Clinical Excellence (NICE) is thought to have applied a value of £30 000 for a QALY, although this has not been made public (Devlin & Parkin, 2004). Should this be true, it can be stated that any treatment that has an ICER of less than £30 000 per QALY gained will be funded. The USA uses an ICER of US$ 50 000 as its threshold (NICE, 2010). Although this has been debated in South Africa, the Council of Medical Schemes has not agreed to a set value in South Africa but has argued that different levels should be set for different conditions (Personal meeting with CMS, December 2010).

The advantages of cost-utility analysis are that unlike cost-effectiveness analysis it allows comparisons to be made using different conditions and, unlike cost-benefit analysis, CUA enables the comparisons to be made without placing a monetary value on life. CUA utilises both mortality and morbidity data and, with the use of established rating scales like EQ-5D scores as illustrated in Table 2.6, the data are relatively easy and inexpensive to capture and assess.

The main disadvantage of the CUA is that there is concern among healthcare workers that the instruments used to measure the utilities may not be sufficiently sensitive to account for subtle differences in treatment options. With regard to chronic conditions, the assumption is that the utility is independent of the time spent in that particular health state. Also, health gains for critically ill patients may be valued more than moderate gains in less severe conditions.

McCabe (2009) suggests that CUA is not an appropriate foundation to allocate resources as it fails to describe various important factors while enumerating others that may not be of any value.

2.7.4 Cost-benefit analysis (CBA)

Drummond *et al.* (2006:11) state that the main criterion that differentiates practices of economic evaluation resides in the way that the outcomes or consequences of the healthcare programmes are valued. In this regard, cost-benefit analysis (CBA) differs from other health economic methods in that the consequences of the programme are expressed in the same units, which are frequently monetary. CBA is used to determine the efficiency of the allocation of resources, for example, by comparing the costs and benefits relating to programmes serving different patient groups. It is important to note that although it may not always be possible to measure some of the items of resource or benefit in the same common unit of account (for example, monetary) these should not be excluded from the analysis. Drummond *et al.* (2006) usually define cost-benefit analysis in health economics as a technique in which all costs and benefits are measured in terms of monetary units. These costs may be either actual costs or opportunity costs.

Grosse *et al.* (2008) explain that the clearest difference between CBA and CEA is that for CBA the outcomes are all expressed in monetary units while CEA allows the difference in costs between two interventions to be compared with the difference in health outcomes. Another, and perhaps more important difference, is that in a resource-constrained healthcare system, using CEA provides information as to whether an intervention maximizes the health of a population while CBA aims to determine whether the social welfare benefits, which include both health and non-health related outcomes and values, are best utilised within the societal budget constraints.

The history of cost-benefit analysis (CBA) dates to 1848 when an article was published by Dupuit (2006). The process was later formalised by Alfred Marshall in 1920. Traditionally, cost-benefit analysis was used to assess the monetary value of large private and public sector projects. An example of how CBA was used relates to the Federal Navigation Act of 1936, when the Corps of Engineers used it as a proposal for a federal waterway infrastructure. After the Flood Control Act of 1939 was promulgated, CBA was established as federal policy (Nas, 1996: 67).

Other examples of using a cost-benefit analysis in the 1950s and 1960s include the investment in motorways in both the UK and the USA. Many countries around the world now utilise CBA to evaluate transport projects; perhaps the most famous of these is the Victoria Line of London’s underground system.

Cost-benefit analysis is typically an analysis of the cost-effectiveness with different alternatives. It is performed to measure whether the benefits offset the costs, thereby evaluating the efficiency of the new intervention relative to the *status quo*. Both costs and benefits are a measure of the public's willingness to pay for them (benefits) or willingness to pay to avoid them (costs) and, as such, the input is measured in terms of opportunity costs. Cost-benefit analysis attempts to put all relevant costs and benefits on a common chronological basis. Cost-benefit analysis usually involves time

value of money formulas by converting the future expected streams of costs and benefits into present value amounts by means of a chosen discount rate (Drummond *et al*., 2006: 210). In practice, analysts try to estimate costs and benefits by either using survey methods or by drawing inferences from market behaviour.

Some of the basic cost-benefit elements used by various organisations around the world include the following:

- NPV (net present value)
- Net benefit (= PVB - PVC)
- PVC (present value of costs)
- PVB (present value of benefits)
- BCR (benefit to cost ratio = PVB/PVC)
- NPV/k (where k is the level of funds available).

The use of CBA in healthcare dates to the early part of the 1960s as result of research done by Burton Weisbrod as published in *Economics of Public Health* (Weisbrod, 1961). One of the inherent problems in using CBA in healthcare is that it requires that a monetary value be placed on human life. Many decision makers find this difficult to do and the public in general may question the ethics of this approach and thus trying to place a monetary value on health outcomes remains a very controversial topic.

In spite of this, CBA has in many instances a far broader scope than either CEA or CUA. This is because all benefits and all costs are translated into money, making it possible to compare two or more diverse programmes, for example, a vaccination programme vs speed calming humps near a park. In order to assign monetary values to both costs and benefits, a method known as willingness to pay is used. Gold *et al*. (as quoted by Drummond *et al*., 2006), question the validity of using methods such as willingness to pay as they argue that this approach intrinsically favours programmes or diseases of the privileged over the underprivileged.

2.7.4.1 Allocating monetary values to health outcomes

Drummond *et al.* (2006) describe three methods used to allocate monetary values to health outcomes, namely: the human capital approach; the stated preferences of willingness to pay (WTP) approach; and the revealed preferences approach. Each of these methods is briefly explored below.

- **The human capital** approach places a monetary weighting on a person's healthy life and uses market-related wages to evaluate the programme's present value in terms of future earning capabilities. Mishan (1971 as cited by Drummond *et al*., 2006), criticises this approach, arguing that it is not consistent with welfare economics, which is a branch of

economics that presumes that each individual in society makes up the welfare of social welfare, and that each individual is the best judge of their own welfare.

- **The willingness to pay** or contingent valuation approach relies on a survey where respondents are offered a hypothetical situation and asked to submit the maximum, they would be prepared to pay for such a service or benefit. At the outset it can be expected that the responses could have significantly wide deviations based on to whom, by whom and how the questions are asked. A young single mother with a brood of children under five years of age may not consider it worth paying for an infertility programme, whereas the same young mother with breast cancer may regard a new treatment for breast cancer as invaluable (Caro *et al*., 2006).
- **The revealed preferences** model utilises the welfare economics approach and is based on an individual's choice with regard to the decreased health risk, such as an injury at work traded off against a decreased income. This is also referred to as a wage-risk approach (McIntosh, 2006: 855).

While cost-benefit analysis, in theory at least, is the most powerful method of economic evaluation, it is fraught with accuracy problems as both costs and benefits are usually estimated. Flyvbjerg *et al*. (2002: 280) found actual costs for a rail project to be almost 45% higher than the estimated costs and, in road projects, actual costs to be 20.4% higher than the estimates. The possible reasons for these inaccuracies are set out below.

The estimates rely heavily on past projects, while not taking into account differences in function, size and skill levels of the team members.

The estimates assume that the project's members will identify all the possible and significant cost drivers.

The estimates may rely on very crude empirical studies to estimate the monetary value of the intangible elements.

There may be unconscious biases of the team members with vested interests in the projects.

Finally, it should be noted that cost-benefit is a term which is often used to describe new treatment options. However, Zarnke *et al*. (1997: 815) found that in 60% of all studies claiming cost-benefit, they were in fact only cost comparison studies as the benefits had not been measured in monetary terms, confirming the intrinsic difficulty of measuring these outcomes which could account for the fact that healthcare payers are reluctant to embrace CBA (McIntosh, 2006: 856).

2.7.5 Cost-minimisation analysis (CMA)

Cost-minimisation analysis is another method of health economic evaluation with a far more limited scope than some of the methods described above. Cost-minimisation can only be used when comparing two or more therapies which have exactly the same efficacy and tolerability. The clinical outcome or therapeutic equivalence must be proven to be the same.

An example of where cost-minimisation would be applicable is where drug A at dose x lowers blood pressure by 10mmHg, while drug B at dose Y also lowers blood pressure by 10mmHg. If efficacy and tolerability are demonstrated by the author prior to the cost- minimisation study being performed, then a comparison of "cost/course of treatment" is an easy measure to make and the "'cost-effective" comparator is simply the one which costs less. Table 2.8 illustrates nine possible outcomes when two treatment options are compared. Only in Boxes 2 and 8 can the choice really be made on cost, as the efficacy is the same.

Table 2.8: Incremental cost vs incremental effectiveness of a treatment

Incremental cost of treatment compared to control	Incremental effectiveness of treatment compared to control: More	Same	Less	
More	1	2	3	**Strong dominance for decision** 7= accept treatment 3= reject treatment
Same	4	5	6	**Weak dominance for decision** 2= reject treatment 4=accept treatment 6= reject treatment 8=accept treatment
Less	7	8	9	**Non dominance-no obvious decision** 1= Is the added effect worth the added cost? 9= Is the reduced effect acceptable given the reduced cost? 5= Neutral on cost and effects. Other reason to adopt treatment?

Source: Adapted from Drummond et al., 2006: 13.

As a result of the uncertainty around estimates of cost and effectiveness, the results of any study rarely fit into any one box; thus, the use of cost-minimisation as a tool for health economic evaluations has limited application (Drummond *et al*., 2006: 13).

2.7.6 Cost-effectiveness analysis (CEA)

Cost-effectiveness analysis differs from cost-benefit analysis in that it does not assign an absolute value to the cost or the benefits but rather describes the benefit in terms of a ratio of the cost of the therapeutic measure to an applicable measure of its efficacy. Cost refers to the resource spent for the therapy and is usually expressed in fiscal terms.

The most common healthcare measure is the QALY which makes CEA similar to CUA, but a number of different measures can be used; for example, deaths averted, premature births averted, life years gained or years free from atrial fibrillation.

CEA was first developed for use in the military and received its name after World War II, after which it was applied to healthcare in the mid-1960s. It has been suggested by *Effective Clinical Practice* that it was in 1977 that the authors Weinstein and Stason (1977) presented it with fervour to clinicians. CEA, like other methods of health economic evaluation, is a technique which allows the decision makers the opportunity to compare the relative value of different clinical strategies. Most often it is used when a new therapy is introduced into the market and this new therapy is compared with what is used in current practice.

Generally, CEA is used either to assess the consequences of expanding existing programmes or to compare alternative programmes with a common health outcome (Rabarison *et al*., 2015). As described above CEA is a ratio between differences in cost and differences in effect, as illustrated in the cost-effectiveness ratio in Figure 2.16.

$$\text{CE ratio} = \frac{\text{cost}_{\text{new strategy}} - \text{cost}_{\text{current practice}}}{\text{effect}_{\text{new strategy}} - \text{effect}_{\text{current practice}}}$$

Figure 2.16: Cost-effectiveness ratio

Source: Adapted from Rabarison et al., 2015.

An important concept to understand with regard to CEA is that, should a CEA determine a therapy to be cost-effective, it is only cost-effective in comparison to the comparator. This does not conclude that the cost-effective strategy will necessarily save money. The converse is true in that a therapy which saves money is not necessarily cost-effective. In reality, a therapy is cost-effective based on a value judgment or predetermined value. Figure 2.17 demonstrates the cost-effectiveness plane.

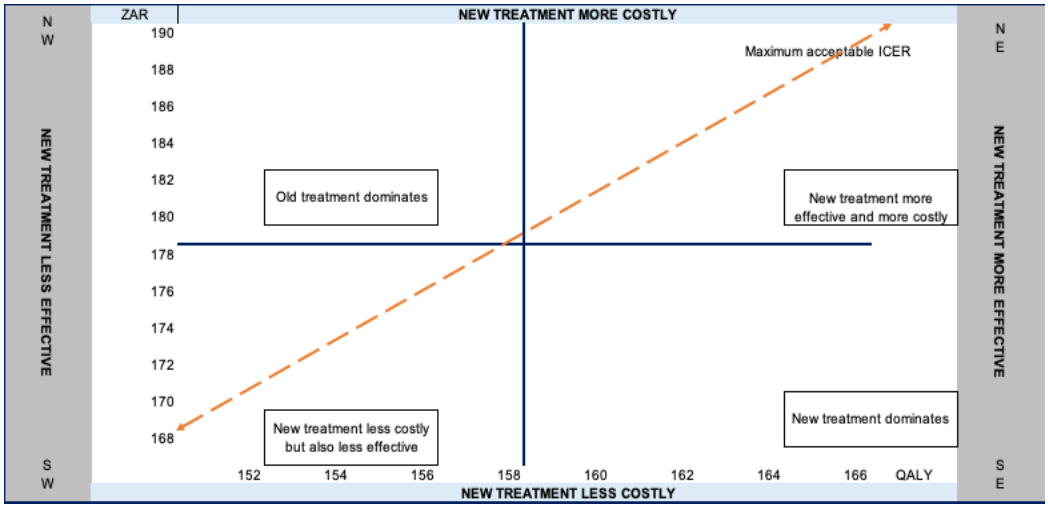


Figure 2.17: The cost-effectiveness plane

Source: Health Knowledge, 2011:6.

Costs are conventionally placed on the north-south axis (Y axis) while effects are placed on the east-west axis. These effects can be positive, zero or negative. Incremental cost effectiveness ratios (ICERs) can be presented graphically as a combination of the costs and the effects of a health intervention comparing a treatment option compared to an alternative treatment.

Based on this, an intervention can be positioned anywhere on this diagram matching its incremental costs and benefits. An example of this is point A, which is found in quadrant I, where the costs of the intervention (treatment) are greater than the alternative, while its benefits are less, indicating that the treatment option is poorer and said to be dominated by the alternative.

When one examines quadrant II, the opposite is found. Here the costs are lower, and the benefits are greater. In this instance the treatment option is said to dominate the alternative.

In quadrant III the benefits gained are greater at a net cost over the alternative. In this case we can calculate an ICER, which is the cost per unit of effect gained. The ICER is measured as the slope of the line from the origin to the point as indicated by the red line in Figure 2.17.

Finally, in quadrant IV, it may be noted that the costs may be less but so are the benefits. This allows for the calculation of an ICER; however, this now refers to a cost saving per unit of effect lost as opposed to the cost per unit of effect gained.

The ceiling ratio can be demonstrated using a cost-effectiveness plane diagram, where it is often referred to as demonstrating cost-effectiveness acceptability.

The threshold line demonstrated in Figure 2.17 as a red line can move up or down in the quadrant and in some societies, it may even change in accordance with the disease entity. An example of this was Herceptin, a new biotechnical pharmaceutical used to treat breast cancer. Neyt *et al.* (2006) studied the cost-effectiveness of Herceptin by setting up a standard cost model for the treatment of

breast cancer. The results showed that from the period of diagnosis to the end of the metastatic phase the monthly hospital costs rose from €112.81 to €121.07, an increase of 7% per patient per month of treatment. Neyt *et al*. (2006) found that there was an extra cost of €3 981.44 per extra life month or €47 777.28 per life year gained (Neyt *et al*., 2006: 17). In these early studies, Herceptin did not replace any other drug but was rather adjunct to the current therapy. It was obvious that total cost would increase. The original study was European based, but the drug and its related costs made world headlines when intense public debate ensued in the UK. Tabloids claimed that Herceptin costs "would put thousands of other patients at risk" (Boseley, 2006) and it was estimated that to treat 75 patients for whom the drug was indicated would cost the NHS £1.9 million per year. The public debate raged as it became known that not all women being treated by the NHS were receiving the same approach to the use of the drug. Patients in Wales were receiving the drug as needed, even if they were being treated in a hospital in England, while women in certain areas in England were being denied the same drug and were expected to pay £30 000 per year for it. A patient named Ann Marie Rogers won a High Court victory against her local healthcare body. The High Court ruled in favour of Mrs. Rogers, stating that the Primary Care trust policy which resulted in her treatment being denied was irrational and unlawful. The drug, which was estimated to cost four times more than other drugs to treat a range of cancers, was approved by NICE supposedly because it was more cost-effective. This emphasizes, as demonstrated in Figure 2.17, that the question is not only about the financial aspect, but also requires examination of the extra effectiveness. However, in this instance, had there not been pressure from the public, the treatment may have been rejected, illustrating the point made by Brown and Calnan (2010) who argue that NICE may be influenced by other means besides pure evidence-based medicine.

While CBA, CUA and CEA appear very similar, their main differences are described below:

- CBA assigns a monetary value to the outcomes attributable to the programme being studied.
- CEA uses natural units, e.g. number of lives saved, or premature births prevented to express the outcomes.
- CUA is a more specialised form of CEA which uses QALYs or DALYs as a measure of morbidity impact.

By measuring cost-effectiveness in terms of lives saved, all lives are treated equally whether the person is an infant who could live to 80 years old or a person in their 40s who may live another 20 years. This alleviates some of the ethical complexities surrounding CBA, for example (Brock, 2004).

To perform a rigorous cost-effectiveness study, some critical issues need to be addressed. If one considers an example of two strategies for patients with cardiac disease, as demonstrated in Table 2.9, it can be noted that both strategies A and B improve the outcome in these patients and have an impact on mortality data.

Table 2.9: Cost and effectiveness of three strategies for patients with heart disease

Option	Strategy	Cost per year	Effectiveness (years gained)
A	Simple (aspirin and β blockers)	$5 000	5 years
B	Complex (Medication, angio, stent, CABG)	$ 50 000	5.5 years
C	Nothing	$ 0	0 years

Source: Adapted from American College of Physicians (ACP), 2000: 2.

The first strategy (A) is uncomplicated and inexpensive and requires that the patients take both aspirin and β blockers. The second strategy (B) is far more complicated and includes, amongst other things, medication, cardiac catheterisation, balloon angioplasty, coronary stenting and, finally, coronary artery bypass grafting. The basic assumption is that doing nothing accrues no cost and is not effective; this therefore becomes the third strategy (C).

The underpinning of CEA is about marginal or incremental changes in both cost and benefits. Therefore, if one again examines these three strategies examining the incremental changes in costs and benefits it is possible to calculate the cost-effectiveness ratio as seen in Table 2.10.

Table 2.10: Cost-effectiveness ratio of three strategies for treating heart disease

Option	Strategy	Cost per year	Incremental costs	Effectiveness (years gained)	Incremental effectiveness	CE ratio
A	Simple	$5 000	**$5 000**	5 years	**5 years**	$1000/yr.
B	Complex	$ 50 000	**$45 000**	5.5 years	**0.5 years**	$90 000/yr.
C	Nothing	$ 0	**-**	0 years	**-**	-

Source: Adapted from ACP, 2000: 2.

The incremental cost of the uncomplicated strategy (A) is the variance between the uncomplicated strategy and the strategy of doing nothing (C) i.e. (A-C). At the same time the incremental cost of the complicated strategy (B) is the difference between the complex strategy (B) and the uncomplicated strategy (A) or (B-A). The final outcome measure for CEA is the cost-effectiveness ratio or put more simply, the ratio of incremental costs to incremental effectiveness (ACP, 2000).

While in principle these comparisons appear to be straightforward and uncomplicated, it would be prudent to note that, when evaluating CEA, the following should be considered to ensure the analysis is sound. An important aspect when starting a CEA is to determine whether the pertinent strategies being compared as CEA are sensitive to the type of strategies being compared. In the example above, had only the complex strategy (B) been compared with the doing nothing strategy (C) the cost-effectiveness of strategy B appears positive, completely ignoring strategy A as an option. Using only B and C the CEA ratio would have decreased significantly from $90 000 per life year to only

$ 9 091 per life year (Table 2.11).

Table 2.11: Cost-effectiveness ratio comparing only strategy (B) and (C)

Option	Strategy	Cost per year	Incremental costs	Effectiveness (years gained)	Incremental effectiveness	CE ratio
B	Complex	$ 50 000	**$50 000**	5.5 years	**5.5 years**	$9 091/yr.
C	Nothing	$ 0	**-**	0 years	**-**	-

Source: Adapted from ACP, 2000: 3.

Another example of choosing the correct strategy is demonstrated in Table 2.12, which evaluates the cost per life year gained when screening for cervical cancer, demonstrating that screening versus no screening is very cost-effective while screening every three years versus every four years is less cost-effective.

Table 2.12: Example data from an analysis of cervical cancer screening frequency

	Screening every 4 years vs no screening	Screening every 3 years vs screening every 4 years
Life expectancy increase (days)	93.8	1.6
Life expectancy increase days at 5% discount	9.5	0.2
Cost increase in $ at 5% discount rate	$264	$91
Cost per life year gained	**$10 101**	**$184 528**

Source: Eddy, 1990: 113, 214-226.

Therefore, CEA is useful when the primary goal of the study is to recognise the most cost-effective strategy from a group of options that are competing for the same resource. It is of great importance at the outset to ensure that the options being compared are clinically relevant.

A second factor that is very important to consider before starting a CEA is to critically appraise the level of evidence to be used. Empirical evidence is needed and for that reason data for cost-effectiveness analysis should come from either Meta-analysis studies or randomised clinical trials. The quality of the data can have an impact on the validity of the CEA.

Another important aspect when considering the data selected, even if it comes from randomised trials, is to consider the clinical significance of the trial. Section 2.6 above refers to the availability of the treatment. CEA may not be generalizable to all populations, as there may be differences in the prevalence of disease or even access to care. If the study, for example, shows cost-effectiveness in a therapy which is not of value to a majority of the patients in that area, one needs to ask whether it

really matters. Similarly, if the selection criteria in the randomised trial does not reflect patient selection that is easy to replicate then one should consider the generalizability of the effectiveness data as it must be accepted that to utilise the data one needs to make inferences.

Finally, one should pose the question of inherent bias. In spite of the claims made by people in academia, it is often difficult to be free of any value judgment or bias. There may or may not be a consideration when looking at who funded the CEA. When studies are funded by drug companies, the data are more likely to report favourably. While the author does not suggest that all studies funded by drug companies are biased, she does caution that such bias may well be present and should be noted.

2.8 CONCLUSION

Healthcare costs continue to rise in all countries around the world. This may be attributed to the fact that people are living longer, are more educated and have greater exposure to information, and that huge advances have been made in healthcare technology. Financing for healthcare is complex and likely to become more so rather than less so. Decision makers, who may be seen as the gatekeepers to treatment options, are required to perform fine balancing acts between ensuring that the lives for which they are responsible benefit from the best treatment options with the resources available. This is not an easy task. The use of statistical lives rather than real lives may help refine the allocation of healthcare resources, but health is an emotive subject and, in spite of empirical data on willingness to pay, when faced with a life and death situation, many people find it difficult to place a monetary value on life.

Health economic studies have been designed to help the decision-makers with the allocation of resources, but these studies are not perfect. The true complexities of ensuring correct comparisons are not well understood. The type of data required to model health economic studies take time to gather. Many multi-centre, randomised trials may take five to ten years to complete. But the current data are better than nothing in many instances and therefore the use of health economic measures is a useful guide to decision-makers.

The benefit of using a cost-effectiveness analysis is that, unlike cost-benefit analysis, it does not assign an absolute value to the cost or the benefits. The measure of benefits in absolute value is not only difficult to achieve but has also shown to be inaccurate in as many as 60% of studies. Cost-effectiveness analysis allows the opportunity to compare different types of medical interventions and describes the benefit in terms of a ratio. The measure looks at incremental changes in both cost and benefits.

Therefore, CEA is useful when the primary goal of the study is to recognise the most cost-effective strategy from a group of options that are competing for the same resource.

Chapter 3 examines the demographic, economic and healthcare outlook for South Africa in order to gain a better understanding of the unique needs and challenges within the South African population and healthcare sector.

CHAPTER 3: DEMOGRAPHIC, ECONOMIC AND HEALTHCARE OUTLOOK FOR SOUTH AFRICA

3.1 INTRODUCTION

At a time when there is continued economic stagnation globally and, at the same time, upward pressure on costs, especially the costs associated with healthcare, it is important to understand the possible implications of introducing high tech medical therapies such as catheter ablation for atrial fibrillation into a society such as South Africa. With the European financial crisis and rising unemployment, many investors and multi-national companies are looking at the emerging markets for growth opportunities. Many of the emerging markets and particularly those in the old Eastern European block do not have the same degree of diversity and dichotomous disease profiles as are present in South Africa. These potential investors need to understand the uniqueness of South Africa where a population of 52 million cannot be expected to offer the same business opportunities as a European country with a population of a similar size. The dichotomies within South Africa lie within the social sector, income inequality, life expectancy at birth and, in particular, the difference in healthcare provision by the public and private healthcare sectors.

This chapter focusses on the issues mentioned above by describing the demographic, economic and healthcare structure of South Africa. The following topics will be discussed in more detail:

- The demographics of South Africa, including life expectancy, infant mortality and death rates. These are described in terms of South Africa but are also compared with other countries around the globe
- The economy at a macro-economic level
- Healthcare in South Africa; and
- The proposed National Health Insurance Scheme.

3.2 THE SOUTH AFRICAN CONTEXT

South Africa is a middle-income, emerging market that has an abundant supply of natural resources, amongst others, gold, platinum and iron-ore (Bassett, 2010). South Africa is considered the economic powerhouse of Africa and, more particularly, of sub-Saharan Africa, with a GNI that is ranked 24th (at PPP) as seen in Table 3.1 (Central Intelligence Agency, 2012; Roux, 2011).

Table 3.1: The economies of selected African countries and South Africa's provinces, 2009

Country	% of total PPP (GNI) USD b	% of total African population, million	PPP GNI per capita USD
South Africa	17.6	4.9	10 050
• **Gauteng**	5.8	0.98	16 538
• **KZN**	2.9	0.99	8 189
• **W Cape**	2.5	0.52	13 632
Egypt	16.8	8.2	5 680
Nigeria	11.4	15.4	2 070
Algeria	10.1	3.5	8 110
Angola	3.4	1.8	5 190
Kenya	2.2	4.0	1 570
Botswana	0.89	0.2	12 840
Mozambique	0.72	2.3	880
Namibia	0.49	0.2	6 350
Swaziland	0.2	0.1	850
Lesotho	0.13	0.2	1 800
Zimbabwe	-	1.3	360

Notes: GNI (gross national income) = total domestic and foreign value added by residents. PPP=purchasing power parity.

Source: Adapted from Roux, 2011.

South Africa accounts for 17.6% of the total African economy and almost 30% of the sub-Saharan economy (Roux, 2011). The financial, legal, communications, energy and transport systems within South Africa are well developed (SA INFO, 2009).

South Africa has a modern infrastructure which is able to support efficient distribution of goods to major urban centres throughout the southern African region and a stock exchange that is the 18th largest in the world. The country was ranked 45th out of 133 countries in 2009, 54th in the period 2009/2010 and 52nd in the Global Competitiveness Index of 2012-2013 (World Economic Forum, 2010; Schwab, 2012: 13).

South Africa benefited from macroeconomic stability and the global commodities boom after 2004, but the country has also been affected by the global recession of 2009 (World Economic Forum (WEF), 2010-2011). Real disposable income per capita showed a decline from 1980 to 1993 after which there

was growth of 30% by 2009 (Roux, 2011). Unemployment remains a problem at around 25% (Stats Online, 2012) and minimal, if any, progress has been made in reducing poverty or narrowing the income gaps since 1994 (Basset, 2010; Henry, 2003: 105; Central Intelligence Agency, 2010; Roux, 2011).

At the end of 2007, South Africa began to experience an electricity crisis because the state power supplier Eskom suffered supply problems as a result of its old and outdated power plants, thus necessitating sporadic power cuts ("load-shedding") in many of the major cities. These cuts affected both businesses and residents alike and have had an impact on the confidence level in South Africa, raising international concerns about the country's ability to host major international events such as the FIFA World Cup of 2010 as well as concern from foreign investors. While daunting economic problems and, in particular, poverty, unemployment and lack of economic empowerment among the disadvantaged groups remain from the apartheid era, the new government, now in power for 18 years, has made some improvement to these situations. However, the country is still influenced by high crime rates, corruption and a high prevalence of the Human Immunodeficiency Virus (HIV/AIDS) (Henry, 2003: 127). Nonetheless, the South African economic policy stance is fiscally and monetarily conservative and pragmatic, with a strong focus on controlling inflation through inflation targeting, maintaining a low level of government debt, and using state-owned enterprises to deliver basic services to low-income areas as a means to increase job growth and household income (Central Intelligence Agency, 2010).

3.3 DEMOGRAPHICS

The 2011 mid-year estimate of the total population of South Africa was 50.3 million, the 26th largest population in the world and 5th largest in Africa *(*Central Intelligence Agency, 2012*)*. The largest provincial population is found in Gauteng, which has approximately 11.3 million people or 22.4% of the population. KwaZulu-Natal (KZN) has the second largest population of 10.8 million or 21.4% of the total. Of those younger than 15 years, approximately 23% (3.66 million) live in KwaZulu-Natal and 19.4% (3.07 million) live in Gauteng (StatsSA, 2012: 3).

Migration has become important in transforming the age structure and distribution of the provincial populations and the estimated loss of people from the Eastern Cape through migration for the period of 2006 to 2011 was almost 390 000 people with a further 200 000 people migrating from Limpopo province. During the same period the estimated net inflow of migrants to Gauteng and Western Cape was approximately 450 000 and 140 000 respectively. This raises the challenge in the provinces for job creations and also places added burden on the social structures and healthcare system.

As seen in Table 3.2, data from the general household survey, released in May 2012 reveals that the total population growth for South Africa for the period 2002 to 2011 was 11% with Eastern Cape

growing at only 2% over the period and Limpopo province at 5%. By contrast, the population of the Western Cape and Gauteng grew by some 20% in the same period.

Table 3.2: Number of individuals per province, 2002-2011 (thousands)

Province	2002	2005	2008	2011	Total Change 2002 to 2011
Western Cape	4 646	4 964	5 258	5 656	20%
Eastern Cape	6 521	6 574	6 633	6 657	2%
Northern Cape	1 088	1 115	1 140	1 159	7%
Free State	2 777	2 826	2 884	2 932	6%
KZN	9 683	10 025	10 348	10 632	10%
NW province	3 227	3 325	3 421	3 500	8%
Gauteng	9 189	9 766	10 348	10 950	19%
Mpumalanga	3 391	3 493	3 576	3 665	8%
Limpopo	5 011	5 111	5 230	5 264	5%
Total	**45 533**	**47 199**	**48 794**	**50 324**	**11%**

Source: StatsSA, 2012:14.

Almost two-thirds (63.8%) of the total South Africa population is between the age of 15 and 64 years, 31.4% are younger than 15 years and only 4.8% of the populations are over 65 years. This age composition profile differs considerably from developed nations like those of the EU where only 15.7% of the population is estimated to be less than 14-years old, while17.1% are above the age of 64. In the USA one-fifth of the population is younger than 14-years old, 67.1% between 15-64 years and 12.7% are over 65 years. These figures are important as, on average, older members of society tend to consume more healthcare resources than in younger ones (Table 3.3).

Table 3.3: World population by age group as % of total

Country	Age 1-14 years	Age 15-64 years	Age 65 years over	Median
European Union	15.7	67.2	17.1	+-41 years
Japan	13.7	64.7	21.6	43.8 years
Kenya	45.2	55.2	2.6	18.6 years
Mozambique	44.5	52.7	2.8	17.4 years
Namibia	36.7	59.5	3.8	20.7 years
South Africa	29.2	65.5	5.3	24.7 years
Swaziland	39.9	56.5	3.6	18.7 years
United Kingdom	16.9	67.1	16	39.9 years
United States	20.1	67.1	12.7	36.7 years

Source: Central Intelligence Agency, 2010.

In South Africa the female cohort makes up 52.4% of the total population and has a life expectancy at birth of 57.2 years (StatsSA, 2010:3). While being higher than in many of the neighbouring countries, South Africa's life expectancy is substantially lower than in the EU, USA and even the Far East (UK 82, USA, 79 and Japan 83, respectively) (WHO, 2012). The infant mortality rate is estimated at 45.7 per 1000 live births and the prevalence of HIV infections in South Africa is estimated between 10% and 11% where 17% of the age group between 15 to 49 years is HIV positive. This means that approximately 5.2 million South Africans are living with HIV (StatsSA, 2010:3). The estimated number of new HIV infections in 2009 was 413 000, of which 59 000 were children.

The birth rate in South Africa is 19.32 births/1000 of the population, when compared with the world average of 19.14 (Central Intelligence Agency, 2012). The median age for South Africa is 24.7 years (Central Intelligence Agency, 2010). The higher than average for sub-Saharan Africa, but significantly lower in the developed world (see Table 3.3).

The importance of the median age for South African from a healthcare perspective is highlighted to a degree in Table 3.4, which explores the death rates. It is significant that South Africa not only has an overall younger population when compared with many developed nations but also has a far higher death rate per 1000 of the population and is now ranked as having the fifth highest death rate in the world out of 222 countries. The healthcare challenges in South Africa are thus very different from those in developed nations.

Table 3.4: Number of deaths per 1 000 of the population

Country	Death rate per 1000	Rank	Country	Death rate per 1000	Rank
Angola	23.74	**1**	Zimbabwe	14.90	**15**
Zambia	21.15	**2**	EU	10.39	**60**
Mozambique	19.83	**3**	UK	10.0	**62**
Afghanistan	17.65	**4**	Botswana	9.02	**78**
South Africa	16.99	**5**	USA	8.38	**99**
Nigeria	16.31	**6**	World Average	8.37	**98**

Note: Total of 222 countries in ranking

Source: Central Intelligence Agency, 2010.

As seen in Table 3.5, of the 20 countries of the world with the highest infant mortality rate, 19 are in Africa, with Angola being the highest with 182 deaths/1000 live births. This is four times the world average and 30 times higher than in the USA and EU. South Africa is ranked at 61st place with an average at 43.78 deaths per 1000 live births.

Table 3.5: The 20 countries with the highest infant mortality rates measured as deaths per 1 000 live births

Rank	Country	Infant mortality rate*	Rank	Country	Infant mortality rate*
1	Angola	182.31	**11**	Chad	100.36
2	Sierra Leone	156.48	**12**	Djibouti	99.13
3	Afghanistan	154.67	**13**	Nigeria	95.74
4	Liberia	143.89	**14**	Malawi	90.55
5	Niger	115.42	**15**	Sudan	86.98
6	Somalia	110.97	**16**	Burkina Faso	86.02
7	Mozambique	107.84	**17**	Equatorial Guinea	83.75
8	Mali	103.83	**18**	Rwanda	83.42
9	Guinea-Bissau	101.64	**19**	DRC	83.11
10	Zambia	100.96	**20**	Ethiopia	82.64

*Note: *(deaths/1 000 live births) rankings out of 224 countries.*

Source: Central Intelligence Agency, 2008b.

The infant mortality rate for the world is ranked 59th, with a mortality rate of 44.13 deaths per 1000 live births. While the South African average is better than the world average, it remains seven times higher than the EU and USA and 18 times higher than Japan and Singapore, as illustrated in Table 3.6.

Table 3.6: Infant mortality rates of South Africa, some of its neighbours, the world average and the EU, USA and Far East

Rank	Country	Infant mortality rate*
59	World	44.13
61	South Africa	43.78
62	Bolivia	43.41
143	Botswana	11.79
180	European Union	6.38
181	United States	6.30
63	Japan	2.79

*Note: *(deaths/1 000 live births) ranked out of 224 countries.*

Source: Central Intelligence Agency, 2008a.

3.3.1 Population pyramids and their importance in healthcare related costs

A population pyramid is a graphical illustration that shows the distribution of various age groups in a population. Population pyramids can offer information about the extent of development of a specific population as it is broken down by age and sex. In general terms a young population is one where more than 30% of the population is younger than 14 years of age and less than 6% is older than 75. On the other hand, an "aging population" is often seen in a developed country with adequate health services, and where less than 30% of the population is younger than 14 years of age and more than 6% of the population is older than 75 years.

It stands to reason that not all countries' population pyramids will look the same. Based on the fertility and mortality rates of countries, four types have been identified, as demonstrated in Figure 3.1.

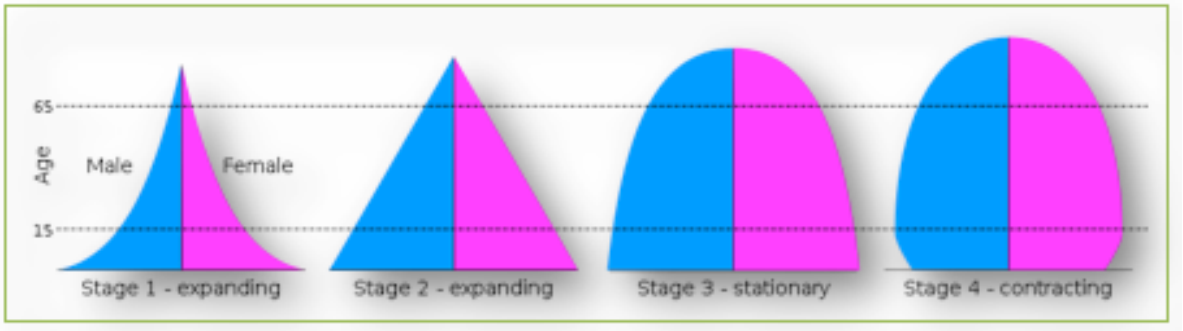


Figure 3.1: Four different types of population pyramids

Source: Allaway, 2013.

As seen in Stages 1 and 2, an expanding population pyramid demonstrates a broad base which tapers to the top, illustrating true pyramid shape. This is indicative of a high birth rate, rapid population growth,

a large proportion of children, and a lower proportion of older people or a high death rate; and is typical of developing countries such as South Africa.

Stage 3 illustrates an example of a stationary pyramid, which may also be referred to as a constrictive pyramid. Finally Stage 4 shows declining and low numbers of young people as the fertility or birth rate drops and the number of older people increases. These populations may be referred to as "greying populations" and are typically found in countries with good healthcare systems, such as Australia and Canada.

3.3.2 Life expectancy

Life expectancy is a statistical measure of the average number of complete years of a person's life at a given point and is based on a particular mortality experience. It is usually measured and calculated separately for both men and women. Women often live longer than men. In some instances, life expectancy at age 5 is used where infant mortality is high in order to negate the effect on the calculation of these early childhood deaths (Sullivan & Sheffrin, 2003).

The *Central Intelligence Agency World Factbook 2008* estimates the life expectancy for the South African population at 49.2 years, while StatsSA's estimates for 2009 are given as 53.5 years for males and 57.2 years for females. Globally, South Africa is ranked 215th, with many of the higher ranked countries being developing nations. Figure 3.2 illustrates the global median age as described by the Central Intelligence Agency (2009).

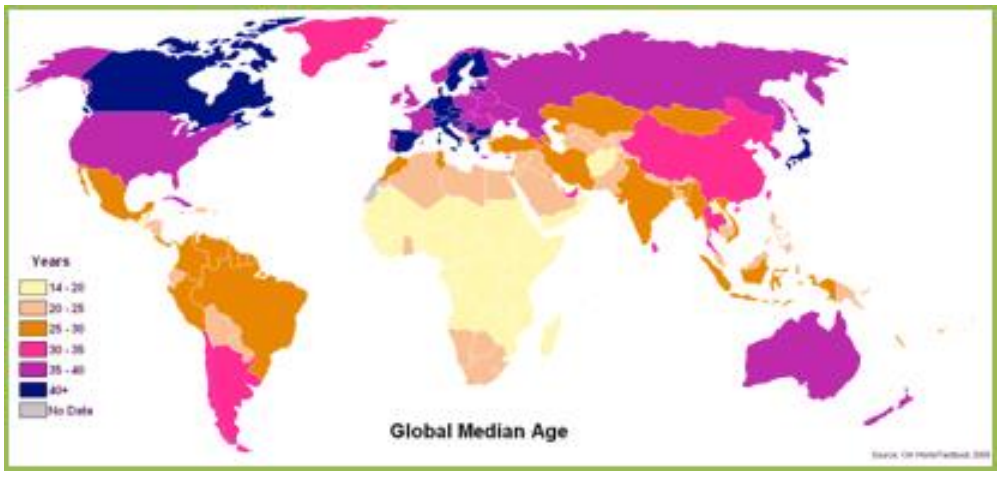


Figure 3.2: Global median range for 2009

Source: Central Intelligence Agency, 2009.

Table 3.7 illustrates average life expectancy at birth through various stages in history. Life expectancy has changed significantly over time: for instance, as recently as the early 20th century, the average life span was not much more than 40 years. The World Bank (2010a, as cited by the South African Institute of Race Relations (SAIRR) Dimant *et al*., 2009: 62) indicate that for South Africa the life expectancy at

birth from 1990 to 2007 declined by almost 20%. Currently life expectancy for the world is estimated at 67 years, although the figures range from 38 years in Angola to 90 years in Monaco.

Table 3.7: Life expectancy variation over time

Historical era	Average life span in years at birth
Upper Palaeolithic	33
Neolithic	20
Bronze Age	35+
Classical Greece	28
Classical Rome	28
Pre- Columbian North America	25–30
Medieval Islamic Caliphate	35+
Medieval Britain	30
Early modern Britain	40+
Early 20th century	30-45
Current world average	67.2

Sources: Adapted from Kaplan et al., 2000; Caspari & Lee, 2004; Galor & Omer, 2007; Conrad, 2006; Britannica Online Encyclopedia, 2010.; Lancaster, 2010.

What makes the time we live in different is that an ever-increasing number of people are now octogenarians. Figure 3.3 illustrates an example of the expected number of people in the UK over the age of 65 years by 2025. These numbers are projected to continue increasing beyond 2025.

The typical population of developed nations as demonstrated by the population pyramid of the UK for 2000 differs significantly from the population pyramid for South Africa for the same period (see Figures 3.3 and 3.4) but when examining the population pyramids of South Africa for 2025 and 2050 in Figure 3.5, changes should be noted with regard to the growing aged population. This is significant because of the impact on resources, in particular, healthcare resources.

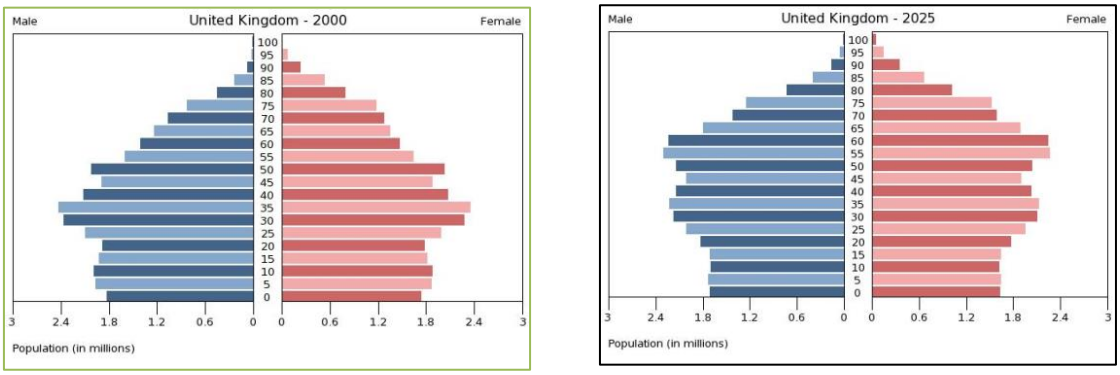


Figure 3.3: Population pyramid for the United Kingdom for 2000 and 2025

Source: Central Intelligence Agency, 2008a.

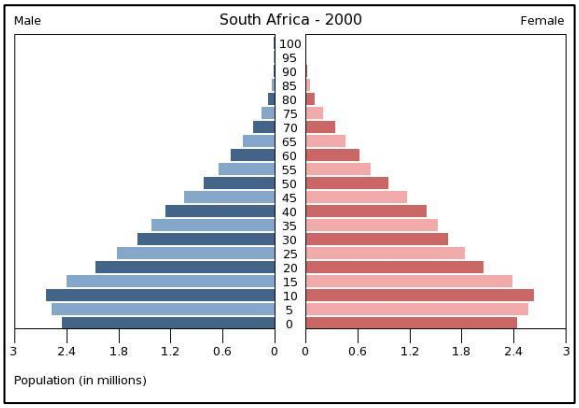


Figure 3.4: Population pyramid for South Africa, 2000 (typical of an expanding population)

Source: Central Intelligence Agency, 2008a.

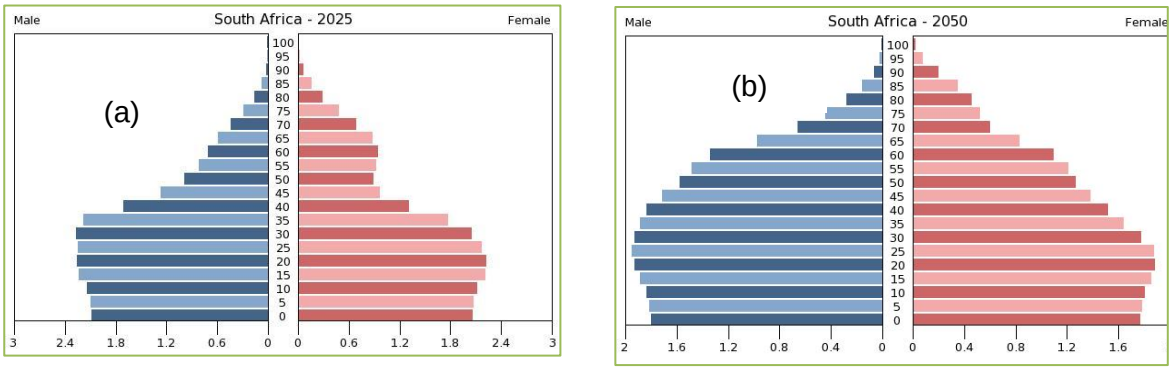


Figure 3.5: Population pyramid for South Africa, (a) 2025 and (b) 2050

Source: Central Intelligence Agency, 2008a.

In 1981 a new syndrome known as acquired immune deficiency syndrome (AIDS) was recognized by the USA for the first time. This new disease was at first thought to only affect homosexual men. In 1983 the virus responsible for AIDS was identified as the human immunodeficiency virus (HIV).

The first AIDS-related death in South Africa was recorded in 1985 and in the early 1990s, AIDS amongst heterosexuals (Type II) had overtaken AIDS amongst homosexual men. (Type I) (McLeod, 2009e: 2). Today one of the biggest issues facing the South African government and health department is the prevalence of HIV. McLeod cites the *Mail and Guardian* of 1999 which stated that many South Africans still did not believe that AIDS existed. This denial, both by the populations at large and the government, together with an impasse on the issue of anti-retroviral therapy, saw a growth of around 750% in HIV infections from an estimated 553 000 in 1994 to 4.7 million in 2003.

Although the estimated prevalence rate for HIV in South Africa ranges from 10% (StatsSA, 2012) to 18.1% (Central Intelligence Agency, 2009) both figures are alarmingly high, and the South African prevalence is ranked 4th highest in the world, after Swaziland, Botswana and Lesotho. South Africa, with an estimated 5 million people living with HIV, accounts for 15% of the world's total HIV infected

population and is home to the largest number of infected people. This figure is more than double the 2nd ranked country, Nigeria (McLeod, 2009a: 1).

While the number of HIV infections continue to grow, so did the debate about providing anti-retroviral therapy to infected patients. In 2003 the South African government finally approved the plan to provide anti-retroviral treatment to infected patients. The plan was implemented in 2004 and South Africa is now considered to have the largest ARV programme in the world (McLeod, 2009e: 3).

From January 2005 it was mandated that all medical aid schemes provide the treatment for HIV as a prescribed minimum benefit (PMB). This is an example of where the private and public sector provide the same level of care. (McLeod, 2009e: 10).

The population pyramids for South Africa by age and race for 2008 are shown in Figure 3.6 to 3.9. It is important to note that the most striking feature of these pyramids is the impact that HIV/AIDS has had on black South Africans. The significant decrease in the number of black South Africans between the ages of 35 to 45 years can be explained solely by the high prevalence of HIV/AIDs in this group (Dimant *et al.,* 2009: 11).

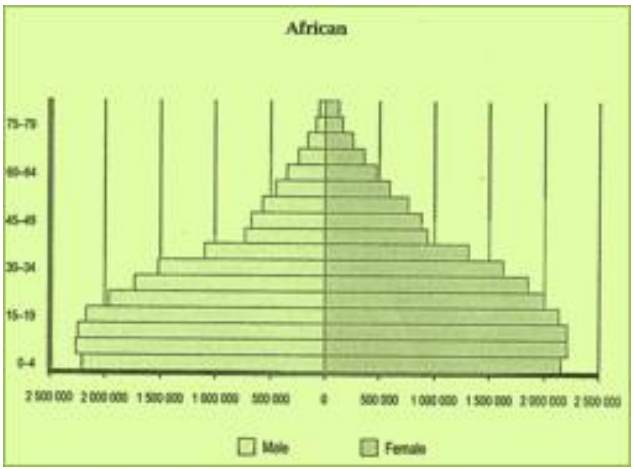


Figure 3.6: Population pyramid of black South Africans, 2008

Source: South African Survey 2008/2009 (Dimant *et al.,* 2009:12).

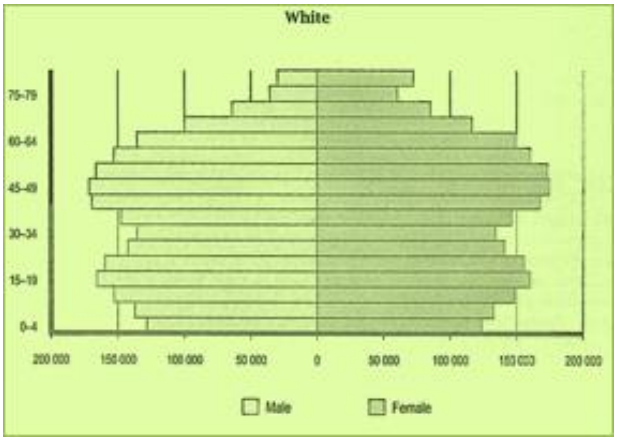


Figure 3.7: Population pyramid of White South Africans, 2008

Source: South African Survey 2008/2009 (Dimant et al., 2009: 13).

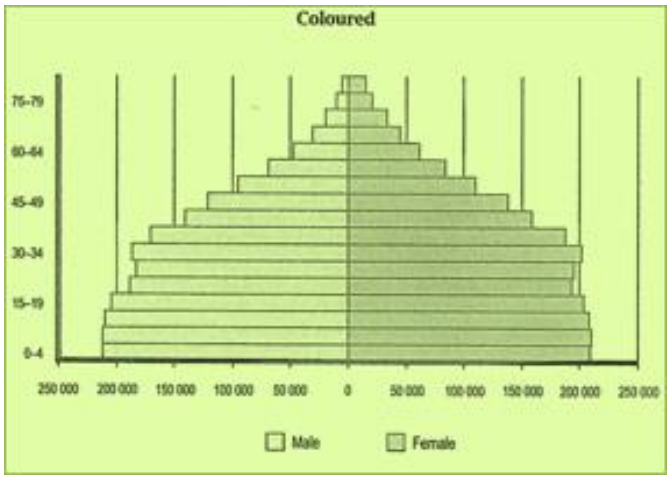


Figure 3.8: Population pyramid of Coloured South Africans, 2008

Source: South African Survey 2008/2009 (Dimant et al., 2009: 12).

It should be noted that there is also a marked decrease in the white South Africa population, aged 25-34 years old. This can be attributed to the high rate of emigration of the white working age population. This emigration trend has attributed to the critical shortage of trained young professional and has become known as the “brain drain.” When compared to all the other race groups it is note that there are far greater numbers of elderly people in the white population. This is as result of the fact that traditionally the white populations have had better access to private healthcare, experience less poverty and generally has a better quality of life. In 2008, of the estimated 308 900 octogenarians, 33% were white. This also points to the fact that needs within the healthcare sector have and are changing.

Another trend of importance is found in the coloured population where there is a high mortality rate in the age group 15 to 24. SAIRR suggests that this is due to the increased incidence of violence and substance abuse (both alcohol and drugs) in the coloured population.

As seen in Figure 3.9, the population pyramid for South African Indians is more representative of a developed economy and is similar to that of white South Africans.

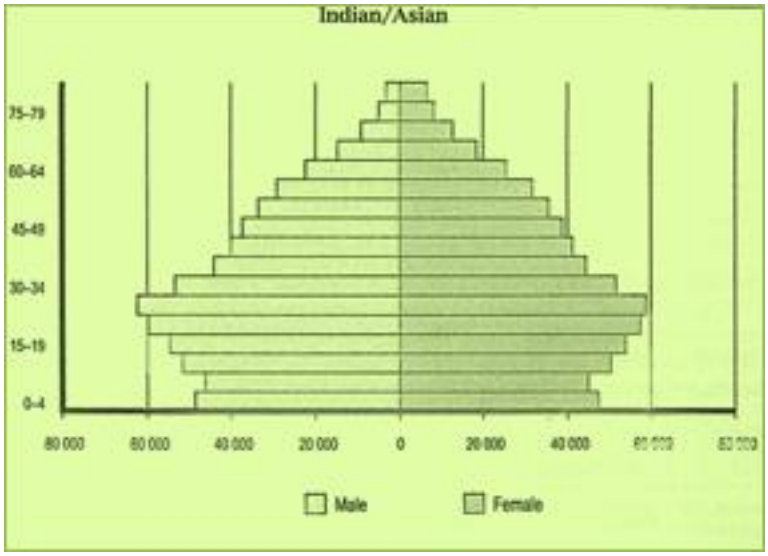


Figure 3.9: Population pyramid of Indian/Asian South Africans, 2008

Source: South African Survey 2008/2009 (Dimant et al., 2009).

The economic impact of HIV/AIDS is of great importance for a number of reasons, not least of which the fact that most of the people infected with HIV are between 15 and 49 years. Patients with HIV/AIDS may also be too ill or weak to work, they are at a greater risk of opportunistic diseases like TB, and productivity levels may be lower than age matched populations in countries with a low prevalence of HIV/AIDS. There is a high mortality rate among these patients, which adds to the economic burden through loss of skills and costs associated with dying. Many thousands of children are left orphaned by AIDS, which imposes a further economic burden on the country through the need for welfare grants and heightens the problem associated with child-headed households or households being cared for by grandparents. (Dimant *et al.* 2009: 11).

From a medical point of view, a significant proportion of the budget for healthcare is allocated to treating HIV/AIDS with ARVs or to costs related to the treatment of opportunistic diseases associated with HIV/AIDS even at a primary level. While the epidemic cannot be ignored, a significant volume of healthcare resources is funnels into education, prevention and treatment of the disease. This raises questions about the more limited focus on the management of cardiovascular risk with 32 million heart attacks and strokes annually in what the WHO terms “only the tip of the iceberg” (WHO, 2002: 14). While research about the risks of cardiovascular disease in South Africa occurs, the focus may not be sufficient.

3.3.3 Death rates

Data from the Actuarial Society of South Africa (ASSA) as quoted by SAIRR suggests that between 1985 and 2008 the death rate per 1000 of the population in South Africa doubled while the population

grew by 50%. While KwaZulu-Natal (KZN) has the second largest population, in 2008 it recorded the highest number of deaths (see Table 3.8). This was 23% higher than Gauteng which has the largest population in the country. The Free State and North West provinces with only 5.9% and 7% of the population respectively recorded death rates of 6.8% and 8.3% in 2008. As pointed out above, many of these deaths are HIV/AIDS related.

Table 3.8: The percentage of the population in each province and the number of deaths in each province as well as the percentage of deaths per province

Province	% of population by province	Number of death in 2008 by province	% of deaths by province for 2008
Eastern Cape	13.5	110 343	14
Free State	5.9	53796	6.8
Gauteng	21.5	162 796	20.7
KZN	20.8	200 476	25.5
Limpopo	10.8	65 295	8.3
Mpumalanga	7.4	59 117	7.5
North West	7	65 024	8.3
Northern Cape	2.3	12 261	1.6
Western Cape	10.8	57 762	7.3
Total	**100**	**786 870**	**100**

Source: Dimant et al., 2009: 18 & 55.

The Western Cape attracts a lot of retirees, meaning that on average it has a slightly older population and that the expected death rate should be higher than average. With 11% of the total population living in the Western Cape the number of recorded deaths was only 7.3% of all deaths. This may be attributed to the fact that the Western Cape has the lowest HIV prevalence and also may be as a result that many of the population of the Western Cape are members of medical aid schemes, suggesting that they possibly have access to private healthcare and are not dependent on public healthcare.

The number of AIDS-related deaths was recorded at 0 per 1000 of the population in 1985 but had reached 375 per 1000 of the population in 2008. As discussed above, HIV/AIDS has made a significant impact on the death rates in South Africa. Table 3.9 illustrates the changes in AIDS-related deaths by province between 2000 and 2010, where in a ten-year period the number of AIDS-related deaths grew by 167%.

Table 3.9: AIDS-related deaths by province for 2000, 2008 and 2010

Province	2000	2008	2010	Change 2000 -2010
Eastern Cape	15 566	44 942	49 811	220%
Free State	11 385	28 012	28 537	151%
Gauteng	33 770	90 389	92 851	175%
KZN	52 167	115 483	116 720	124%
Limpopo	9 996	26 715	29 290	193%
Mpumalanga	16 239	33 340	33 439	105%
North West	12 748	34 561	36 343	185%
Northern Cape	1 135	4 039	4 670	311%
Western Cape	4 114	14 794	17 623	328%
South Africa	**147 525**	**374 655**	**393 777**	**167%**

Source: Dimant et al., 2009: 64.

The Western Cape, which has the lowest prevalence of HIV/AIDS, has shown the fastest growth in HIV/AIDS-related deaths, from only 4114 in 2000 to an expected 17623 in 2010. This represents a growth of 328%. KZN was expected to record 116720 HIV/AIDS-related deaths in 2010, a growth of 124% since 2000. It is however important to note that the rate of growth slowed down significantly from 2008 to 2010 when compared to the previous eight years. The rate of infection seems to have plateaued in all provinces since 2008. This may be attribute to the successful implementation of the ARV programme (see Figure 3.10).

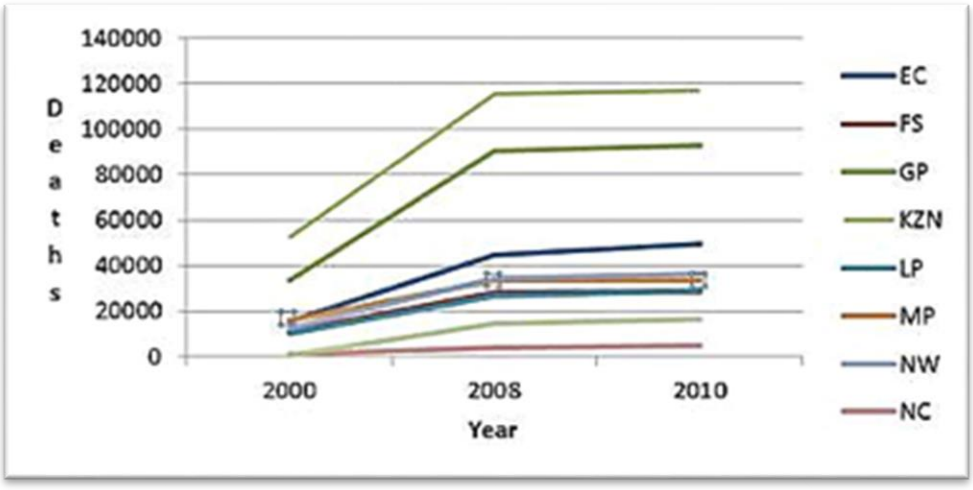


Figure 3.10: AIDS-related deaths in South Africa in 2000, 2008 and 2010

Source: Dimant et al., 2009: 64.

Finally, the Human Development Index (HDI), which is a worldwide index of a combination of measures including standard of living as measured by GDP per capita at PPP in US$, life expectancy at birth and educational attainment and literacy is used to measure standard human development over time. The HDI for South Africa showed an improvement between 1980 and 1995 with the trend line was ahead of the HDI median development, the world measure and that of Sub-Saharan Africa.

However, while this improvement continued, *albeit* slowly, South Africa showed a sharp decline from 1995 to 2005. For the period 2005 to 2011 there was again a slight improvement in the HDI for South Africa. This is illustrated in Figure 3.11.

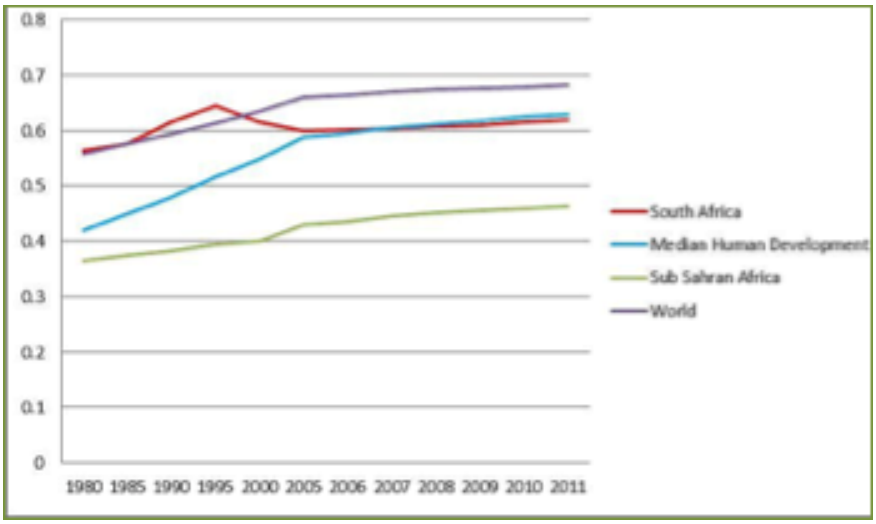


Figure 3.11: South Africa, sub-Saharan Africa and World Human Index, 1980-2011

Source: Dimant et al., 2009: 64.

3.4 THE ECONOMY

South Africa is an upper-middle income economy with the 24th largest GNI (as measured by PPP) and a GDP (at PPP) estimated at $578.6 billion in 2012 (Central Intelligence Agency, 2013). It is also considered the economic powerhouse of Africa. The economy of Gauteng is only exceeded in size by the following African countries namely Nigeria, Algeria and Egypt (Roux, 2011).

South Africa contributes close to 18% of the total African economy dominates the sub-Saharan economy by contributing 29% towards that entire economy. South Africa thus leads the continent in industrial output, mineral production. It is also responsible for generating a large proportion of Africa's electricity. In addition to this, the South African financial system are sophisticated and robust, and the banking regulations are ranked among the best in the world.

The primary sectors within the South African economy are mining and agriculture while the major components of the secondary sector are manufacturing, electricity, gas, water and construction, as seen in Table 3.10.

Table 3.10: Contribution by sector to the South African economy measured as percentage value added at 2005 constant prices

Sector	1960	1970	1980	1990	2000	2010
Primary	**27.5**	**23.0**	**15.9**	**14.0**	**11.6**	**8.6**
Agriculture, forestry and fishing	4.3	3.0	3.2	3.4	3.0	2.5
Mining and quarrying	23.2	20.0	12.7	10.6	8.6	6.1
Secondary	**18.0**	**24.0**	**28.4**	**25.4**	**24.0**	**22.8**
Manufacturing	12.9	17.1	20.5	20.3	19.2	17.1
Electricity	1.1	1.2	1.7	2.3	2.5	2.1
Construction	2.7	4.1	3.8	3.0	2.3	3.6
Tertiary	**51.6**	**51.0**	**54.7**	**60.5**	**64.5**	**68.5**
Wholesale and retail, catering & accommodation	10.0	11.8	12.1	13.0	13.9	13.3
Transport, storage, communication	5.0	5.2	6.6	6.6	8.9	10.2
Financial, insurance, real estate and business services	13.7	14.1	14.5	16.5	20.2	23.5
Community, social and personal services	22.9	19.0	20.8	25.1	23.1	21.5

Source: Roux, 2011.

While South Africa is an emerging economy, it is also a gateway to other African markets, playing an important role in supplying among other things energy, transport, communications, investment, and relief aid to the rest of the continent. The road and rail system allow for ground transportation deep into Africa (South Africa Info, 2010).

Between 1946 and 1974 the real GDP growth was on average 4.8% per annum, which realised a significant growth in the GDP per capita of 42% greater than the GDP per capita in 1960 and more than 85% growth in the GDP per capita since 1946. However, the political instability between 1974 and 1993 had a significant impact on the economy where the real growth in GDP was about 1.6% per annum at a time when the population was growing on average 2.2% per annum.

South Africa experienced 16 years of positive economic growth after the 1993/1994 period where the average annual growth was 3.6% compared to a population growth for the same period of about 1.7% per annum. The growth rate has declined since 2008, largely as a result of negative and constrained growth in the economies of the country's major trading partners, combined with various domestic structural constraints (see Figure 3.12).

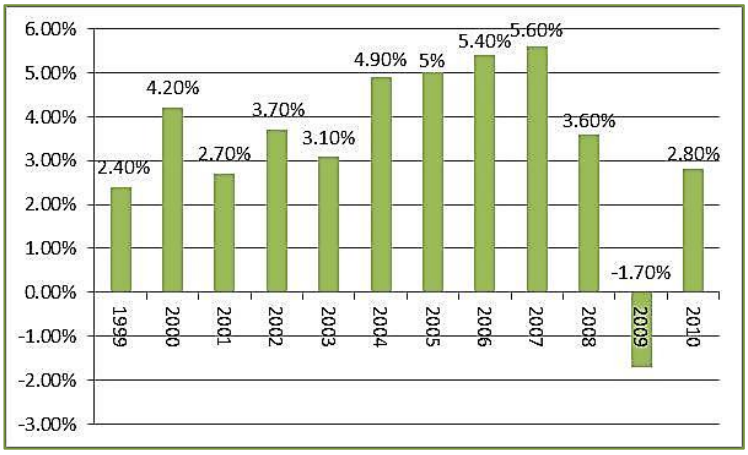


Figure 3.12: GDP growth in South Africa from 1999 to 2010

Sources: StatsSA, 2012; World Bank, 2012.

In 2008 the total imports into South Africa were worth ZAR721 billion, with Germany and China being the two largest contributors at ZAR81.4 billion and ZAR81.2 billion respectively. Exports on the other hand were worth ZAR637 billion in 2008. Japan received ZAR65.6 billion in exports and the second largest export market was the USA, accounting for ZAR65.3 billion (Dimant *et al.*, 2009: 78).

The GDP per capita was estimated at US$10 000 for South Africa in 2009, which was below the world average of US$10 500. This is however, the third highest in Africa with Gabon at US$13 900 and Botswana at US$13 100 per capita (Central Intelligence Agency, 2012). In ZAR terms the 2008 GDP per capita at constant 2000 price was ZAR25 897. At provincial level, Gauteng had the highest regional GDP per capita for 2008 at ZAR44 735 with the Western Cape second at ZAR38 214. KZN, with the second largest population, and as a percentage, the highest death rate, had at ZAR20 753, the 7th highest regional GDP per capita. Finally, Limpopo had the lowest GDP per capita of all provinces at only ZAR14 651.

Table 3.11 compares various industries' contribution to the GDP in 1951, 2008 and 2011.

Table 3.11: Breakdown of the value added by industry to the GDP in 1951, 2008 and 2011 as percentage of total GDP

Sector	1951	2008	2011
Agriculture	16.6	3.3	2.3
Construction	3.1	3.1	3.1
Electricity	1.7	2.3	1.9
Finance	9.3	21.7	21.1
Government	7.4	14.8	16.7
Manufacture	18.1	18.8	12.4
Mining	12.1	9.5	5.4
Personal services	8	5.7	5.5
Trade	13.2	12.7	12.2
Transport	9.3	8.1	9.1

Source: Dimant et al., 2009: 100.

3.4.1 Inflation

3.4.1.1 Consumer Price Index (CPI)

It is evident that for the 1990s as well as the first few years of the new century, inflation in both OECD countries and emerging markets was lower than in the 1980s (see Table 3.12).

Table 3.12: Consumer price inflation for selected countries, 1980-1990, 1990-2000, 2000-2008, mid-2009 and mid-2011

Country	Average annual inflation rate (%)				
	1980-1990	1990-2000	2000-2008	Mid- 2009	Mid-2011
OECD countries					
Australia	7.9	2.1	3.0	2.5	3.6
Canada	5.3	1.7	2.2	0.4	3.1
France	5.8	1.6	1.9	0.1	2.2
Germany	2.2	2.0	1.7	0	2.3
Japan	1.7	0.8	-0.1	-0.1	0.5
UK	5.8	2.9	3.0	2.3	4.5
USA	4.2	2.7	2.8	-0.7	3.8
Emerging markets					
China	n/a	8.6	2.2	-1.5	6.2
India	8.6	9.1	4.8	8.4	8.4
Malaysia	2.6	3.6	2.3	3.0	3.3
Korea Rep	4.9	5.1	3.1	2.7	5.3
Argentina	390.6	8.9	10.4	5.7	9.8
Brazil	371.1	199.5	7.3	5.5	7.2
Chile	20.6	8.9	3.2	4.5	3.2
Israel	101.7	9.7	1.7	3.1	3.4
South Africa	**14.8**	**9.7**	**4.3**	**8.4**	**5.3**
Poland	50.9	25.3	2.4	4.0	4.3
Russian Federation	n/a	99.1	12.7	13.1	8.2

Sources: World Bank, 2006; 2010c; The Economist, 2010: 109.

After recording an average inflation rate of 14% in the 1970s and 1980s, South Africa realized an average inflation rate below 10% between 1992 and 2007 (see Figure 3.13). It was during this time (23 February 2000) that the Minister of Finance announced in the Budget Speech that South Africa would adopt a policy of inflation targeting, with a target range of 3 to 6% (Henry, 2003: 114). Prior to the global financial crisis, inflation crept up to above 7% and in 2008 reached 11.5%, the highest average since 1992. Since 2009 there has again been a decrease in inflation, reaching 4.3% in 2010, and 5% in 2011 and close to 6% in 2012 (StatsSA, 2010, 2012).

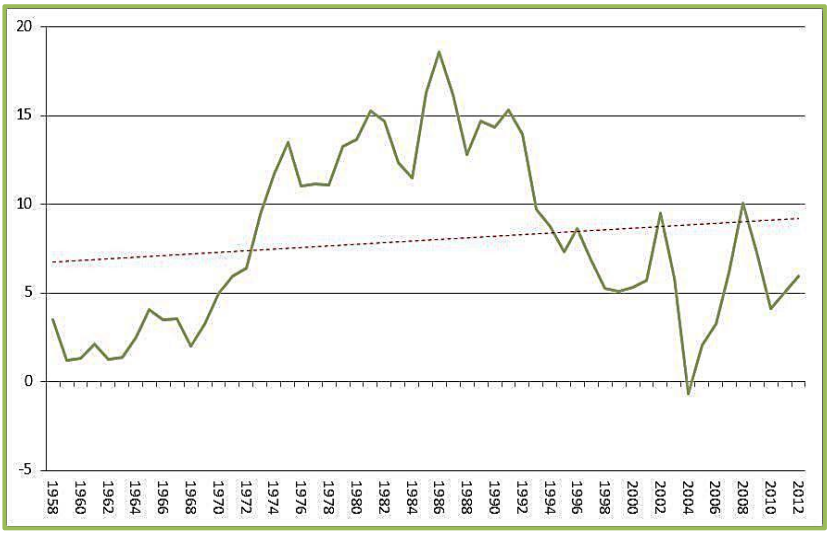


Figure 3.13: Average annual inflation in South Africa, 2000-2012 (%)

Source: StatsSA, 2012.

3.4.1.2 Medical inflation

Medical inflation refers to the annual increase in the prices of healthcare goods and services. It arises from a variety of sources. Figure 3.14 illustrates the increase in costs broken into four categories, two of which should be considered “outside” of the healthcare sector. These two components are general inflation or CPI (labelled “economy wide”), which includes goods and services that affect all sectors within an economy. The second component referred to as “population” refers to the growth of the population as well as the growth of the ageing population, which some may argue is as a direct result of improvements in healthcare services (Boonin, 2009).

The third component is an increase in demand for healthcare services, which refers to an increased utilisation per capita, which in Figure 3.14 is referred to as intensity. Intensity or increased utilisation refers to the fact that in 2005, for instance, a diagnosis or hospitalisation would likely have involved more tests, procedures, and supplies compared to what would have been requested or required for the same condition in 1995.

The fourth component driving medical inflation is the consequence of the higher cost of goods from suppliers, referred to in Figure 3.14 as “medical”. This is often interpreted as high cost and high profit by companies, but it is often the result of new technologies introduced into the system. These new technologies often contribute significantly to the success of the treatment but unlike the rest of the economy, for example laptop computers or refrigerators, these newer technologies in healthcare are usually at higher costs. Other factors which may contribute to inflation of health care costs can be the outcomes of inefficiencies in various parts of the system. These include inefficiencies in consumption (for instance, when services are inappropriately utilised). Inefficiencies may exist in the allocation of

services, for example, when health services could be delivered in a way which is less costly but without compromising on quality (Freudenheim, 2009; Boonin, 2009).

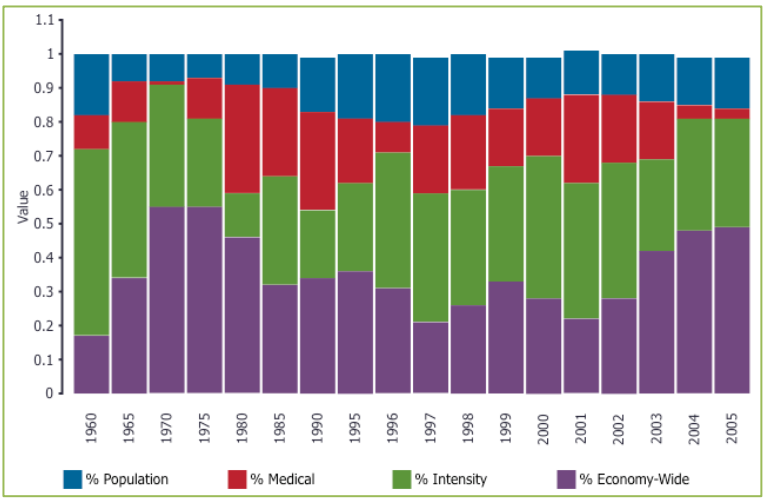


Figure 3.14: The drivers of medical inflation in the USA from 1960-2005

Source: Boonin, 2009.

As mentioned earlier, expenditure on healthcare as a percentage of GDP between 1960 and 2008 has grown rapidly, with the Unites States of America showing over 200% growth for this period, (Zweifel & Breyer, 1997; OECD, 2010). In the ten-year period from August 2000 to August 2010 medical costs in the USA increased by 48%, while the overall CPI for the same period increased 26% (Commins, 2010). This trend is not unique to the USA as revealed in a global survey performed by Towers Watson (2011), which showed that medical costs have risen rapidly since 2006 in nearly all the markets surveyed, with many of the countries experiencing double-digit growth trends. In most countries medical inflation exceeded the rate of general inflation.

The key findings of the survey were as follows:

In 95% of the countries included in the survey, the medical trends (inflation) exceeded the rate of general inflation.

The rate of growth of medical trend (inflation) showed signs of slowing in the emerging markets, whereas some developed markets continued to record higher rates compared to the previous five years (2006-2011).

Almost three-quarters (72%) of total survey respondents expected higher medical costs over the next five-year period (2012-2017).

The average gross medical inflation for 2009 was 10.2% compared with an average of 6.9% for general inflation. Latin America and Middle East/Africa recorded the highest rates in the regions. This was at least two to three times the rate of general inflation.

In 2011, the average medical inflation rate globally was expected to be 10.5%, with medical inflation being on average 2.5% higher in emerging economies than in advanced economies. The survey noted that respondents from Europe expected a single digit growth of 9.1% for 2011 while Latin America expected a growth in medical inflation of 13.7% and North America of close to 11.6% (Towers Watson, 2011). Since significant growth in demand for medical products in the Middle East and Africa is expected as some of these countries move towards mandated healthcare coverage, it is not unexpected to see high medical inflation. The same situation was expected in South Africa, with the return of double-digit medical inflation rates forecast.

Figure 3.15 demonstrates the annual medical inflation rate and compares it to the headline CPI inflation rate between 2000 and 2007 for South Africa. Medical inflation slowed down over this period and in 2007 was equal to or below that of the overall inflation rate.

Figure 3.15: Headline CPI *vs* medical inflation in South Africa from 2000 to 2007

Source: Twine, 2008.

Table 3.13 illustrates the global medical trend in inflation for selected countries and compares it with the net medical trend (net of general inflation) for the same countries for the period 2006, 2009, 2010 and 2011. Medical inflation in South Africa is of great concern to the government and medical aid schemes; however, it should be noted that for the years 2006, 2009, 2010 and 2011, the medical inflation rate in South Africa was lower than that of the other emerging markets surveyed and tabulated, and also lower than “all regions” in 2006 and again in 2011.

Table 3.13: Global average medical trends from 2006 to 2011 (percentage)

Region	Global medical trend				Net medical trend (net of general inflation)			
	2006	2009	2010	2011	2006	2009	2010	2011
All regions	10.6	10.2	9.8	10.5	6.8	6.9	5.7	6.8
Advanced economies	6.6	9.1	8.9	9.3	4.7	8.8	7.2	7.7
Emerging economies	13.9	11.3	10.7	11.8	8.5	5.0	4.2	5.8
China	15.2	10.1	8.9	9.4	13.7	10.8	5.3	6.7
India	22.0	12.0	13.2	12.2	15.8	1.1	0.0	5.7
France	5.6	6.5	6.1	8.4	3.7	6.4	4.5	6.8
Italy	5.5	8.3	8.3	9.5	3.3	7.5	6.6	7.8
UK	6.0	9.3	8.8	9.5	3.7	7.1	5.7	7.0
Saudi Arabia	13.3	12.0	10.0	10.8	11.0	6.9	4.5	5.5
Egypt	10.0	13.3	10.8	11.3	5.8	-3	-1	1.3
South Africa	7.4	12.5	10.4	9.3	2.7	5.4	4.8	3.4
Canada	12.3	12.5	12.5	13.3	10.3	12.2	10.7	11.3
USA	8.3	9.1	10.1	9.9	5.1	9.4	8.7	8.9
Brazil	9.2	10.4	9.8	11.0	5.0	5.5	4.8	6.4
Chile	5.8	13.9	13.8	18.3	2.4	12.3	12.1	15.3
Venezuela	31.3	20.0	21.7	25	17.6	-7.1	-7.5	-7.2

Source: Towers Watson, 2011: 3.

3.4.2 Inequality

Among the countries that have been assessed globally, the Gini coefficients for income ranges from the highest at 0.7 in Namibia to the lowest (approximately 0.25) in Denmark. The Gini coefficient for South Africa for 2005 was estimated at 0.65, highlighting the vast income inequalities in the country (see Figure 3.16).

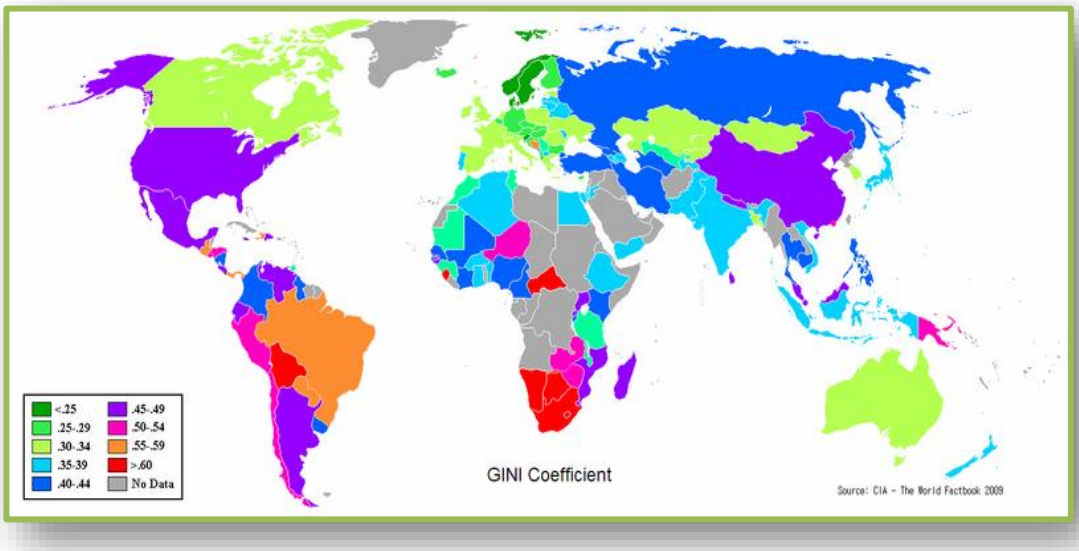


Figure 3.16: GINI coefficients, World Central Intelligence Agency Report

Source: Central Intelligence Agency, 2009.

Available data from the World Bank on the Gini index for South Africa is limited to 5 measurements as seen in Table 3.14. Between 1993, (one year prior to the first democratic elections in South Africa) and 2009 the index rose from 0.59 to 0.63.

Table 3.14: GINI Index for South Africa

South Africa					
Year	**1993**	**1995**	**2000**	**2006**	**2009**
Index	0.59	0.57	0.58	0.67	0.63

Source: World Bank, 2009

In South Africa the amassed income of the top 10% of earners is 90 times greater than the amassed income of the bottom 10% of earners. In 2010 more than 80% of all Black/African households had a monthly expenditure of less than ZAR2500 per month, compared with the more than 84% of white households who spent more than ZAR2500 per month.

In 2009 approximately 4.6 million households or 25% of the population did not have access to either sanitation or electricity (see Table 3.15), and the country's Human Development Index had whittled away by more than 30% as a result of inequality in particular education, income and healthcare (Roux, 2011).

Table 3.15: Basic services in South Africa

	1996	2001	2007	2008
Number of households (millions)	9.1	11.2	12.5	13.5
% of households in formal dwellings	64.0	68.5	70.5	73.5
% of households with access to water infrastructure	68.5	86.8	95	96.5
% of households with access to sanitation	54.1	68.3	72.0	73.0
% of households with access to electricity in formal dwellings	54.1	69.0	72.0	73.0

Source: The Presidency, 2011.

3.4.3 Poverty in South Africa

The definition of poverty and the poverty line may vary significantly based on where in the world the measurement is made. A common method used to measure poverty is based on income or consumption levels. Someone is thought to be poor if their consumption or income level falls below a minimum level necessary to meet basic needs. This minimum level is often referred to as the "poverty line".

The World Bank (2010b) uses a more defined reference of poverty by setting the poverty line at $1.25 and $2 per day in 2005 purchasing power parity (PPP) terms. The global poverty goal calls for reducing the proportion of people living on less than a dollar a day by half by 2015. This requires a reduction from 28 percent of the world's population in 1990 who lived in poverty to 12.7% by 2015, thereby reducing the number of extreme poor people by 363 million. Poverty estimates released in August 2008 based on a new measurement, indicated that in 2005 about a quarter or 1.4 billion people in the developing world lived on less than $1.25 a day. This had decreased from 1.9 billion or 50% of the population in 1981. This change may be attributed to the fact that in 1981, East Asia which was the world's poorest region with almost 80% of the population living on less than $1.25 a day had by 2005 only 18% or 340 million living on less than $1.25 per day. This change is largely as a result of the meaningful progress in poverty reduction in China and the goal of halving extreme poverty between 1990 and 2015 which has already been achieved in East Asia.

While poverty has been seen to decline in the previously poorest place in the world, the opposite is true in Sub-Saharan Africa where in 1981 about 200 million people were estimated as living on less than $1.25 per day; a number that has since increased to 380 million. As the population of sub-Saharan Africa has almost doubled in the same period, it means that 50 percent of the population lives below the poverty line, which is a decrease from 58% in 1996 to 50% in 2005 (World Bank, 2010b).

In 2006, Woolard and Leibbrand prepared a report for the National Treasury to propose an official poverty line for South Africa, in keeping with practice in many other countries. This measure would

assist South Africa to monitor the extent of household poverty and observe progress in poverty reduction. The report stated that the idea of a poverty line was not to reduce the household vulnerability for analytical purposes to a single index, but rather to propose a consistent measure, to gauge household needs, which would serve as a useful comparative index of trends over time and of relative wellbeing across the social landscape (Woolard & Leibbrand, 2006: 2).

While there has been a decrease in poverty in South Africa from 56% in 1993 to 54% in 2008, mainly because of a decrease in the incidence of poverty among the black African population, it is important to note the following:

- The incidence of poverty in rural areas remained unchanged at 77% between 1993 and 2008.
- The incidence of poverty in urban areas increased from 34% in 1993 to 39% in 2008.
- As a result of the increased urbanisation, the incidence of poverty increased from 30% in 1993 to 43% in 2008.
- There is generally a decrease in poverty levels where there is an increase in levels of education. In 2008 the poverty incidence in households where there was no schooling was 80%.
- Children are more likely to live in poverty than older people and some 50% of all South Africans living under poverty are under 20 years of age (see Table 3.16).

Table 3.16: Poverty measures by age, gender and population group for 1993, 2000 and 2008

Share of population %				
Population group and gender		**1993**	**2000**	**2008**
Black African	**Female**	40	41	42
	Male	36	38	38
Coloured	**Female**	4	5	5
	Male	4	4	4
Asian/Indian	**Female**	1	1	1
	Male	1	1	1
White	**Female**	6	5	5
	Male	6	5	4

Source: Adapted from OECD, 2010: 36.

According to the World Bank (2010b) the poverty headcount ratio in South Africa as a percentage of the population was 31% in 1995. This increased to 38% by 2000 and by 2006 had again declined to 23%. Other poverty measures are tabulated in Table 3.17.

Table 3.17: Poverty measures for South Africa, selected years

Year	Number of poor at $1.25 per day (PPP) (millions)	Number of poor at $2 a day (PPP) (millions)	Poverty gap at national poverty line (%)	Poverty headcount ratio at $1.25 a day (PPP) (% of the population
1993	9	15	-	24
1995	8	16	-	21
2000	12	19	16	26
2006	8	17	7	17
2009	7	15	-	13.8

Source: The World Bank, 2010.

3.4.4 Unemployment

According to the strict definition South Africa's unemployment rate in 2011 was 25.7%, with little progress having been made in this regard over the previous 15 years. The unemployment rate in the age group 15-24 years was 50.5%. The highest unemployment in 2011 was found in the Northern Cape Province where 31.3% of the population was unemployed, while the lowest rates recorded for the same period were Limpopo province at 19.3% and KwaZulu-Natal at 20.3% (Roux, 2011). Table 3.18 tabulates the unemployment by province for the period March 2001, 2003, 2008, 2010 and 2011.

Table 3.18: Unemployment rate by province for March 2001, 2003, 2008, 2010 and 2011

Province	**March 2001 %**	**March 2003 %**	**March 2008 %**	**March 2010 %**	**March 2011 %**
Average RSA	24.6	29.3	23.5	25.2	25.0
Eastern Cape	30.6	33.3	28.1	27.9	26.9
Free State	24.0	27.5	25.0	27.8	27.9
Gauteng	27.9	31.2	22.7	26.9	26.9
KwaZulu-Natal	19.6	28.2	22.7	20.9	20.3
Limpopo	30.7	42.3	31.7	22.4	19.3
Mpumalanga	19.1	23.3	23.7	27.7	30.8
Northern Cape	21.7	25.0	24.8	29.9	31.3
North West	22.7	26.8	22.3	27.9	25.0
Western Cape	20.9	22.0	18.1	21.8	22.2

Source: StatsSA 2008–2011 (http://www.statssa.gov.za).

3.5 HEALTHCARE

3.5.1 Introduction

The South African healthcare sector is a complex system which boasts a highly developed private healthcare sector not unlike healthcare systems in developed nations, an under-performing public healthcare system and finally a number of non-government, non-profit organisations all under the custodianship of the Minister of Health as noted in the National Health Act of 2003 (McLeod, 2009f: 5).

The total expenditure on health as a percentage of GDP in South Africa for 2007/8 was 8.5% (this amounted to ZAR124.8 billion), increasing to 8.9% in 2010. As shown on Table 3.19, when compared internationally, 8.0% to 8.9% of GDP spent on health compares favourably with many developed nations, like the UK and Italy, and is higher than other emerging markets like the Russian Federation (5.1%) and India (4.1%).

Table 3.19: Healthcare expenditure in selected countries for 2010

	Total health expenditure as % of GDP	Per capita expenditure in USD (2010)
USA	17.9	8 362
Switzerland	11.5	7 812
Germany	11.6	4 668
Italy	9.5	3 248
UK	9.6	3 503
South Africa	8.9	649
Botswana	8.3	615
Uganda	9.0	47
Egypt	4.7	123
Russian Federation	5.1	525
Ghana	5.2	67
Mozambique	5.2	21
India	4.1	54
Indonesia	2.6	77

Source: The World Bank, 2010c.

Since 1996 the total number of medical aid (insured) beneficiaries has remained stagnant at around 7 million or 14-15% of the South African population. It is often stated that 60% of the total healthcare expenditure is for only 15% of the population. This statement could, however, be misleading. McIntyre (as cited by McLeod, 2009d), suggests that as many as 21% of the population who are not covered by medical insurance choose to utilise the private sector for their healthcare needs. This would thus

indicate that 64% of the South African population is wholly dependent on the public sector for their healthcare needs. It is important to note that there is a very large disparity in healthcare services provided by these two sectors, as can be seen in Tables 3.20 and 3.21, with regard to per capita expenditure and the number of medical practitioners.

Figure 3.17 illustrates the growth in per capita expenditure in both the medical aid population as well as the public sector from 1996 to 2008. The per capita expenditure in the medical aid population grew from about ZAR5 000 in 1996 to close to ZAR9 500 in 2008. The public sector expenditure declined from about ZAR1 500 in 1996 to about ZAR1 000 in 1999, where it remained flat until 2003 and since 2008 has again grown to about ZAR2 000 per capita. General inflation in South Africa was between 5 and 10% from 1996 to 2000 and close to 5% from 2001 to 2008, indicating the government's expenditure per capita on healthcare did not keep pace with general inflation.

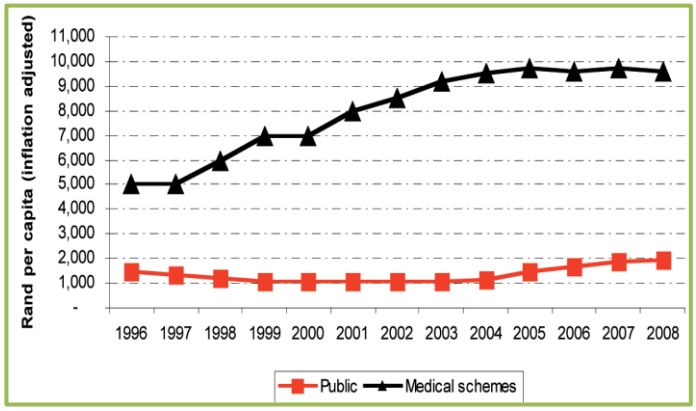


Figure 3.17: Per capita expenditure from 1996 to 2008 for public and medical aid patients (ZAR)

Source: Ataguba & Akazili, 2010.

Data from 2005 suggest that private insurance, known in South Africa as Medical Aid schemes accounted for 55% or 66.5 billion of the healthcare expenditure. The second largest contributor was the public healthcare system at 32.7% (ZAR39.2 billion). Almost 21% or ZAR14.7 billion of all healthcare expenditure comes from out of pocket spending (SA INFO, 2009; McLeod, 2009f: 5). Figure 3.18 illustrates the number of people in millions with or without medical aid cover between 1993 and 2008. This does not reflect any out-of-pocket expenditure, which is demonstrated in Table 3.20. It is particularly noteworthy that an estimated ZAR2.9 billion is spent on traditional medicines each year by approximately 27 million people. This is 5.6% of the government's budget for health, but it is rarely accounted for as part of the healthcare expenditure. It is important to note that, as in the case of traditional medicine, fully private healthcare expenditure does not contend with other social expenditure, but rather competes for expenditure such as entertainment.

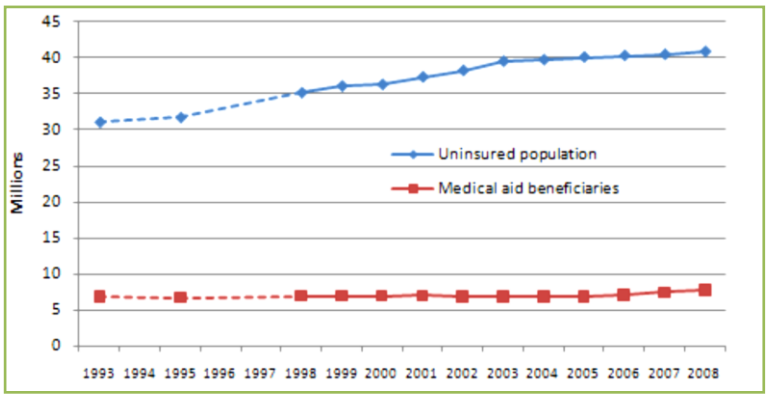


Figure 3.18: Number of people with and without medical aid from 1993 to 2008

Source: Harrison, 2009: 35.

Table 3.20: Healthcare coverage and resources in South Africa in 2005

Delivery of healthcare	Private health medical schemes (a)	Out of pocket some public some private (b)	Public sector (c)
Population covered	7 million	9.8 million	30.2 million
Percentage of population	14.8%	21%	64.2%
Expenditure per beneficiary per annum	ZAR9,500	ZAR1,500	ZAR1,300
Percentage of total expenditure	55%	12.3%	32.7%
Total Expenditure (ZAR)	ZAR66.5 billion	ZAR14.7 billion	ZAR39.2 billion

Notes: (a) Private care for primary health and private hospitals; (b) primary care in private and hospitalisations in public; and (c) both primary and hospital care in public.

Source: Adapted from McLeod, 2009f: 5.

Many South Africans choose to pay for the privilege of private healthcare by sacrificing part of their income which may have been spent on luxuries like entertainment. However, when the poor choose to access private healthcare it often means that they choose private healthcare over essential items such as food (McLeod, 2009f: 6). When evaluating the available resources within both the public and the private sector and with particular reference to this study and the treatment of patients with abnormal heart rhythms it should be noted, as seen in Table 3.21, that in the private sector, the number of patients per electrophysiologist is 875 000, while the number of patients in the public sector per trained electrophysiologist is 1:42 million lives.

Table 3.21: Healthcare staff in South Africa in 2005

Delivery of healthcare	Private health medical schemes	Public sector
Population per specialist	470	10 811
Population per nurse	102	616
Population per hospital bed	194	399
Population by physician performing electrophysiology (EP) **	875 000	42 million

Source: Adapted from McLeod, 2009f: 5.

3.5.2 Healthcare financing

The Director General of WHO, Bro Harlem Brundtland as cited by McLeod (2009f: 1) states that the purpose of healthcare financing is to first make funds available and second to provide incentives for the providers of services to ensure that all people have access to effective healthcare. In order to make this access available three main functions of healthcare financing are vital. These are the collection of revenue, the pooling of resources and finally the procurement of interventions.

Revenue may be collected through a number of different means, such as from general taxation or mandatory social insurance, which is most often related to the individual's income rather than the individual's risk. In other words, a person (a) with no risk factors for disease and a healthy lifestyle who earns a higher income will contribute more than a person (b) with high risk factors with low or no income, even if the risk factors in person (b) are as a result of being for example overweight, or cigarette smoking. Voluntary health insurance is another means of collecting funds to finance healthcare and the contribution may or may not be related to the individual's risk factors. Finally, healthcare can be financed by means of out-of-pocket expenditure.

Once revenue has been collected by whichever means used, the accumulation and management of the revenue is referred to as pooling, which ensures that the cost of healthcare and risk profile is carried by all members of the pool and not by the individual contributors. Finally, the collective funds are used to pay providers for services rendered.

If general taxation revenue is used to fund the healthcare sector, it is referred to as a "tax funded" healthcare system. This refers to a system where all citizens and, at times, to obtain healthcare services free of charge. The coverage is therefore universal. In a social health insurance system, the contributions are collected from workers, government, enterprises and the self-employed and then pooled into a single "health insurance fund." Social health insurance uses the funds available from these various sources to pay for services, with government paying the contributions of those who are unable to pay for themselves, for example the unemployed, children and the infirm.

In South Africa in 2005/6, general tax accounted for about 40% of the total healthcare funding, medical aids 45% and out-of-pocket payments 14% (Harrison, 2009: 24).

Harrison suggests the South African healthcare sector financing is very progressive. This is attributes to the fact that the contributions made by the wealthiest 20% of the population as a share of their income was approximately three times higher than the contributions made by the poorest 60% of the population as a share of their income. Thus, as demonstrated in Figure 3.19, the wealthiest quintile, who earn 68.7% of total income, contribute 82% of the total health care funding. Of this amount 45% is used for direct healthcare benefits, 32% for private health care and 13% is allocated to public healthcare services. Finally, 55% of total contribution made by the wealthiest quintile is redistributed to the other quintiles. This means that all the other income quintiles derive a greater share of the benefit than the actual financial contributions they make (Harrison, 2009: 24).

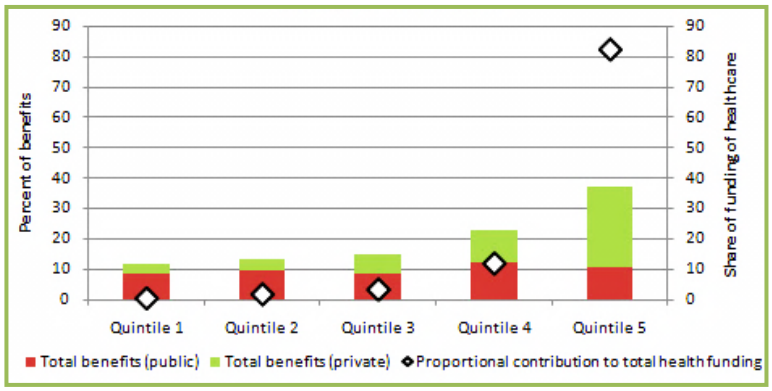


Figure 3.19: The relative distribution of healthcare financing and benefit across income quintiles for 2005/06

Source: Harrison, 2009: 24.

3.5.3 Private healthcare in South Africa

The private healthcare sector is made up of those members who belong to medical aids and those who choose to pay for healthcare out-of-pocket. In 2008 there were 119 registered medical schemes in South Africa which offered 200 different types of benefit options. The number of members who belong to medical schemes has remained largely unchanged since 1996, *viz.* approximately 15% of the country's population. The number of principal members of these schemes rose by 3.5% in 2008 to 3.38 million, while the number of dependents rose by 2.6% to a total of 2.4 million. The total number of medical aid beneficiaries for 2008 was 7.8 million (Council for Medical Schemes (CMS), 2009: 16).

Figure 3.19 illustrates an observation which is commonly made regarding the disproportionate expenditure on the private sector, relative to the number of beneficiaries. In 2008 the public sector expenditure per capita was close to ZAR2 000. This is one-fifth of the amount spent on each person who was on a medical aid. What is important to note is that, while the distribution of benefits is unfairly skewed in favour of the richest quintile that have the lowest burden of disease, there is no

financial cross-subsidisation of these medical aid patients by the poor. The private sector generates significant tax benefits for the government which could be used to improve the public sector healthcare if the latter improved its efficiency. It is important to acknowledge the fact that healthier or wealthier people who are prepared to spend more on private health care do not interfere with public sector financing. Within the private sector, the poorest 20% of people on medical aids contribute twice as much of their income compared to the wealthiest 20% of the medical aid population. Unaffordability has been cited as a reason why the size of the medical aid population has remained essentially unchanged since 1994.

In 2008 alone, it was suggested that as much as ZAR17 billion was spent as out-of-pocket expenditure, most of this in the private sector (Day & Gray, 2008: 365). This expenditure is more difficult to measure, not only from the total expenditure but also from its source. Not all costs incurred by those who are privately insured are covered by the medical aids, and not all patients who are uninsured rely on the public sector for health. It is known that various components make up out-of-pocket expenditure and are discussed below.

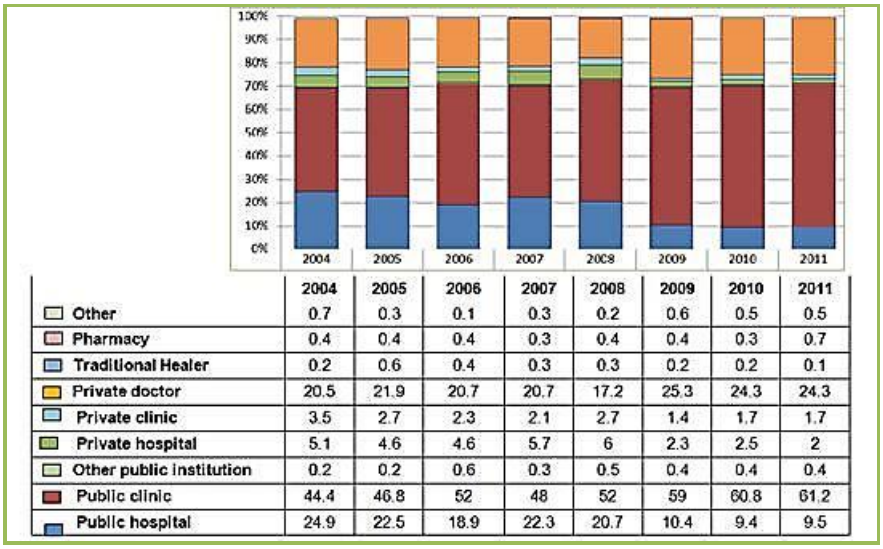
Some of these costs are made up from costs incurred by people who are employed but whose choice it is not to join a medical aid but rather cover their own medical costs, or those who are employed but for whom medical insurance is too expensive. For those who are insured through a medical aid, their contribution to out-of-pocket expenditure is usually the result of costs not covered by the medical aid or from having used up their benefits for any year before the end of the same year. Many medical procedures now also have a self-payment portion as is often the case where a medical prosthesis is required.

Other patients who contribute to out-of-pocket expenditure are those involved in what is known as “medical tourism”. These are patients who travel to South Africa for procedures which may vary from cosmetic to cardiac surgery. These visits may or may not include a period of recreation, for example a visit to a game park. The total value of medical tourism is undefined.

The final groups of patients who contribute to out-of-pocket spending are those who traditionally would receive treatment at a public hospital but who choose to pay for a private practitioner in the case of an emergency or to avoid long waiting times. The *SA Health Report of 2008* states that while only 6.5% of patients who belong to medical schemes made use of public facilities in the previous year, as many as 28.3% of the uninsured population made use of some private healthcare (Day & Gray, 2008: 354).

In the 2008 report, Day and Gray offer another perspective on this claiming that of all the people who accessed public healthcare in 2007, 97.1% were uninsured but in contrast almost 52% of people who accessed private healthcare were also uninsured.

Other than visits to traditional healers, uninsured patients who sought the services of the private healthcare sector did so because of dissatisfaction with long waiting times, medication not being available, staff shortages and the attitude of the medical staff. Figure 3.20 illustrates data from the 2011 General Household Survey. In 2004 29.1% of respondents said that they would consult either a private doctor (20.5%) a private clinic (3.5%) or a private hospital (5.1%). This declined to 28% in 2011, with consulting a private doctor increasing to 24.3% while private clinic consultations declined to 1.7% and private hospital consultations declined to 2%.



	2004	2005	2006	2007	2008	2009	2010	2011
Other	0.7	0.3	0.1	0.3	0.2	0.6	0.5	0.5
Pharmacy	0.4	0.4	0.4	0.3	0.4	0.4	0.3	0.7
Traditional Healer	0.2	0.6	0.4	0.3	0.3	0.2	0.2	0.1
Private doctor	20.5	21.9	20.7	20.7	17.2	25.3	24.3	24.3
Private clinic	3.5	2.7	2.3	2.1	2.7	1.4	1.7	1.7
Private hospital	5.1	4.6	4.6	5.7	6	2.3	2.5	2
Other public institution	0.2	0.2	0.6	0.3	0.5	0.4	0.4	0.4
Public clinic	44.4	46.8	52	48	52	59	60.8	61.2
Public hospital	24.9	22.5	18.9	22.3	20.7	10.4	9.4	9.5

Figure 3.20: Type of healthcare facility consulted first by the households when members fall ill or get injured, 2004-2011

Source: StatsSA, 2012: 16.

It is difficult to accurately define the number of South Africans who regularly make use of private healthcare resources but no matter what the reason is for people incurring out-of-pocket expenditure it has increased significantly over the past 10 years. This increase in out-of-pocket spending for healthcare is not unique to South Africa; in the UK, for example, where many patients tire of the long waiting lists of the NHS prefer to self-fund their medical treatment.

The Council for Medical Schemes in their 2011/12 report showed that a total of ZAR107.4 billion was made in medical aid contributions. This was an increase of 11.3% over 2010. A total of ZAR93.2 billion (86.7%) was paid as healthcare benefits for 2011, an increase of 10% since 2010. As seen in Figure 3.21, private hospital visits accounted for the largest portion of the pay-out, amounting to ZAR33.8 billion in 2011, an increase of 129.9% since 2000, when private hospitals accounted for 29.9% of all benefits paid. In 2011 private hospitals accounted for 36.3% of all benefits paid. Benefits paid to medical specialists accounted for 22.8% of all benefits paid and totalled ZAR21.3 billion in 2011. The total bill for medicines in 2011 was ZAR15.2 billion, or 15.2% of the total benefits paid. Total benefits paid to dentists increased from ZAR2.4 billion in 2010 to ZAR2.5 billion in 2011 and

visits to general practitioners cost the medical schemes a total of ZAR6.8 billion in 2011 (Council for Medical Schemes (CMS), 2012: 36).

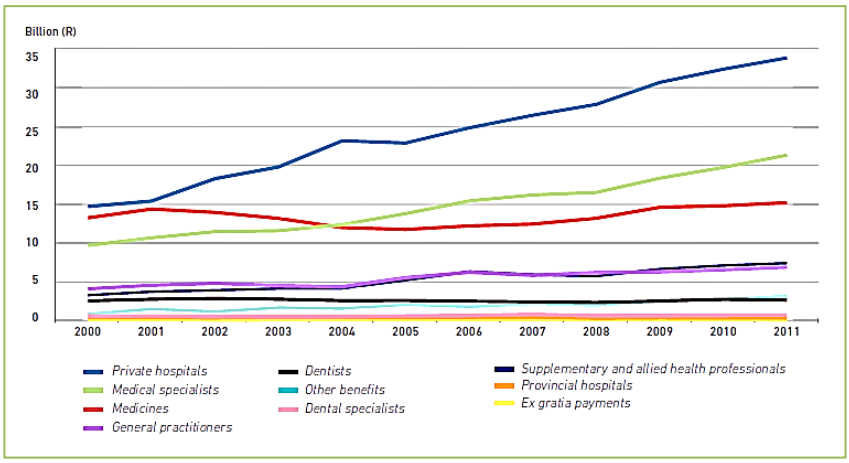


Figure 3.21: Total healthcare benefits paid 2000-11; at 2011 prices

Source: Council for Medical Schemes, 2012: 36.

The average number of GP visits in 2011 was three (per average beneficiary per annum), while the average number of visits to a dentist was 0.4. Both of these were unchanged over 2010. The 2011 report indicated that there was a 5.3% increase in the number of beneficiaries admitted to private hospital with a total of 178.81 hospital admissions per 1 000 beneficiaries. The total number of hospitalisations in the private sector is influenced by gender; in 2011 the hospital admission rate for females in the age band 15-59 was higher than for men. This seems to be affected by the reproductive years of women. However, in the age band from 60-64 years the hospital admissions in men were higher. The average time spent in hospital per beneficiary in 2010 was 3.2 days as seen in Figure 3.22.

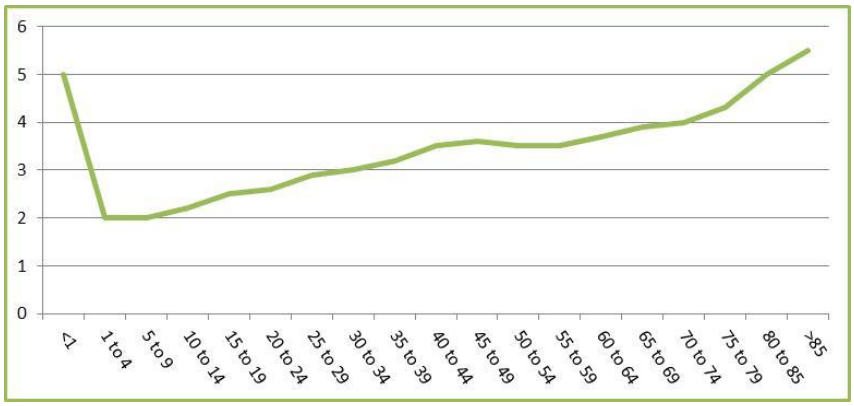


Figure 3.22: Average length of stay in hospital by age group in 2011

Source: Council for Medical Schemes, 2012: 122.

McLeod and McIntyre (as cited by Day & Gray, 2008) suggest that the private medical schemes have shown a trend away from primary healthcare to major medical benefits including chronic disease. This long-term shift may be noted in the fact that in 1974 major medical expenditure accounted for 42.5% of pooled funds; by 2005 this ratio had reached 71.4% (Day & Gray, 2008: 368).

While primary healthcare may meet the needs of the majority of the population of South Africa, the well-established private sector demands medical treatment that is on a par with any first world country. This is illustrated in Figure 3.21 which demonstrates that almost 60% of private healthcare expenditure is on hospitalisation costs and specialist fees. Section 3.5 reports that the GDP per capita is highest in Gauteng province.

Figure 3.23 demonstrates that more than 36% of all beneficiaries of medical aids schemes are from Gauteng. The 2011 mid-year population statistics for South Africa indicate that the population of Gauteng was 11 328 203 (StatsSA 2012: 3). There are 3 095 086 people in Gauteng who are covered by medical aid (CMS, 2012: 117). This means that close to one out of every three people in Gauteng has private health insurance, while only one out of 13 people in Limpopo Province have private insurance. This supports the argument that private health insurance favours those who can afford it (StatsSA, 2012: 3; CMS, 2012: 118).

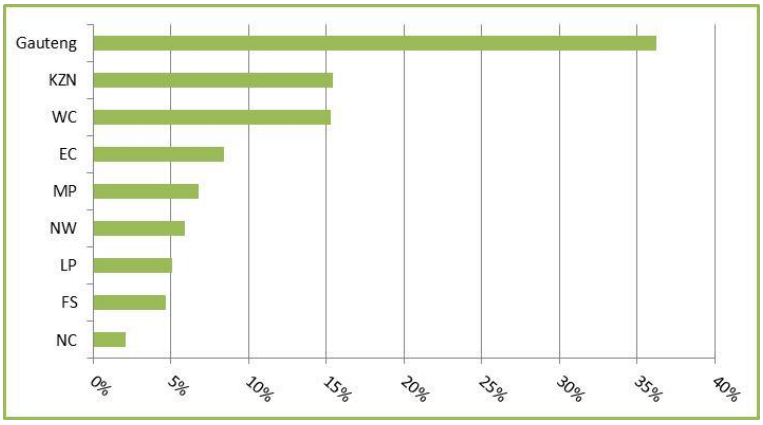


Figure 3.23: Distribution of beneficiaries by province, 2011 (%)

Source: Council for Medical Schemes, 2012: 118.

In 2011 67% of all the medical aid beneficiaries were found in only three of the nine provinces, namely Gauteng (36.2%), KwaZulu-Natal (15.4%) and the Western Cape (15.3%). These three provinces comprise only 54% of the country's population. Private health insurance not only differs from region to region, but also varies according to ethnic group, as seen in Table 3.22.

Table 3.22: Medical aid coverage by province and ethnic group, 2011 ('000s)

		WC	EC	NC	FS	KZN	NW	GP	MP	LP
Covered	**Black**	186	370	53	287	622	353	1001	353	307
	Coloured	594	92	48	19	38	11	90	15	9
	Indian/Asian	11	12	*	1	346	1	148	16	3
	White	601	261	49	192	294	113	1361	140	61
	Total	**1393**	**735**	**150**	**498**	**1301**	**477**	**2600**	**524**	**380**
Not covered	**Black**	1475	5468	622	2264	8540	2865	7284	2994	4816
	Coloured	2461	337	346	62	70	54	231	26	5
	Indian/Asian	11	14	2	11	539	6	171	11	6
	White	206	81	36	92	99	92	609	89	32
	Total	**4153**	**5900**	**1005**	**2428**	**9248**	**3018**	**8249**	**3121**	**4860**

Source: StatsSA, 2012: 83.

The General Household Survey of 2011 demonstrates that 62% of all people belonging to a medical aid scheme were from the previously disadvantaged groups (StatsSA, 2012). However, in spite of significant changes and job opportunities among the African population, only 9% of all Africans in South Africa are members of medical aids (illustrated in Table 3.23). This again supports the argument that private insurance benefits mainly the white population while the previously disadvantaged populations remain disadvantaged with regard to healthcare.

Table 3.23: Percentage of ethic group who are covered by medical aid, 2011

Ethnic group	% who have medical aid
Black	9
Coloured	20
Indian/Asian	41
White	70

Source: Adapted from StatsSA, 2012: 81.

3.5.4 Public healthcare in South Africa

Public sector healthcare in South Africa is funded by the National Treasury. In 2010/2011 this budget was ZAR21.7 billion. This grew by 15.3% to ZAR25.7 billion in 2011/12. The following programmes benefited from the additional funding:

- The HIV and AIDS conditional grant.
- The hospital revitalisation conditional grant.
- The mass measles immunisation campaign.
- Stabilising personnel expenditure.
- The improving of the conditions of service for employees in the department, including the National Health Laboratory Service and South African Medical Research Council.

The increased funding for the comprehensive HIV/AIDS conditional grant is based on an expected increase in the number of people on treatment, which more than doubled from 1.2 million in 2011 to 2.6 million by 2013/14. In 2011/12 an additional amount of ZAR442 million was allocated and ZAR692 million was set aside for 2012/13. A further ZAR2.28-billion has been budgeted for 2013/14 to improve the quality, strengthen public healthcare teams, upgrade and maintain nursing colleges, and to improve maternal and child health. Additional funding of ZAR16.1 billion over a three-year period was allocated at provincial level for preparatory work for the National Health Insurance scheme. This funding is earmarked for registrar posts, specialist posts at district level, for family health teams and for helping hospitals comply with norms and standards. Although the state contributes about 40% of all expenditure on health, the public health sector is under pressure to deliver services to about 80% of the population. Despite this, most resources are concentrated in the private health sector, which sees to the health needs of the remaining 20% of the population (Media Club South Africa, 2012).

A study conducted by Castro-Leal *et al.* (2000) under the auspices of the WHO asked whether the poor benefited from public spending on health in Africa (Castro-Leal *et al.*, 2000: 66). The study investigated healthcare expenditure in seven countries, namely Cote d'Ivoire, Ghana, Guinea, Kenya, Madagascar, South Africa and the Republic of Tanzania. In all these countries except for South Africa, typically two-thirds of all health care expenditure is in public facilities. In South Africa about 40% of all healthcare expenditure is from public institutions. Data in Table 3.24 is from household surveys in these countries who responded to the occurrence of either injury or illness. The authors believe that the responses reflect the availability of healthcare services, the quality of services, as well as the cost.

Table 3.24: Public health expenditure in selected countries for 2006

	Public spending as % of total health expenditure	Out of pocket spending as % of total private expenditure
Botswana	76.5	27.5
Egypt	41.4	94.9
Germany	76.9	57.1
Ghana	34.2	77.8
India	25	91.4
Italy	77.2	88.5
Mozambique	70.8	40.6
Russia	63.2	81.5
South Africa	37.7	17.5
UK	87.3	91.7
USA	45.8	23.5

Source: Dimant et al., 2009: 513.

The evidence from this study indicated that, as seen in South Africa, there are vast differences in healthcare spending among different households. There are some of the poor who seek private healthcare, but these are obviously less than the wealthy, while in most countries the poor relied mainly on the public healthcare sector. The fact that the private healthcare sector was of growing importance in all of these countries, is noteworthy. This observation verifies the earlier argument that there is a continual increase in out of pocket spending by the poor.

The study found that often the allocation of resources was not favourable to the poor who were often rural and more likely to use primary health centres as opposed to tertiary care cents. Governments were inclined to allocate more resources to hospital-based services which can be justified to an extent as it is here where medical personnel are trained (Castro-Leal *et al.*, 2000: 69).

As discussed above, most of the healthcare expenditure in South Africa is in the private sector, with an increasing amount of out-of-pocket expenditure. While disparity is known to exist between the public and the private sector, there appears to be a degree of disparity between the budgets for public healthcare in the various provinces when compared to the percentage of total expenditure allocated to each province, the percentage of the population in each province, the GDP per capita per province and finally the expected growth in the budget for the period 2009/10 to 2010/11 and 2011/12 (Table 3.25).

Table 3.25: Public healthcare budget by province for period 2009/10 to 2011/12 (ZAR millions)

% of total population	GDP/capita 2008	Projected HIV prevalence %	Province	Public healthcare spend 2009-2010	% of total spend	Budget 2010-2011	Budget 2011-2012	Growth in budget 2010-2011 (%)	Growth in budget 2011-2012(%)	Growth 2009-2012
10.8	14 651	7.3	**LP**	9 017	11	10 076	10 786	12	7.0	20
13.5	14 883	10.8	**EC**	11 328	14	12 108	12 146	7	8.6	16
20.8	20 753	15.8	**KZN**	17 769	22	20 688	22 211	16	7.5	25
7.0	21 294	13.0	**NW**	4 919	6	5 578	6 054	13	8.5	23
5.9	21 976	14.1	**OFS**	5 179	6	5 883	6 297	14	7.0	22
7.4	22 286	13.5	**MP**	5 429	7	5 874	6 316	8	7.5	16
2.3	23 952	7.5	**NC**	2 240	3	2 561	2 714	14	6.0	21
10.8	38 214	5.8	**WP**	9 892	12	10 925	11 764	10	7.7	19
21.5	44 735	14.7	**GP**	16 589	20	18 351	19 877	11	8.3	20
100			**Total**	82 362		92 024	99 165	12	7.8	20

Source: Adapted from Dimant et al., 2009: 101 & 512.

While issues such as GDP per capita or HIV prevalence may be factors to justify this disparity in the budgets these, in fact, do not seem to have a significant impact on the budgets at provincial level. This can be seen by comparing the budgets of the Western Cape (WC) with the Eastern Cape. On the one hand the WC, which boasts the second highest GDP per capita of ZAR38 214 and the lowest HIV prevalence rate of 5.8%, is allocated a growth in the budget from 2009 to 2012 of 19%. On the other hand, the Eastern Cape, with the second lowest GDP per capita of ZAR14 883, or one-third of the GDP per capita of the WC, and a HIV prevalence rate of 10.8% (almost double that of the WC), is allocated a growth in the public healthcare budget of only 16% for the same period.

The World Health Report, as cited by Day and Gray (2008: 357), suggests that countries with fewer than 230 nurses, physicians and midwives per 100 000 of the population were unlikely to achieve the WHO's Millennium Development Goals (MDGs). It was reported that in certain geographical areas in South Africa only 7% of the number of medical practitioners required in the system were in fact available. The same report stated that at the time a total of 34.6% of medical practitioner posts and 40.3% of registered nursing posts were vacant in the public sector. This is in spite of the fact that the number of health professional posts in the public sector had grown from 123 268 in 2005 to 136 985 in 2008.

In 2008 the number of enrolled nurses per 100 000 of the population was 55.4, while nursing assistants accounted for 83 per 100 000 of the population. Professional nurses were 116.6 per 100 000, medical practitioners only 26 per 100 000, and medical specialists were 9.8 per 100 000. This is 290.8 medical personnel per 100 000 of the population, which is in the range for the MDGs to be achieved.

In 2006/07 costs associated with staff accounted for almost 54% of total public health expenditure and while large investments have been made at a tertiary care level for the revitalisation of hospitals, medicines and equipment, the focus of the public sector remains primary healthcare. This focus on primary healthcare is not unique to South Africa as noted in the idealistic Alma Ata declaration which was signed in 1978 by 134 countries declaring the principle of *"Health for All"* where Primary Healthcare *"based on practical, scientifically sound and socially acceptable methods and technology made universally acceptable through people's full participation"* in order to deliver health for all by the year 2000 (*SA Health Report*, 2008: 4). At that time South Africa was at the height of Apartheid ideology and did not sign the declaration. A number of community health centres erected in the 1940 to 1950 period became models for primary healthcare centres later.

In 2000, the United Nations set out the MDGs which were to, *inter alia*, eradicate poverty, hunger, ill health and lack of access to education and clean water by 2015. All of these factors have either a direct or indirect impact on health. In 2008, halfway through the given time to reach the MDGs and the 30th anniversary of the signing of the Alma Ata Declaration, a renewed focus on primary healthcare was ushered in, which was to become a central theme in many developing nations.

In 2008/09 funding for the public sector health services was 14.1% of total government expenditure and accounted for 3.5% of the GDP. The largest health service programme on a provincial level is the District Health Services. The total amount spent on primary healthcare, excluding the cost of district hospitals and HIV and AIDS, amounted to 22% of total health expenditure in 2008/09 and represented an increase per capita in real terms from ZAR263 in 2004/05 to ZAR395 in 2010/11.

Data from the National Treasury publications, as shown in Table 3.26, illustrate how the public funds are spent, along with the annual growth in this expenditure.

Table 3.26: Public sector healthcare services expenditure from 2004/05 to 2010/11

ZAR millions	2004/05	2005/06	2006/07	2007/08	2008/09	2009/10	2010/11	Annual growth 2004/5 to 2010/11 (%)
PHC sub programmes	7128	8164	8983	11069	12923	14291	15838	8.4
Local government revenue	1247	1317	1478	1566	1597	1 629	1662	(0.4)
Community Health facilities	445	588	620	968	984	1 467	1515	16.4
PHC training	65	85	74	148	133	199	213	15.6
Total	8885	10154	11156	13751	15637	17586	19229	8.0
Rand per capita uninsured	224	255	277	337	380	424	460	7.0
Rand per capita 2007/8	263	287	297	337	358	381	395	7.0
PHC as % of total spend	21.3	21	20.2	21.5	22	22.3	21.9	

Source: National Online Statistics, 2008: 183.

Public spending in district hospitals has grown from ZAR7 552 million in 2004/05 to ZAR13 411 million in 2010/11 which represents an annual growth of 4.5%. In the same period the expenditure on HIV and AIDS grew from ZAR1 147 million to ZAR5 068 million, an increase of almost 22% (National Online Statistics, 2008: 182). While it is clear that the government is placing a lot of emphasis on the focus of the Alma Ata declaration and the MDGs of healthcare for all, the question remains as to whether enough is being done to bridge the gap in healthcare provision in South Africa between the "haves" and the "have-nots" and whether, under the current framework, these inequalities can ever be overcome.

3.5.5 Universal coverage for health

Different types of universal coverage systems exist, namely Social Health Insurance and National Health Insurance. The usual distinction made between these two systems is as follows:

- **National Health Insurance (NHI):** contributions are made by the tax-payer but everyone is entitled to benefits.
- **Social Health Insurance (SHI):** only those who contribute are entitled to benefits.

In the case of NHI, the main source of funding comes from general tax revenue which is pooled to manage risk. All citizens and even some foreign residents are entitled to services and coverage is universal. In the case of SHI, specific contributions are collected from employers, employees and government and placed into a single pool; however, entitlement is linked to the contributions made by or on behalf of individual. SHI often combines different sources of funds and the government usually makes contributions on behalf of those who are unable to pay.

In the 2008 annual report of the Council for Medical Schemes, the author states that the strategic plan for 2009 to 2012 of the Department of Health indicates their intention to establish an NHI system in order to ensure healthcare that is efficient, equitable and sustainable for all (CMS, 2009: 25). This was in fact not the first occasion that the subject of National Health had been on the agenda for South Africa. As early as 1944 the WHO proposed the introduction of a National Health system for South Africa on similar lines as the British system. The proposal was rejected at that time by the government of the day and it was not until the ANC came into power in 1994 that a system of National Health again became part of the government's agenda, as laid out in the ANC's health plan (McLeod, 2009b: 3).

The 2009 election manifesto of the ANC included proposals for a National Health system and stated amongst other things that the National Health Insurance system would be phased in over a period of five years. This system would be publicly funded and administered and would provide the right of all to access quality healthcare. This healthcare would not only be free at the point of service, but

the patient would also have the choice of who delivered the service (McLeod, 2009d: 1). The proposal of the NHI also states the following:

> *Contribution will be less than what members and their employers currently pay to medical schemes. Certain categories of workers, due to their low-income status, will be exempt from the contribution. All these funds would be placed in a single pool that would be available to fund the entire healthcare in the public and the private health sector under conditions that would apply to all healthcare service providers (Econex, 2009).*

This begs the question as to how quality healthcare should be defined. For those members of the public who currently belong to medical aids, nothing less than what they currently have access to may constitute quality, while those who currently only have access to the public sector and who experience long waiting times and lack of resources, may expect that quality healthcare will be in line with the services experienced in the private sector.

In February 2008 Trevor Manuel, then minister of finance, was quoted as saying:

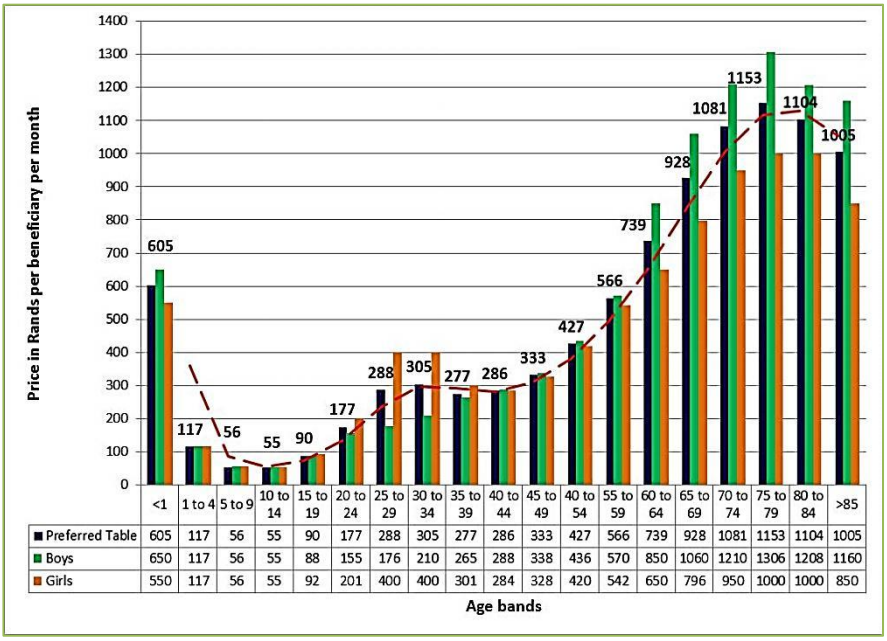
> *... The same goes for the national health insurance (NHI) scheme…l. It's another ambitious and potentially expensive commitment in the manifesto. The budget makes no promises on the NHI and, at most, promises to 'investigate' it (Paton, 2009).*

This is an example of how healthcare often becomes politicised as it is used by politicians to secure votes. Many South Africans expectations are raised by these statements and at the same time the medical industry has to prepare itself for the possibility of such a change.

It is estimated that in order to offer every South African access to healthcare at the same standard as that found in private practice in South Africa, the total cost would be between 15.7% to 20.8% of GDP (ZAR318 to ZAR358 billion per year). This would be considered unaffordable in all countries whereas illustrated in Table 3.9 above, the highest expenditure as a percentage of GDP, is in the USA at 15.3% (McLeod, 2009d: 14). Moreover, included in this expenditure is an amount of ZAR127 billion for service providers that as yet, do not exist in South Africa (McLeod; 2009d: 14).

Yet, in spite of the affordability issues of the NHI system, the government continues to raise the expectations of voters and the NHI has been carved into the strategic plan of the ANC for realisation over coming years. In order to fulfil this promise, one of the first reforms approved by cabinet in January 2005 was to create a Risk Equalisation Fund (REF). While no money exchanged hands, the idea was to shadow transfers as a way to monitor this process with the expectation that the REF would be fully implemented in January 2007. At the time of writing (September 2012) no implementation had taken place and transfer was delayed (*Private Practice Review*, 2012: 2). The creation of the REF is the first step required towards universal coverage as it ensures that all members pay a similar rate for the same benefits or prescribed minimum benefits (PMBs).

When analysing what a PMB should include, it is vital to examine the cost of healthcare by gender and age in both the public and private sectors. Although relevant public sector data availability is problematic, a comparison can be made against other countries. Figure 3.24, which illustrates the cost of providing a PMB in the private sector by age and gender, reveals some interesting figures.



	<1	1 to 4	5 to 9	10 to 14	15 to 19	20 to 24	25 to 29	30 to 34	35 to 39	40 to 44	45 to 49	40 to 54	55 to 59	60 to 64	65 to 69	70 to 74	75 to 79	80 to 84	>85
Preferred Table	605	117	56	55	90	177	288	305	277	286	333	427	566	739	928	1081	1153	1104	1005
Boys	650	117	56	55	88	155	176	210	265	288	338	436	570	850	1060	1210	1306	1208	1160
Girls	550	117	56	55	92	201	400	400	301	284	328	420	542	650	796	950	1000	1000	850

Figure 3.24: Price by age and gender of prescribed minimum benefits in 2009

Source: Adapted from McLeod, 2009c: 4.

From Figure 3.24 we can see that the medical costs for children under the age of 1 year old are significantly higher than children younger than 14 years. Much of this cost may be attributed to the costs associated with pre-term babies. We would expect this cost to be different in the public sector where premature babies are not always resuscitated. Male babies have higher associated costs than female babies, which may be attributed to the procedure of circumcision which is performed on young males.

Costs remain low for those older than one and up to the age of 20 years. However, there is a sharp increase from about the age of 20. This sudden increase in costs can most likely be attributed to maternity costs, motor vehicle accidents, substance abuse and in some population groups an increase in violence. It is noteworthy that the cost among the young female population associated with maternity costs is significantly higher in South Africa than in other countries. The reason for this has been cited as the high number of elective Caesarean sections performed on South African women. Lifestyle choices affect the cost of healthcare for both men and women around the age of 40. However, after 40 men utilise more healthcare resources than women. One of the major differences in healthcare expenditure between the public and private sectors are the costs associated with HIV/AIDS. These data are vital when estimating the costs of healthcare expenditure for the country as well as stratifying risk (McLeod, 2009c: 7).

As seen in Figure 3.25, the second step in setting up the NHI for South Africa could involve rescinding the current tax subsidy received by those members of society who belong to medical aids and in return provide a subsidy to each person, thereby making contributions to a mandatory healthcare system more affordable. The third reform would involve a mandatory income related contribution to cover the difference between the cost of the public sector subsidy and the PMB package. This amount is estimated to be approximately 50% of the current medical aid contributions (McLeod, 2009b).

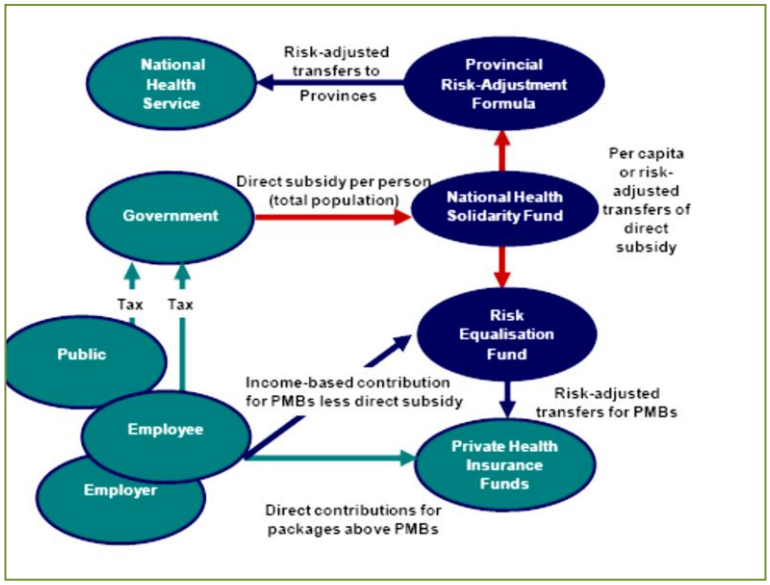


Figure 3.25: The envisaged flow of funds under Mandatory Health Insurance

Source: McLeod, 2009c: 11.

Finally, the question remains: What is to happen with medical aids? In 2009, the ANC task team proposed that Medical Aids Schemes should continue but on a purely voluntary basis. Contributions toward the NHI will be mandatory; payroll related contributions to be collected by the South African Revenue System (SARS).

While the country may be hopeful of a healthcare '*Utopia*' where all South African have the right to the same level of healthcare provision, the reality is that a single tier system of healthcare provision as is found in developed countries with social security systems like Italy, will most likely not be sustainable for all. In a country with a legacy of Apartheid and legislated discrimination, a multi-tier system may be seen as a drawback. In spite of this it must be remembered that South Africa is a developing nation and the implementation of a mandatory healthcare system where all members of society have access to the same level of PMBs, while those who choose to pay for additional cover are free to do so, should not be discouraged.

3.6 CONCLUSION

South Africa is a middle-income emerging market with a high degree of income inequality. More than 30% of the population is under 14 years old, which is double that of countries in the EU and the USA. The life expectancy at birth of the average South African is a little over 50 years and there is a high prevalence of HIV/AIDS and its related co-morbid diseases.

While the economy is the 24th largest in the world, the economic growth rate has slowed to below 3% per annum. Levels of unemployment and poverty are high, and the country has the second highest Gini coefficient confirming the economic inequality of the society.

One of the areas where these inequalities are reflected is the healthcare sector, which has a highly developed private healthcare sector servicing approximately 15% of the population with the other 85% serviced by a less efficient public healthcare sector. While National Health Insurance is an attractive option for creating equal rights for all, the preceding leads quite clearly to the conclusion that South Africa simply does not have the financial resources, trained manpower and infrastructure to implement a mandatory healthcare system at present. If we can accept this conclusion, we are bound to look at other means or methods of providing healthcare for the population. It is in this light that exploring the most cost-effective medical therapies is imperative to the South African society. These alternatives are not always obvious and the possibility of offering superior healthcare at a lower cost by utilising modern technology should not be excluded.

The subject of this study focusses on the treatment of the condition known as atrial fibrillation and challenges not only the efficacy of the current standard of care (drug therapy) but also the cost effectiveness of this seemingly less expensive option. The next chapter introduces the disease of atrial fibrillation and explores among other things the causes, the mechanism of atrial fibrillation, the incidence and prevalence of the disease and the complications of atrial fibrillation, including stroke and death.

CHAPTER 4: ATRIAL FIBRILLATION - THE DISEASE

4.1 INTRODUCTION

Atrial fibrillation (AF) is a ubiquitous yet diverse cardiac arrhythmia (abnormal heart rhythm). Its name comes from the fibrillating (i.e. quivering) of the heart muscles of the two upper chambers of the heart. AF accounts for the majority of arrhythmia-related hospitalisations. The incidence of AF increases with age and it is more frequent in men than women (Allessie *et al*., 2001). It is believed that, in the USA alone, there are more than 2.2 million people with AF (Fogel, 2004). The condition carries an increased risk of arterial thromboembolism (blood clots) and stroke which can be up to seven times that of the average population, depending on the presence of additional risk factors (Allessie *et al*., 2001). Stroke in patients with AF is associated with greater mortality, morbidity, and longer hospital stays than that in patients without AF.

With an estimated population of 50.5 million people in South Africa, 89% of whom are younger than 55 years old (StatsSA, 2012), the estimated prevalence of non-Rheumatic AF in the South African population is between 204 455 and 215 147. This is based on data from Go *et al.* (2001) and Heeringa *et al.* (2006), which also reveal that there are an estimated 342 135 new patients at risk of developing the disease each year.

Chapter 4 is a descriptive chapter which introduces the reader and, in particular, the non-medical reader to the disease of atrial fibrillation. The chapter covers the following topics:

- The nature of the disease.
- The classification of the disease.
- The epidemiology.
- How the disease is diagnosed.
- The causes of atrial fibrillation.
- Thromboembolism and the risk thereof.
- Mortality and AF.
- The clinical impact of AF.

4.2 BACKGROUND OF ATRIAL FIBRILLATION

Atrial fibrillation is the most common of all cardiac arrhythmia (irregular heartbeat) which involves the two upper chambers (atria) of the heart. While it may not cause any symptoms it is often associated with palpitations, fainting, chest pain, or congestive heart failure. It is a disease that is defined by the absence of co-ordinated atrial systole (contractions) as the normal regular electrical impulses generated by the Sino-atrial node are subjugated by disorganised electrical impulses which often originate in the pulmonary veins, resulting in irregular conduction of impulses to the ventricles which generate the heartbeat.

Although AF is typically associated with other structural heart diseases, there are a significant number of patients with "lone" AF, that is, patients with AF without any identifiable cause and who do not have any significant cardiac history. AF is also closely associated with other conditions such as hypertension, valvular heart disease, coronary artery disease, congestive heart failure, left ventricular hypertrophy, sinus node dysfunction, congenital heart disease, endocrinopathy (thyroid disease or diabetes), pulmonary disease, neurologic disease, familial/genetic predisposition, and alcoholism. Additionally, a self-limited form is frequently seen after cardiothoracic surgery (Allessie *et al*., 2001; Fogel, 2004; Gage *et al*., 2004).

During atrial fibrillation, the heart's two upper chambers beat chaotically and out of coordination with the two lower chambers (the ventricles), resulting in an irregular and often rapid heart rate that commonly causes poor blood flow to the body with symptoms of heart palpitations, shortness of breath and weakness (see Figure 4.1). Blood not completely pumped out of these chambers may pool and clots may develop. If a fraction of a blood clot in the atria leaves the heart and becomes lodged in an artery in the brain, a stroke results. About 15% of all strokes occur in people with atrial fibrillation (Adams *et al.,* 2008).

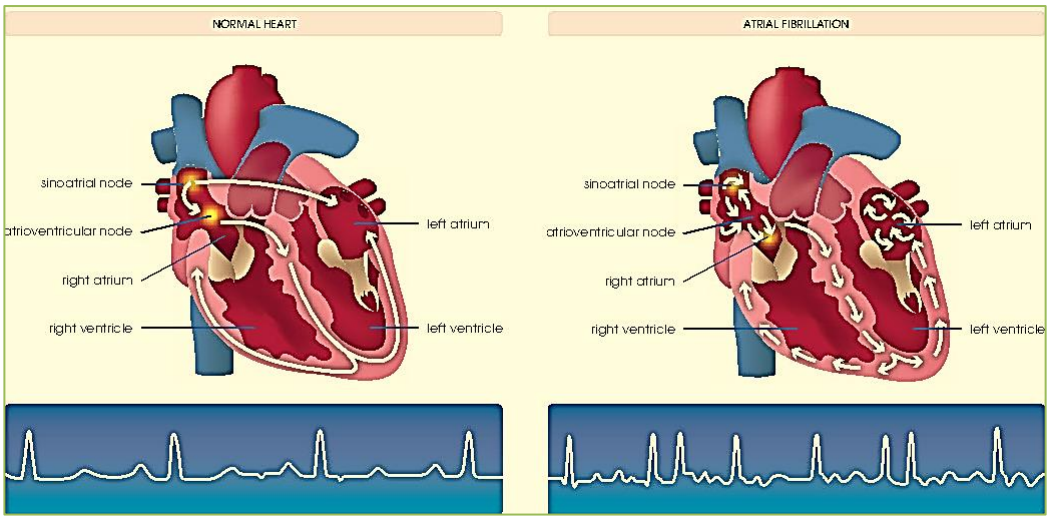


Figure 4.1: Atrial fibrillation - many electrical impulses causing the atria to fibrillate

Source: US National Library of Medicine, 2013.

In AF the normal electrical impulses that are generated by the sino-atrial (SA) node are overwhelmed by electrical impulses that originate in the atria and pulmonary veins. These irregular electrical impulses are then conducted to ventricles that generate the heartbeat. These irregular heartbeats may occur in episodes lasting from minutes to weeks, or they could occur continuously. The natural tendency of AF appears to become a chronic condition. Chronic AF is associated with an increase in the risk of death.

In patients with AF, the p waves, which on electrocardiogram (ECG), are characteristic of normal sinus rhythm, and are replaced by irregular, chaotic fibrillatory waves, often with a concomitant

irregular ventricular tachycardia (see Figure 4.2). The rate at which the atrial electrical impulses are transmitted to the ventricle is determined by a number of factors, including the relative refractory period within the atrioventricular (AV) node, hydration status and the presence or absence of pharmacological agents used to control the rate. When the ventricular rate increases to tachycardic levels, a situation of atrial fibrillation with rapid ventricular response (AF with RVR) ensues. This, in turn, can lead to decompensation in the form of either myocardial ischemia or advancement to congestive heart failure (CHF).

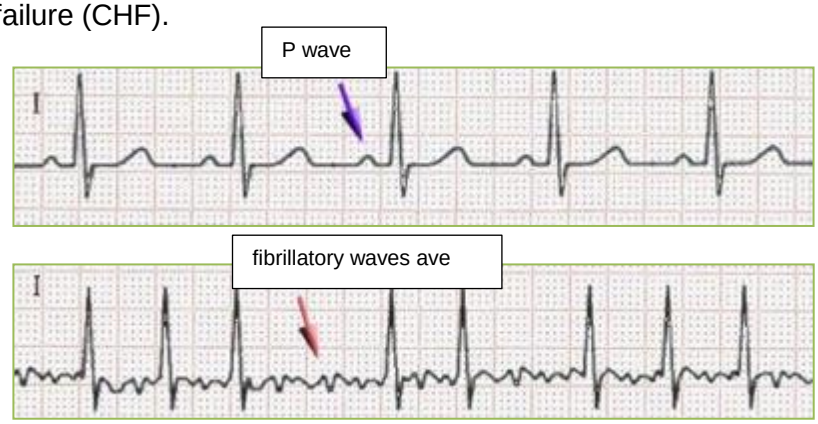


Figure 4.2: ECG of normal sinus rhythm (top) and atrial fibrillation (below)

Note: The purple arrow indicates a p wave as found in sinus rhythm; the red arrow demonstrates the loss of p wave in atrial fibrillation.

Source: Heuser, 2005.

AF increases mortality up to two-fold, primarily due to embolic stroke. This risk exists as the lack of coordinated atrial contraction leads to an unusual fluid flow state through the atrium that allows for the formation of thrombus, which, as stated, is at risk to embolise. This risk is particularly present upon return to normal sinus rhythm when coordinated atrial contraction can entrain a thrombus into the blood flow. The risk of embolism associated with cardioversion is stated to be as high as 2%. Thus, part of the challenge for physicians is the question of managing rate versus rhythm and the issue of when cardioversion through any mechanism should be attempted.

Atrial fibrillation is often asymptomatic and, in general, is not life-threatening, but may result in palpitations, fainting, chest pain, or congestive heart failure. People with AF usually have a significantly increased risk of stroke (up to seven times that of the general population). The level of increased risk of stroke depends on the number of additional risk factors for each individual patient. If a person with AF has no risk factors, then the risk of stroke is similar to that of the general population (Dresing & Schweikert, 1985). However, many people with AF have additional risk factors and then AF becomes a leading cause of stroke (Rietbrock *et al.*, 2008).

Atrial fibrillation may be treated with medications which either slow the heart rate or restore the heart rhythm back to normal. Synchronised electrical cardioversion may also be used to convert AF to a normal heart rhythm. Surgical and catheter-based therapies may also be used to prevent the

recurrence of AF in certain individuals. People with AF are often given anticoagulants such as Warfarin to protect them from stroke (Watson *et al.,* 2007).

Atrial fibrillation may be identified by taking a pulse and observing that the heartbeats occur at irregular intervals. However, a conclusive indication of AF is the absence of p waves on an ECG, which are normally present when there is a coordinated atrial contraction at the beginning of each heartbeat (see Figure 4.2) (Lazar & Clark, 2007).

4.3 THE CLASSIFICATION OF ATRIAL FIBRILLATION

As recommended in the guidelines of the American College of Cardiology (ACC), the European Society of Cardiology (ESC) and the American Heart Association (AHA), the following classification system is based on simplicity and clinical relevance. AF may be classified on the basis of the frequency of episodes and the ability of an episode to convert back to sinus rhythm. According to these guidelines, if a patient has two or more episodes of AF, it is considered to be recurrent. Recurrent AF may be paroxysmal or persistent. If the AF terminates spontaneously, it is designated as paroxysmal and, if the AF is sustained, it is designated as persistent. In the latter case, termination of the arrhythmia with electrical or pharmacological cardioversion does not change its designation. The category of persistent AF also includes permanent AF, which refers to long-standing AF (generally longer than one year), for which cardioversion is not indicated or attempted (Dressing & Schweikert, 1985).

All atrial fibrillation patients are initially in the category called *first detected AF* (see Table 4.1). These patients may or may not have had previous undetected episodes. If a first detected episode self-terminates in less than seven days and another episode begins later on, the case has moved into the category of *paroxysmal AF*. Although patients in this category may have episodes lasting up to seven days, in most cases of paroxysmal AF the episodes will self-terminate in less than 24 hours.

Table 4.1: Categories of atrial fibrillation (AF)

AF Category	Defining Characteristics
First Detected	Only one diagnosed episode
Paroxysmal	Recurrent episodes that self-terminate in less than 7 days
Persistent	Recurrent episodes that last more than 7 days
Permanent	An ongoing long-term episode

Source: Fuster et al., 2006.

Episodes lasting more than seven days are unlikely to self-terminate (Dressing & Schweikert, 1985), and are thus referred to as persistent AF. Termination of AF in persistent AF may be attempted by cardioversion. If cardioversion is not attempted or is unsuccessful and the episode is ongoing for a long time (e.g. a year or more), the patient's AF is referred to as permanent AF.

Episodes that last less than 30 seconds are not considered in this system of classification. Also, this system does not apply to cases where the AF is a secondary condition that occurs in the setting of a primary condition that may be the cause of the AF, for example after cardiac surgery. Using this system, it is not always clear how to classify AF. For example, a patient presenting with AF may fit into the paroxysmal AF category some of the time, while at other times their AF might present with characteristics similar to persistent AF. It may be possible to decide which category is more appropriate by determining which one occurs most often in the case under consideration (see Figure 4.3).

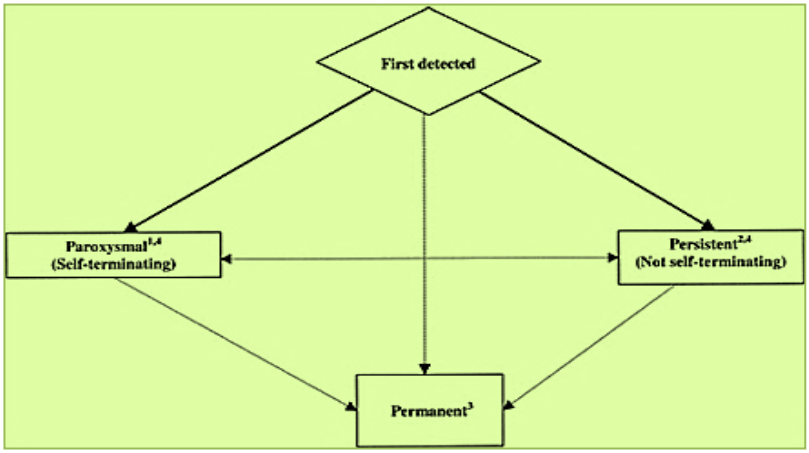


Figure 4.3: Patterns of atrial fibrillation (AF)

Notes: (1) Episodes lasting less than 7 days (2) Episodes lasting more than 7 days (3) Cardioversion failed or not attempted (4) Both paroxysmal and persistent AF may be recurrent.

Source: Fuster et al., 2006.

In addition to the four categories above, which are mainly defined by episode timing and termination, the ACC/AHA/ESC guidelines describe additional AF categories in terms of other characteristics of the patient. These are described below (Fuster *et al.,* 2006):

- **Lone Atrial fibrillation (LAF)** – This is the absence of clinical or echocardiographic findings of other cardiovascular disease (including hypertension) or related pulmonary disease, and in patients under the age of 60 years.

- **Non-valvular AF** – This is the absence of rheumatic mitral valve disease, a prosthetic heart valve, or mitral valve repair.

- **Secondary AF** – This occurs in the setting of a primary condition which may be the cause of the AF, such as acute myocardial infarction, cardiac surgery, pericarditis, myocarditis, hyper-thyroidism, pulmonary embolism, pneumonia, or other acute pulmonary disease.

- **Acute atrial fibrillation** is rapid, irregular, with chaotic atrial activity that lasts less than 48 hours. It includes both the first symptomatic onset of chronic or persistent atrial fibrillation and episodes of paroxysmal atrial fibrillation. It is sometimes difficult to distinguish new-onset atrial fibrillation from previously undiagnosed long-standing atrial fibrillation. Atrial fibrillation within 72 hours of onset is sometimes called recent-onset atrial fibrillation. By contrast, chronic atrial fibrillation is more sustained, and can be described as paroxysmal (with spontaneous termination and sinus rhythm between recurrences), persistent, or permanent atrial fibrillation (Watson *et al.*, 2007).

Although atrial fibrillation is not usually life-threatening, it is a medical emergency that can lead to complications. Treatment for atrial fibrillation may include medication and other interventions to try to alter the heart's electrical conduction (Mayo Clinic, 2009).

4.4 EPIDEMIOLOGY

4.4.1 The incidence of atrial fibrillation

The Framingham Study revealed that nearly 2% of the USA population had AF. Men were more likely to be diagnosed with AF than women. Both the incidence and prevalence of this disease increases with age. Go *et al.* (2001) found in their prospective study that the incidence of AF in people younger than 40 years old was less than 0.1% per year. The incidence of AF in patients aged 50 to 59 years was 0.5%, and 8.8% of the 80- to 89-year-old group was diagnosed with AF (Dressing *et al.,* 1985). The incidence of AF among older adults studied over a three-year period in the Cardiovascular Health Study (Lip & Watson, 2009) was 19.2/1000 person years. In the West Birmingham atrial fibrillation project (Rietbrock *et al.,* 2008), the prevalence of AF, as found in general practices, was 2.4%. The most common aetiological causes were hypertension and ischaemic heart disease (Fogel, 2004). Crijns *et al. (*2000) demonstrated in a study published in the *European Heart Journal* that patients with congestive heart failure (CHF) had a three-year incidence of AF of almost 10% (Crijns *et al.,* 2000).

A recent study by Chugh *et al.* (2014) confirmed that both the incidence and prevalence of atrial fibrillation were increasing. This, they stated, as have others, is the consequence of an ageing population and the resultant inverted population pyramids in many geographical areas. However, the study added that, even when adjusted for age, there was an increase in the incidence and prevalence of atrial fibrillation, which appears to be linked to other associated co-morbidities.

This data, which are based on the Worldwide Epidemiology of Atrial Fibrillation (Chugh *et al*., 2014)) serve to confirm that the incidence of atrial fibrillation was higher in men than in women. The methodology used to estimate the incidence of atrial fibrillation was the number of new cases of atrial fibrillation divided by the population at mid-year. Based on this data it was shown that the estimated annual incidence of atrial fibrillation in 2010 was 60.7 per 100 000 population in men and 43.8 per 100 000 in women (as seen in Figure 4.4).

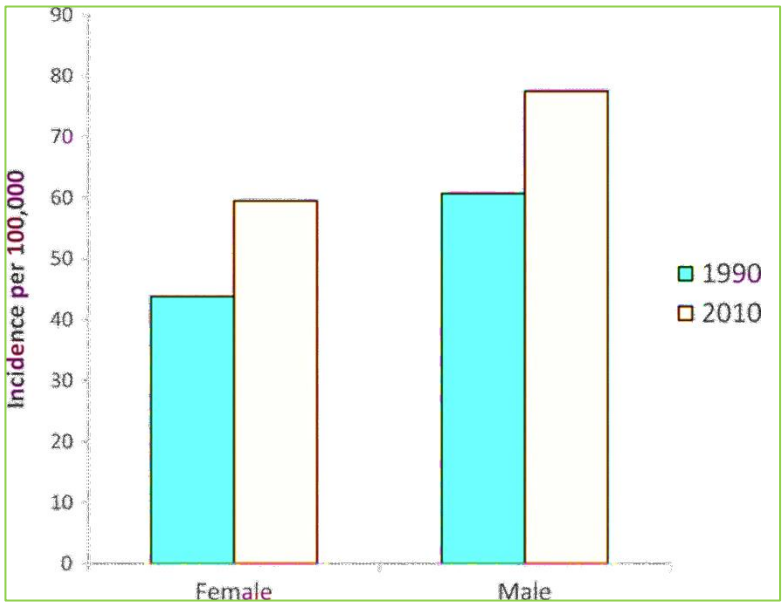


Figure 4.4: Worldwide incidence of AF per 100 000 of the population for both men and women in 1990 and 2010

Source: Chugh et al., 2014.

From the 2014 world epidemiology data by Chugh *et al.* (2014), it may be noted that, when comparing the age standardized incidence of atrial fibrillation in South Sub-Saharan Africa for 1990, the male population had a similar incidence to the male population in Western Europe, while the female population incidence was more similar to that of the female population of Central Europe. The incidence of atrial fibrillation in both males and females was lower than that in North America for both 1990 and 2010. The reason for comparing these groups is because most of the previous studies referenced in this document were performed in these regions. The full detail of the incidence by age group and region may be found in Appendix B.

Table 4.2 illustrates the growth in the incidence of atrial fibrillation between 1990 and 2010 by age group for North America, Western and Central Europe and South Sub-Saharan Africa.

Table 4.2: Percentage growth in the age-standardised incidence of atrial fibrillation by region from 1990 to 2010

	North America		Western Europe		Central Europe		South Sub Saharan Africa	
	Men	Women	Men	Women	Men	Women	Men	Women
<5 years	9%	8%	0%	0%	5%	13%	13%	5%
5-9 years	8%	12%	0%	5%	6%	12%	14%	5%
10-14 years	10%	20%	5%	7%	13%	7%	9%	7%
15-19 years	18%	21%	10%	14%	15%	13%	8%	13%
20-24 years	31%	28%	13%	20%	26%	40%	25%	8%
25- 29 years	30%	32%	12%	26%	15%	24%	23%	12%
30-34 years	30%	32%	12%	24%	13%	21%	24%	13%
35- 39 years	26%	32%	11%	22%	12%	19%	21%	11%
40-44 years	22%	31%	13%	24%	11%	17%	18%	10%
45-49 years	19%	30%	10%	23%	17%	23%	18%	9%
50-54 years	28%	40%	21%	32%	18%	24%	20%	11%
55-59 years	39%	53%	40%	47%	16%	23%	21%	12%
60-64 years	56%	69%	46%	59%	17%	26%	23%	14%
65-69 years	78%	86%	53%	81%	18%	31%	25%	16%
70-74 years	100%	105%	-83%	103%	18%	34%	28%	24%
75-79 years	123%	123%	87%	103%	25%	43%	32%	33%
>80 years	134%	141%	110%	136%	32%	50%	34%	38%

Source: Adapted from Chugh et al., 2014: 71-74.

4.4.2 The prevalence of atrial fibrillation

It was estimated in 2014 that there were more than 2.5 million Americans living with atrial fibrillation (Heart Rhythm Society (HRS), 2014). This has increased from 2.2 million in 2001. The longevity of the world's population is increasing and, as a result, more patients will suffer from this disease, as up to 10% of the population older than 80 years are diagnosed with AF at some point. The prevalence of diagnosed AF in the general population is 0.95% (95% CI, 0.94%-0.96%). Figure 4.5 shows how the prevalence of AF increases with age in both men and women, ranging from 0.1% in persons less than 55 years old to 9.0% among patients more than 80 years old. While women have a lower prevalence of AF at every age group compared to men, the overall number of affected women is similar to the overall number of affected men.

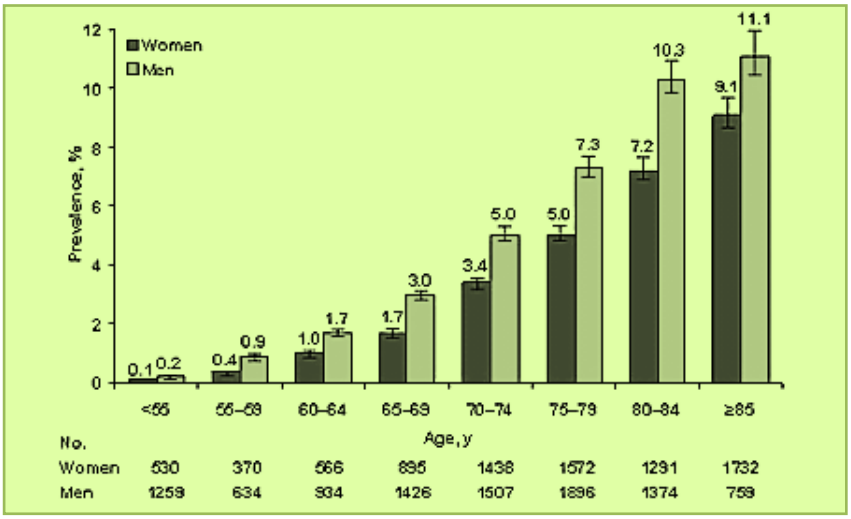


Figure 4.5: Prevalence of AF increases with age in both men and women

Source: Go et al., 2001.

More recent data published in 2014 by Chugh *et al.* (2014) indicate that the global prevalence of atrial fibrillation in 1990 as measured per 100 000 of the population was 569.5 for men and 359.9 for women. This prevalence showed only a modest increase up to 2010 when the prevalence for men and women was 596.2 and 373.1 respectively (Figure 4.6).

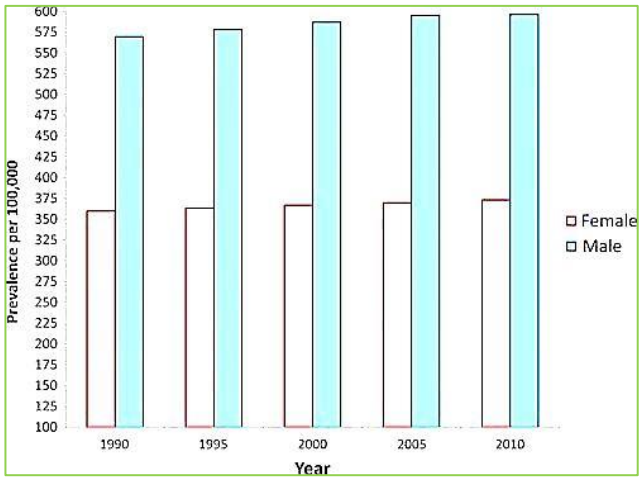


Figure 4.6: Worldwide prevalence of AF per 100 000 people for men and women, 1990 and 2010

Source: Chugh et al., 2014.

Figure 4.7 illustrates that the highest prevalence rates were found in North America at 925.7 for men and 520.8 for women, while the lowest were found in the Asian Pacific region at 340.2 for men and 196.0 for women. The estimated age adjusted prevalence of atrial fibrillation in the sub-Saharan region was 659.8 for men and 438.1 for women, as seen in Table 4.3.

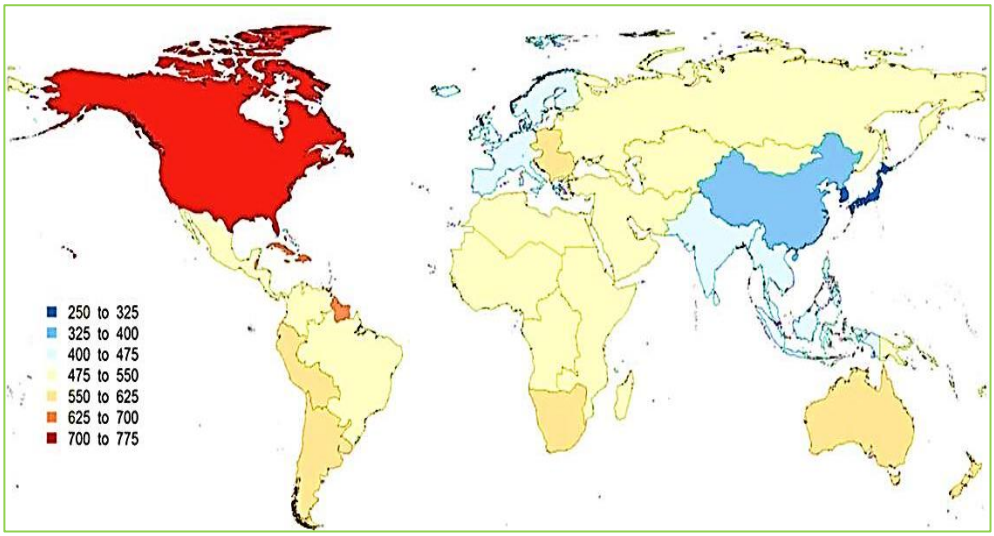


Figure 4.7: Prevalence of atrial fibrillation and atrial flutter (per 100 000 of the population) by regions in 2010

Source: Chugh et al., 2014.

Table 4.3: Prevalence rates for atrial fibrillation in 2010 by region with 95% uncertainty intervals (per 100 000 population)

2010	Global estimated atrial prevalence rates	North America	Asian Pacific region	Sub Saharan super region
Men	596.2	925.7	340.2	659.8
Women	373.1	520.8	196.0	438.1

Source: Chugh et al., 2014.

Table 4.4 shows the median percentage change in the prevalence of atrial fibrillation in North America, Central and Western Europe and Southern Sub-Saharan Africa from 1990 to 2010. The greatest change was noted in North America at 15% with an increase in Southern Sub-Saharan of almost 9%. No distinction is made between Rheumatic and Non-Rheumatic Atrial fibrillation in these data (See Appendix C for full details).

Table 4.4: The median percentage change in prevalence of atrial fibrillation for North America, Central and Western Europe and South Sub-Saharan Africa from 1990 to 2010

	1990	2010	Median % change from 1990 to 2010
North America	612.7 (567.7-662.6)	702.2 (645.2-759.7)	15.0% (1.6 -28.3)
Western Europe	419.4 (378.0-475.1)	464.9 (420.0-536.3)	11.1% (-6.8-30.0)
Central Europe	558.4 (429.5 - 730.1)	602.2 (453.9-802.7)	7.9% (-26.5-56.9)
South Aub Saharan Africa	570.2 (353.0-862.7)	618.1 (382.4-990.5)	8.7% (-42.7-109.4)

Source: Chugh et al., 2014: 69.

Table 4.5 illustrates the growth or decline of the age standardized prevalence of atrial fibrillation in the four regions indicated above. There is significant growth in the prevalence of atrial fibrillation,

especially in North America and Western Europe. There is also growth in the prevalence of atrial fibrillation in the male population of Southern Sub-Saharan Africa, which, for all age groups, is greater than the growth in the female group of this Southern Sub-Saharan population.

Table 4.5: Percentage growth in the age-standardised prevalence of atrial fibrillation by region from 1990 to 2010

	North America		Western Europe		Central Europe		South Sub Saharan Africa	
	Men	Women	Men	Women	Men	Women	Men	Women
<5 years	7%	7%	0%	5%	0%	8%	15%	7%
5-9 years	5%	9%	0%	-1%	1%	8%	15%	6%
10-14 years	7%	9%	-2%	-2%	3%	8%	13%	6%
15-19 years	6%	8%	-2%	-4%	4%	7%	12%	6%
20-24 years	6%	6%	-1%	-4%	4%	8%	13%	6%
25- 29 years	8%	5%	1%	-3%	5%	9%	14%	5%
30-34 years	10%	6%	3%	-2%	5%	10%	15%	5%
35- 39 years	10%	6%	2%	-2%	7%	11%	17%	6%
40-44 years	11%	8%	1%	-2%	8%	12%	16%	6%
45-49 years	9%	6%	1%	-2%	9%	12%	16%	5%
50-54 years	7%	6%	2%	-2%	9%	11%	15%	4%
55-59 years	10%	9%	8%	1%	8%	10%	15%	4%
60-64 years	13%	12%	14%	5%	5%	9%	16%	4%
65-69 years	20%	17%	16%	12%	9%	10%	17%	4%
70-74 years	25%	19%	14%	13%	9%	10%	17%	3%
75-79 years	24%	16%	15%	17%	7%	9%	17%	2%
>80 years	6%	2%	6%	9%	4%	3%	14%	-7%

Source: Adapted from Chugh et al., 2014: 65-69.

Figure 4.8 illustrates that the number of American adults with AF is projected to continue to increase as a result of the aging population, and as a result of the increased prevalence of coronary heart disease, heart failure and hypertension which may also contribute to this trend (Crijns *et al.,* 2000; Madrid *et al.,* 2002; Go *et al.,* 2001).

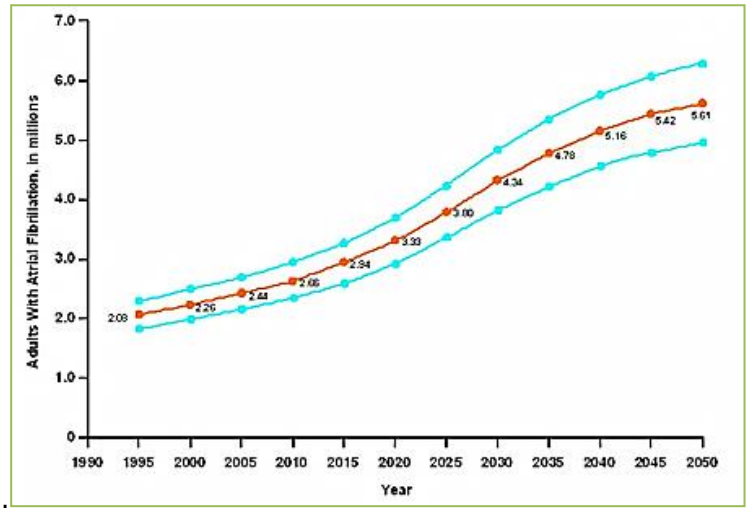


Figure 4.8: Projected numbers of American adults with AF between 1995 and 2050

Source: Go *et al.,* 2001.

In 2000 in the USA, it was shown that of the patients who had AF nearly 82% were over the age of 65 years and 37% were over the age of 80 years. These data are confirmed by Chugh *et al.* (2014) who indicated that, in 2010, 83% of the American population with atrial fibrillation was over the age

of 65 years. Tables 4.6 and 4.7, as discussed by Go *et al.* (2001), suggest that 88% of Americans suffering from AF will be older than 65 years by 2050 and the group of patients over the age of 80 years will increase to 53% of the total American population.

Table 4.6: Projected gender distributions of adults with AF in the United States in 2000, 2025 and 2050

	Year		
Gender	**2000**	**2025**	**2050**
Female	48.6%	46.3%	47.4%
Male	51.4%	53.7	52.6%

Source: Go et al., 2001.

Table 4.7: Projected age distribution of adults with AF in the United States between 2000 and 2050

	Year		
Age group	**2000**	**2025**	**2050**
<65 years	18%	15.5%	11.5%
65 -79 years	45.3%	48.7%	35.9%
>80 years	36.7%	35.8%	52.6%

Source: Go et al., 2001.

Analysis from the Framingham Heart Study demonstrated that when patients with AF were compared to patients without AF but matched by age, sex, and calendar year, the patients with AF were more likely to have risk factors for cardiovascular disease, pre-existing disease including hypertension, myocardial infarction, left ventricular hypertrophy, congestive heart failure, stroke or transient ischaemic attack and valvular heart disease. Women with AF were more likely to develop diabetes and, as illustrated in Table 4.8, an increased relative risk for AF may be related to increased BMI and obesity. This risk for AF in patients with obesity is increased by 50%, as a result of associated left atrial dilation (Stewart *et al.,* 2002).

Table 4.8: Adjusted relative risk for atrial fibrillation from Multivariate Cox Model

Variables	Relative risk	95% confidence interval
Myocardial infarction	3.62	2.59 - 5.07
Angina	2.84	1.91 - 4.21
ST or T wave change	2.21	1.62 - 3.00
Valvular disease	3.15	1.99 - 5.00
Congestive heart failure	3.37	2.29 - 4.96
Hypertension	1.42	1.10 -1.84
Cardiomyopathy	4.07	1.45 -11.45
Palpitations	2.22	1.24 - 2.97
Obesity	1.28	1.02 - 1.62
Supra-ventricular rhythm disturbance	2.28	1.74 - 2.98
Ventricular rhythm disturbance	1.37	1.06 -178

Source: Stewart et al., 2002.

Chugh *et al.* (2014: 3) estimated that in 2010 there were 33.5 million individuals globally living with atrial fibrillation (20.9 million males and 12.6 million females). This translates to one person in just over every 200. A simple extrapolation of these data indicates that in South Africa where the 2012 population was 51.19 million there could have been as many as 248 000 South African affected by AF (Central Intelligence Agency, 2001; StatsSA, 2012).

This type of extrapolation is very crude as it does not take into account any differences in the demographics of the various countries with particular regard to age distribution of the population. However, by examining the population pyramids as seen in Figure 4.7 to 4.8 it is at least possible to begin to project the potential impact the ageing population may have for a disease like AF.

Figures 4.9, 4.10 and 4.11 demonstrate the significant differences between the population pyramids of South Africa and the United Kingdom and the USA in 2000, and projected for 2025 and 2050. .

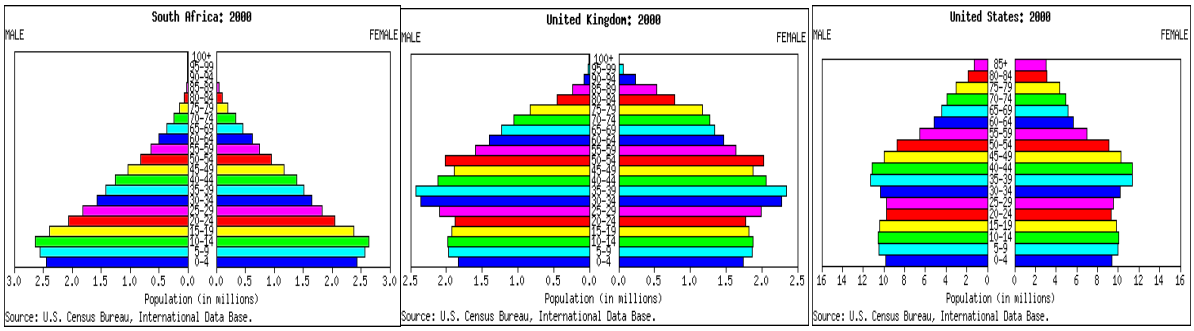


Figure 4.9: Population pyramids of South Africa, UK and the USA in 2000

Source: Fathers for Life, 2010.

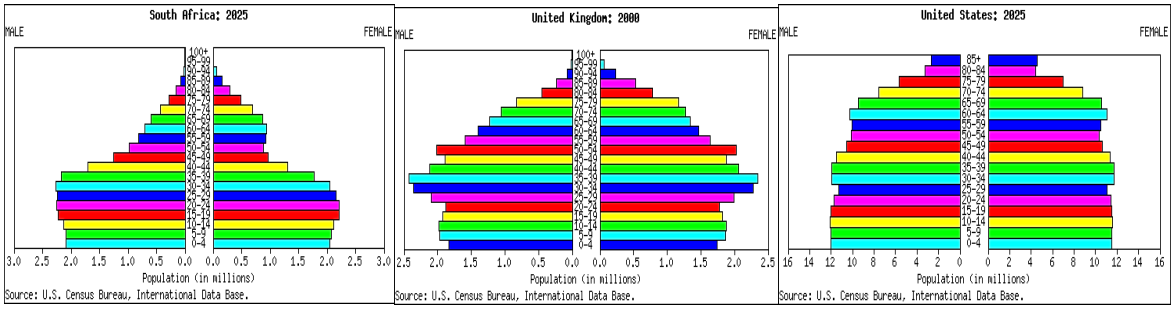


Figure 4.10: Population pyramids of South Africa, UK and the USA in 2025

Source: Fathers for Life, 2010.

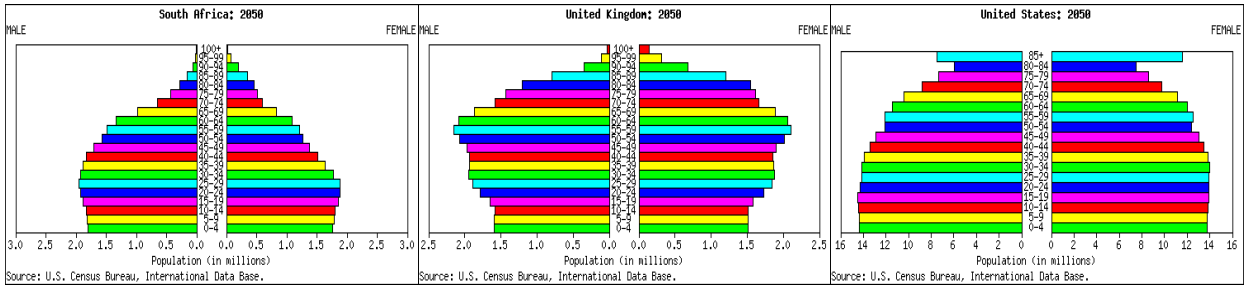


Figure 4.11: Population pyramids of South Africa, UK and the USA in 2050

Source: Fathers for Life, 2010.

The South African pyramid is typical of a country with a high birth rate, a rapid decline in age groups indicating a high death rate and short life expectancy. The UK and USA pyramids are examples of countries with a low to declining birth rate, a low death rate, an increased number of people reaching older ages and a higher dependency rate. The 2011 mid-year population statistics of StatsSA estimate that 41% of the South African population is younger than 20 years old and nearly 81% of the population is younger than 45 years of age. The proportion of the South African population older than 65 years is 5%, while that older than 80 years is 0.7% (StatsSA, 2009; StatsSA, 2012).

This is a vast difference from the USA and UK where, in the USA, only 60% of the population is younger than 45 years old and nearly 13% is over 65 years old (United Nations Statistics Division, 2007).

In the UK in 2008, for the first time, the population of state pensionable age was greater than the population aged less than 16 years, which has shown a decline since 1995. In the UK, the fastest growing age group of the population is over 80 years old. The population over the age of 80 years was estimated at 2 749 507 (or 4.5% of the total population); this had grown from 1.5 million (or 2.8% of the total population) in 1981.

This rapid increase in the number of octogenarians has been attributed to the decrease in mortality at older ages over the course of the second half of the 20th century. Between 1911 and 1915 the mortality rate of the population over 75 was reported at 137 deaths per million of the population. This has decreased substantially to 83 deaths per million of the population between 2006 and 2007. It is also

noted that the mortality rate for the population aged between 65 and 74 declined by two-thirds over the same period, from 57 to 19 deaths per thousand (Stats SA, 2009).

Schnabel *et al.* (2009) used data acquired from the Framingham Heart Study to develop a risk score for atrial fibrillation. The outcome of the study was to determine the first episode of AF among this community-based cohort who were aged between 45 and 95 and who were free of AF at baseline. The participants were followed for a maximum of 12 years. The predictors of AF were based on a point system, as noted in Table 4.9 below, and the points were allocated to the participants. The greater the number of points, the higher the risk for developing AF based on the following criteria:

- Age.
- Gender (male).
- Body Mass Index (mass/height^2).
- Systolic blood pressure.
- Current treatment for hypertension.
- PR interval on ECG.
- Significant heart murmur.
- Prevalence of heart failure...

Table 4.9: Points and risk estimates for development of AF

Total points and risk estimates											
Total points	0	1	2	3	4	5	6	7	8	9	>10
Risk %	<1%	2%	3%	4%	6%	12%	16%	22%	16%	22%	>30%

Source: Schnabel et al., 2009.

Table 4.10 illustrates the significant role that increased age has for the risk of developing AF when compared with other risk factors, for example structural heart disease.

Table 4.10: Age of men and women as a predictor of risk for development of AF

Age	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	>85
Women	-3	-2	0	1	3	4	6	7	8

Source: Schnabel et al., 2009.

4.4.3 Incidence and prevalence of atrial fibrillation in South Africa

There are no specific data on the incidence and prevalence of AF in South Africa. By using the 2011 mid-year population statistics of South Africans younger than 55 years old for both genders and based on the data in the Go *et al.* (2001) study and the Heeringa *et al.* (2006) study, an estimation was calculated for the incidence of AF in South Africa as seen in Table 4.11.

Table 4.11: Estimated incidence of AF by gender and age group in South Africa

	Females			Males		
Age	**Incidence**	**Population**	**Total**	**Incidence**	**Population**	**Total**
56-59	0%	928 220	-	2.60%	745 049	19 371
60-64	2.10%	768 502	16 139	4.90%	582 801	28 557
65-69	4.70%	569 547	26 769	6.60%	419 152	27 664
70-74	10.10%	425 931	43 019	12.40%	289 184	35 859
75-79	11.50%	288 117	33 133	19.90%	172 858	34 399
80-84	18.20%	249 138	45 343	25.50%	125 028	31 882
Total		**3 229 455**	**164 403**		**2 334 072**	**177 732**

Sources: Adapted and computed from Heeringa et al., 2006; StatsSA, 2012.

Table 4.12 shows the projection of the general population of South Africa from 2010 to 2040 by age, adjusted for the impact of HIV/AIDS. (See Appendices D and E). It should be noted that, between 2010 and 2040, the total population is only expected to grow by 5.5%. However, the growth in the number of people over the age of 55 years old, who are potentially impacted by non-rheumatic atrial fibrillation, increases by 82%. In 2010 the total number of the population under the age of 55 years was 88%; by 2040 this is expected to decrease to 79%.

Table 4.12: Age specific projections of the total South African population, 2010 to 2040 (with AIDS projections)

Cohort	2010	2015	2020	2025	2030	2035	2040
0-4	4,863,237	4,787,445	4,677,342	4,480,878	4,335,544	4,180,343	3,988,358
5 to 9	4,873,374	4,764,326	4,695,065	4,591,955	4,402,021	4,263,090	4,114,646
10 to 14	5,025,494	4,852,337	4,730,407	4,664,304	4,555,414	4,369,475	4,228,071
15-19	5,269,854	5,041,173	4,847,594	4,729,627	4,657,146	4,551,887	4,360,600
20-24	4,973,482	5,130,942	4,908,289	4,748,089	4,656,945	4,612,047	4,510,818
25-29	4,431,679	4,635,934	4,775,119	4,593,268	4,475,077	4,437,712	4,423,492
30-34	3,639,673	3,944,200	4,130,731	4,250,810	4,111,576	4,042,635	4,047,514
35-39	3,237,072	3,179,218	3,464,471	3,616,469	3,709,859	3,608,022	3,572,080
40-44	2,888,429	2,896,597	2,850,009	3,100,412	3,207,854	3,260,961	3,173,165
45-49	2,761,344	2,671,341	2,686,787	2,644,064	2,860,210	2,930,492	2,942,275
50-54	2,418,926	2,601,489	2,522,281	2,542,253	2,501,256	2,691,687	2,736,817
55-59	1,923,161	2,271,560	2,446,674	2,377,870	2,397,486	2,357,164	2,527,925
60-64	1,437,389	1,771,965	2,099,840	2,267,132	2,206,527	2,226,098	2,188,264
65-69	1,035,739	1,280,507	1,585,263	1,886,037	2,042,474	1,993,452	2,014,352
70-74	816,362	872,003	1,085,134	1,351,160	1,614,614	1,755,531	1,719,138
75-79	529,264	628,764	677,580	851,318	1,068,637	1,286,348	1,406,290
80+	449,679	558,819	652,358	747,930	912,670	1,142,905	1,409,017
Total	50,574,158	51,888,620	52,834,944	53,443,576	53,715,310	53,709,849	53,362,822
Age more than 55	6,191,594	7,383,618	8,546,849	9,481,447	10,242,408	10,761,498	11,264,986
Age less than 55	44,382,564	44,505,002	44,288,095	43,962,129	43,472,902	42,948,351	42,097,836
% of populatoin over 55	12%	14%	16%	18%	19%	20%	21%

Source: Haldenwang, 2011.

Based on the data for Southern sub-Saharan Africa presented in Table 4.4, the number of people in South Africa who may be affected by atrial fibrillation was estimated at 225 435 in 1990 and 316 354

in 2010. This is an increase of some 8.7% over a 20-year period. However, using another method of analysis and based on data that shows that 33.5 million people in the world are suffering from AF, it can be estimated that, with a world population of around 7 billion people, one in every 209 people have atrial fibrillation. Applied to South Africa, this would imply that there were 242 094 people with AF in South Africa in 2011.

Using data from both the ATRIA and Rotterdam studies, the estimated number of South Africans possibly affected by AF in South Africa is between 204 253 and 207 478, as seen in Table 4.13. This is lower than both the estimates by Chugh *et al.* (2014) and the crude estimation based on ratio of AF to total world population and may be explained by the fact that the study by Chugh *et al.* (2014) did not define the number of Rheumatic cases of AF and that 89% of the South African population is less than 55 years old (see Appendix F).

Table 4.13: Estimated prevalence of AF by population group in South Africa, based on 2011 population statistics

Race	% of population	Number	% under age of 55 years	Prevalence as per ATRIA study	Prevalence a per The Rotterdam study
Total population	100%	50 586 757	89%	207 478	204 253
Black South African	79.5%	40 206 275	91%	140 356	129 363
Coloured South Africans	9%	4 539 790	88%	17 345	16 976
Indian/Asian South Africans	2.5%	1 274 869	84%	7 305	6 452
White South Africans	9%	4 565 825	73%	53 834	40 100

Sources: Adapted and computed from Go et al., 2001; Heeringa et al., 2006; StatsSA, 2012.

Using data from Chugh *et al.* (2014) the average increase in prevalence rates was calculated in five-year cycles for both males and females and projected, based on the 2006 data from Heeringa *et al.* (2006), as demonstrated in Tables 4.14 and 4.15. This data can be found in Appendices D and E. The prevalence was shown to increase across all age groups and both genders, with the exception of females in the age group of 80-84 years old, where the prevalence is shown to decline (Chugh *et al.*, 2014).

The data were then used, together with the population projections by Haldenwang (2011) for both males and females, to estimate the prevalence of AF in five-year periods from 2006 up to 2040. These can be seen in Figure 4.12, Table 4.14 and Table 4.15. Tables 4.14 and 4.15 indicate the estimated prevalence of AF in both the male and female population of Southern Sub-Saharan Africa between from 2006 to 2040.

Full details can be found in Appendix F.

Based on the data in Table 4.16 the estimated number of South Africans currently affected by AF is just under 300 000. Using these data, that number will reach 352 855 by 2015, 526 633 by 2025, 767 572 by 2035 and 884 546 by 2040. This represents a 210% increase in total people affected with AF from 2010 to 2040. When calculating the prevalence of population with AF, it is estimated to increase from 0.6% of the population to 1.7%, as seen in Figure 4.12.

By using the data presented in Tables 4.5, 4.6 and 4.7 the estimated prevalence was calculated by age standardised groups from 56 years old to those older than 80 years old for both males and females. This is presented in Tables 4.16.

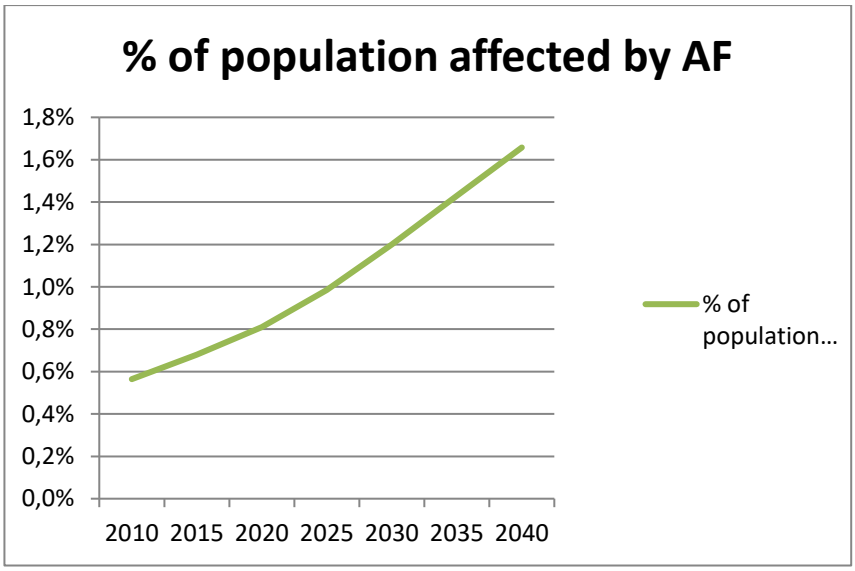


Figure 4.12: Percentage of the South African population living with AF from 2010 to 2040

Source: Adapted from data from Chugh et al., 2014: 65-67; Heeringa et al., 2006; StatsSA, 2012; Haldenwang, 2011.

Table 4.14: The estimated prevalence of AF in the male population of Southern Sub- Saharan Africa between from 2006 to 2040.

PREVALENCE RATES IN MALES IN SOUTH SUB SAHARAN AFRICA 2006 TO 2040									
Age	Growth average per 5 years	Prevalence (2006)	2010	2015	2020	2025	2030	2035	2040
56-59	5%	0.82%	0.87%	0.91%	0.95%	1.00%	1.05%	1.11%	1.16%
60-64	6%	2.58%	2.74%	2.90%	3.07%	3.26%	3.5%	3.7%	3.88%
65-69	6%	5.19%	5.50%	5.83%	6.18%	6.56%	6.9%	7.4%	7.81%
70-74	7%	6.90%	7.38%	7.90%	8.45%	9.04%	9.7%	10.3%	11.07%
75-79	8%	13.03%	14.07%	15.20%	16.41%	17.73%	19.1%	20.7%	22.33%
80-84	9%	17.89%	19.51%	21.26%	23.17%	25.26%	27.5%	30.0%	32.71%

Source: Adapted by Chugh et al., 2014: 65-67.

Table 4.15: The estimated prevalence of AF in the female population of Southern Sub- Saharan Africa between from 2006 to 2040.

PREVALENCE RATES IN FEMALES IN SOUTH SUB SAHARAN AFRICA 2006 TO 2040									
Age	Growth average per 5 years	Prevalence 2006	2010	2015	2020	2025	2030	2035	2040
56-59	1.00%	0.59%	0.60%	0.60%	0.61%	0.62%	0.62%	0.63%	0.63%
60-64	1.0%	1.01%	1.02%	1.03%	1.04%	1.05%	1.06%	1.07%	1.08%
65-69	0.9%	2.88%	2.91%	2.94%	2.97%	3.00%	3.03%	3.06%	3.09%
70-74	0.7%	5.41%	5.44%	5.48%	5.52%	5.56%	5.60%	5.64%	5.68%
75-79	0.4%	12.74%	12.79%	12.84%	12.89%	12.94%	12.99%	13.05%	13.10%
80-84	-1.8%	17.47%	17.16%	16.85%	16.54%	16.25%	15.95%	15.67%	15.38%

Source: Adapted by Chugh et al., 2014: 65-67.

By using these data, together with the data from Go *et al.* (2001), Heeringa *et al.* (2006), StatsSA (2012) and Haldenwang (2011), the estimated prevalence of AF was calculated for both males and females from the age of 55 years and older from 2010 to 2040 in five-year increments, as seen in Table 4.16.

Table 4.16: Projection of AF in the South African population from 2010 to 2040

Year	Total Population	Male	Female
2010	285,428	139,649	145,779
2015	352,855	180,097	172,758
2020	427,904	232,121	195,784
2025	526,633	297,732	228,901
2030	643,908	375,337	268,571
2035	767,572	460,804	306,768
2040	884,546	549,062	335,484

Source: Adapted from data from Chugh et al., 2014: 65-67; Go et al. (2001), Heeringa et al., 2006; StatsSA, 2012; Haldenwang, 2011.

Figure 4.13 illustrates the growth in the estimated number of South Africans who may be affected by AF between 2010 and 2040.

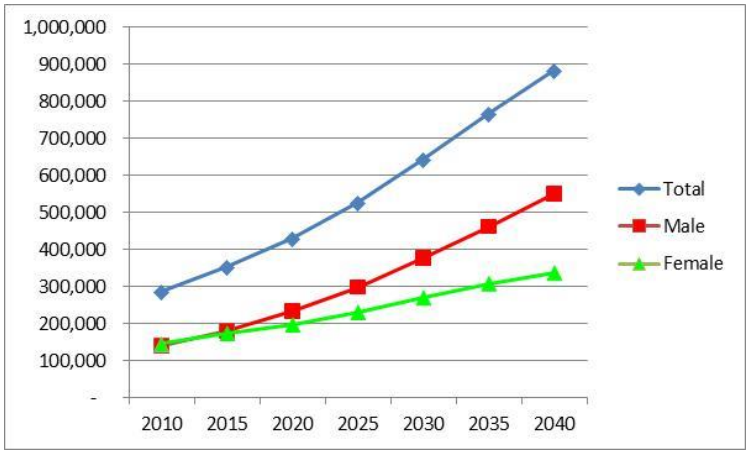


Figure 4.13: Projection of AF in the South African male, female and total population from 2010 to 2040

Source: Adapted from data from Chugh et al., 2014: 65-67; Heeringa et al., 2006; StatsSA, 2012; Haldenwang, 2011.

4.5 DIAGNOSING ATRIAL FIBRILLATION

Many patients present at their physician with symptoms related to a rapid and irregular heart rate or palpitations. These patients may also experience exercise intolerance, occasionally angina, congestive symptoms, and shortness of breath or oedema. Based on the history, physical examination of the patient, and their ECG, the diagnosis of atrial fibrillation (AF) may be made. It is not uncommon for a patient to first become aware of AF during a routine physical examination, or when an ECG is performed for another reason, as AF is asymptomatic in as many as one in five cases (Page *et al.,* 2003). For some patients, the first diagnosis of AF may be at the onset of a stroke or a transient ischaemic attack (TIA).

Often, atrial fibrillation is secondary to other medical problems, and the patient may present with symptoms of hyperthyroidism (an overactive thyroid gland) such as weight loss and diarrhoea, or the presence of chest pain (*angina pectoris*), or symptoms suggestive of lung disease that would indicate an underlying cause. In patients with a previous history of stroke, TIA, heart failure, high blood pressure, diabetes, and rheumatic fever, there may be a higher risk of complications associated with AF.

The physician will take a history, which will include the following details:

4.5.1 Family and medical history

The symptoms and history will include, among other things, blood pressure, a history of palpitations or the sensation of a racing, irregular or uncomfortable heartbeat, shortness of breath, chest pain or discomfort, dizziness and impaired effort tolerance. The medical history includes other health-related problems, as well as a history of heart disease, high blood pressure, lung disease, diabetes and, importantly, thyroid dysfunction. A family history of AF or other heart conditions, such as high blood

pressure, is significant. Finally, social habits such as cigarette smoking, alcohol use and caffeine use are also noted.

4.5.2 Physical examination

The physician should do a complete cardiac examination, listening to the rate and rhythm of the heartbeat, feeling the pulse and measuring the blood pressure. Auscultation of the chest will reveal heart murmurs and crepitations of the lungs, which could possibly indicate heart valve problems and signs of heart failure respectively. The physician may also examine the patient for swelling of the legs or feet and look for an enlarged thyroid gland or other signs of hyperthyroidism.

4.5.3 Diagnostic tests and procedures

4.5.3.1 Electrocardiogram (ECG)

Atrial fibrillation is diagnosed on a standard 12 lead ECG, which is a simple and painless test that detects and records the electrical activity of the heart. It is the most useful test for diagnosing AF, as it shows how fast the heart is beating, as well as the rhythm (steady or irregular). It also records the timing of the electrical signals as they pass through each part of the heart and is usually carried out in a GP surgery or at a local hospital.

Characteristic findings in AF include the absence of p waves, with unorganised electrical activity in their place, and irregularity of R-R interval due to irregular conduction of impulses from the atria to the ventricles.

Paroxysmal AF or episodes that “come and go” may not be detected or documented during an office visit as the standard ECG records the heartbeat for only a few seconds. If paroxysmal AF is suspected, but is not captured on a regular ECG, it may be necessary for the patient to wear a portable or ambulatory Holter monitor for between 24 and 48 hours to increase the likelihood of documenting such an episode. If the episodes are too infrequent to be detected by Holter monitoring with reasonable probability, the patient can be monitored for longer periods (e.g. a month) with an ambulatory event monitor that can record the heartbeat for longer periods. Under certain circumstances, a small device called a loop recorder may be implanted under the skin. This measures the electrical activity of the heart for periods of up to one year.

The use of modalities such as Colour M Mode (CMM) and Tissue Doppler Imaging (TDI) improve the accuracy of the assessment of estimated filling pressures and diastolic function. However, patients in AF are often more difficult to assess for systolic and diastolic left ventricular function as the test may be complicated by irregular RR interval and a rapid ventricular rate. The use of TTE often proves to be sub-optimal for the visualisation of the atrial appendages and thus may be

inadequate in terms of sensitivity and specificity for diagnosing left atrial appendage (LAA) thrombus (Omran *et al*., 1999; Troughton *et al.,* 2003).

4.5.3.2 Blood tests

Depending on an individual's medical history, a variety of blood tests may be performed, but in almost all cases the function of the thyroid gland is measured as hyperthyroidism may provoke AF. Other blood tests may include urea and electrolytes and, in the case where the patient presented with or experienced a form of chest pain, Troponin, a marker of damage to the heart muscle, may also be measured (Prystowsky*,* 2008).

4.5.3.3 Transthoracic echocardiograph (TTE)

Echocardiography or Echo utilises ultrasound waves to generate a moving picture of the heart, as seen in Figure 4.14. It is a non-invasive test and is performed by placing an echo "probe" on the chest wall. Transthoracic echocardiography (TTE) presents information about the size and shape of the heart, including two dimensional (2D) imaging and complete Doppler assessment of the valves. TTE is a quick, rapid, safe and relatively comprehensive assessment of cardiac structure and function and can be extremely useful in helping to define the underlying aetiology of AF as well as the potential risk of complications and is recommended for all subjects with AF (Fuster *et al.,* 2006; Troughton *et al*., 2003).

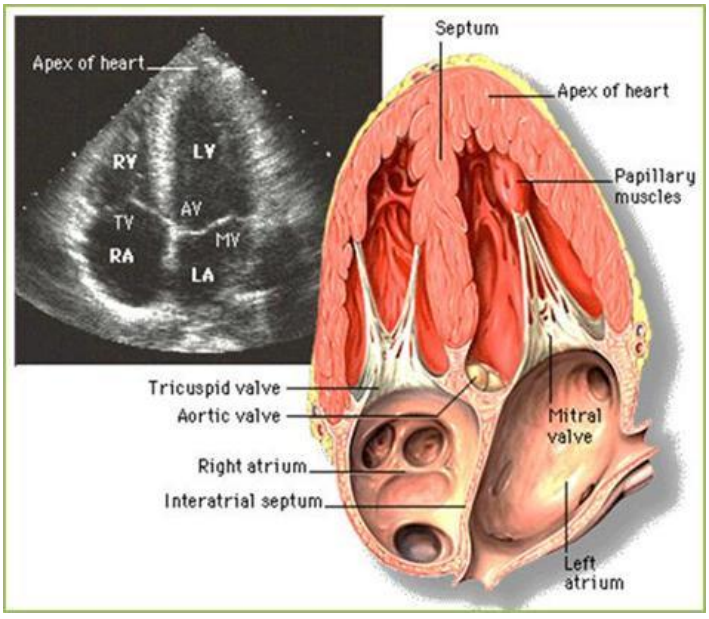


Figure 4.14: Apical four chamber view with transthoracic echocardiography

Source: Lynch & Jaffe, 1999.

Echo can also be performed as transoesophageal echo or as intra-cardiac echocardiography, each with specific but overlapping modalities as seen in Table 4.17.

Table 4.17: Summary of the indices measured by different echocardiographic modalities

Echocardiographic modalities	
Transthoracic echo	LA dimensions and volumes
	LV dimensions and volumes
	LVEF
	LV diastolic function
	Valvular function
Transoesophageal echo	LA/LAA: structure, function, SEC, and thrombus
	RA/RAA structure, function and thrombus
	Pulmonary vein anatomy/flows
	Inter-atrial septum (PFO, etc.)
	Ascending aorta and arch atheroma
	Valvular function
	Guide therapy*
Intra-cardiac echo LA/LAA structure and function	LA/LAA thrombus
	Inter-atrial septum
	Pulmonary vein anatomy/flows
	Guide therapy*

*Notes: *Radiofrequency ablation, valvuloplasty, PFO/ASD closure devices, LAA occlusion device insertion. ASD, atrial septal defect; LA, left atrium; LAA, left atrial appendage; LV, left ventricle; LVEF, left ventricular ejection fraction; PFO, patent foramen vale; RA, right atrium; RAA, right atrial appendage; SEC, spontaneous echo contrast.*

Source: Troughton et al., 2003.

4.5.3.4 Transoesophageal echocardiogram (TEE)

The use of TTE in visualising LAA thrombus is limited and, in those cases where TTE results are not definitive, it is often prudent to perform a transoesophageal echo (TEE) (Omran *et al*., 1999). While transthoracic echo is a non-invasive procedure, transoesophageal echo is a minimally invasive procedure, where a transoesophageal probe is passed down through the oesophagus and the heart is viewed from behind (Omran *et al.,* 1999; Abdulla, 2009). The images produced are generally far clearer and the physician is able to view, amongst other things, blood clots, masses and tumours that may be located inside the heart. TEE can also be used to gauge the severity of valve problems, and to help detect infection of heart valves, certain congenital heart diseases like atrial septal defects (ASDs), and dissection of the aorta. TEE is often very useful in evaluating patients who have had strokes as a result of blood clots. The procedure may detect the responsible clot or thrombus inside the left atrium.

Thrombus is thought to represent the main source of disabling cardio-embolic ischaemic strokes in patients with AF. Thrombus formation is believed to be the result of stasis of blood in the left atrial appendage (LAA). Thrombi are more often encountered in AF patients with ischaemic stroke than in those without stroke (Chimowitz *et al.,* 1993). Although clinical management is based on the

presumption that thrombus formation requires continuation of AF for approximately 48 hours, thrombi have been identified by TEE within shorter intervals (Manning *et al.,* 1995; Stoddard *et al.,* 1995). On average, these thrombi cannot be seen on standard echo (TTE), as discussed. The sensitivity and specificity of TTE is often insufficient to visualize these thrombi (Lundstrom & Ryder, 1988) and, for this reason, performing TEE is a more reliable way to assess LAA function and detect thrombus formation (Fuster *et al.,* 2006; Mugge *et al.,* 1994).

A series of studies has been conducted in patients with AF where TEE was performed during the conversion from AF back into sinus rhythm, to improve the understanding of the mechanical impact that cardioversion has on the heart and, in particular, the LA (Manning *et al.,* 1989) and LAA (Grimm *et al.,* 1993). These studies reveal that the flow velocities in the LAA were reduced at cardioversion and this was related to loss of organised mechanical contraction during AF (Chimowitz *et al.,* 1993).

4.6 ATRIAL PATHOLOGY AS A CAUSE OF ATRIAL FIBRILLATION

Histopathological changes most frequently observed in AF are the loss of atrial muscle mass and atrial fibrosis. It is important to note that these changes may also be associated with other heart disease (Page, 1992). Page (1992) described how the onset of AF may be preceded by atrial fibrosis and that a concurrence of patchy fibrosis with normal atrial fibres may explain the non-homogeneity of conduction (Allessie *et al*., 2002). Aime-Sempe *et al*. (1999) propose that apoptosis may cause interstitial fibrosis, resulting in the atrial myocytes being replaced, a deficit of myofibrils, amassing of glycogen granules, and interference of cell coupling at the gap junctions (Polontchouk *et al.,* 2001). This concludes that the loss of atrial muscle mass and atrial fibrosis is the most frequently observed changes in AF.

4.6.1 The mechanism of atrial fibrillation

The most popular theory, that AF consists of multiple wavelets of a functional re-entry nature, has existed since the 1960s (Veenhuyzen *et al.*, 2004). More recently, strong evidence from both animal models as well as evidence in the human heart, indicates that wandering wavelets could circulate around electrically silent areas (Page, 1992). The mechanism of AF associated with CHF remains under consideration as both focal and re-entrant mechanisms have been observed in animal models with CHF (Everett & Olgin, 2007). These data support both a ‘focal’ triggering mechanism, involving automaticity, and multiple re-entrant wavelets and are not mutually exclusive, i.e. they may coexist (Allessie *et al*., 2002).

Figure 4.15 denotes focal activation as indicated by the star and where the foci frequently lie within the region of the pulmonary veins.

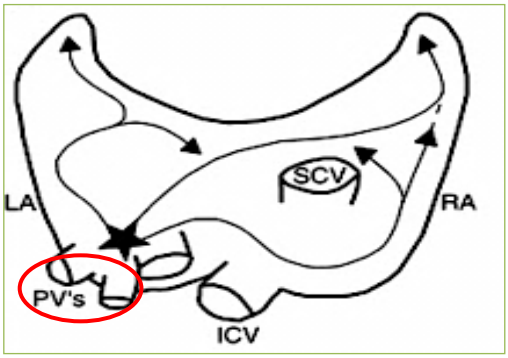


Figure 4.15: Posterior view of left atrium illustrating the focal activation mechanisms of atrial fibrillation

Notes: LA = left atrium; PV = pulmonary vein; ICV = inferior vena cava; SCV = superior vena cava; RA = right atrium.

Source: Konings et al., 1994.

The resulting wavelets represent fibrillatory conduction, as seen in multiple-wavelet re-entry in Figure 4.16, which illustrates these multiple-wavelets (indicated by arrows). These electrical impulses randomly re-enter tissue previously activated by the same or another wavelet, resulting in varied routes being traversed by the wavelets.

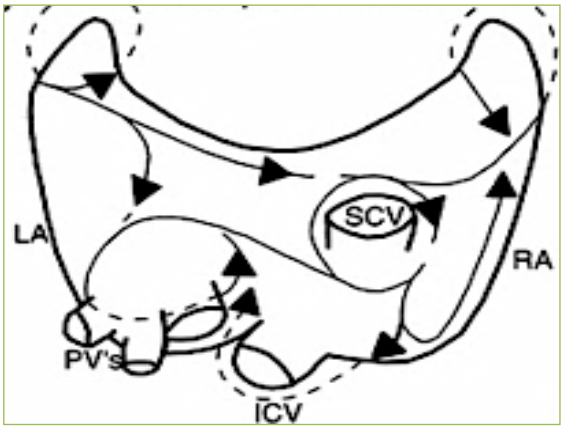


Figure 4.16: Posterior view of left atrium illustrating the multiple wavelet mechanisms of atrial fibrillation

Notes: LA = left atrium; PV = pulmonary vein; ICV = inferior vena cava; SCV = superior vena cava; RA = right atrium.

Source: Konings et al., 1994.

Jaïs *et al.* (1997) demonstrated how ablation could extinguish the source of AF, thus supporting the evidence of focal origin of AF (see Figure 4.17). Most frequently the source of the rapid atrial foci in AF originates from the pulmonary veins, but other areas of the heart have also been identified as the root of these foci, namely the superior vena cava, ligament of Marshall, left posterior free wall, *crista terminalis*, and coronary sinus (Jaïs *et al.,* 1997; Fuster *et al.*, 2006). Histological studies have ascertained that cardiac muscle, with conserved electrical function, stretches into the pulmonary veins (PV) and that, in patients with AF, the atrial tissue inside the pulmonary veins is documented to have shorter refractory periods than those in the control group of patients.

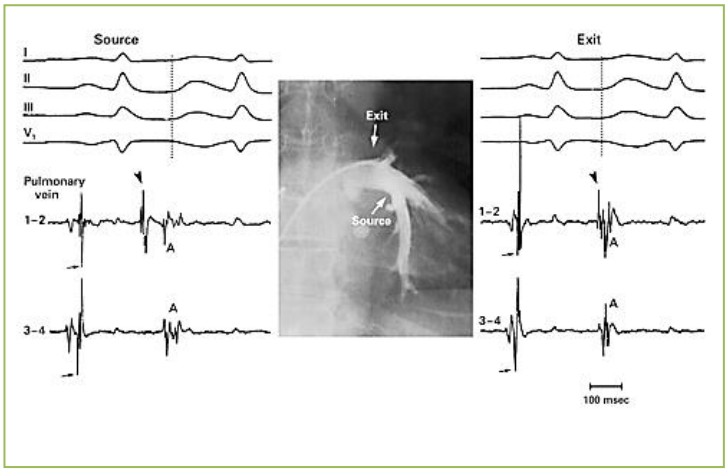


Figure 4.17: Angiogram of a left inferior pulmonary vein depicting the source and exit of ectopic activity

Notes: The electrogram showed characteristic changes in timing depending on the position of the recording catheter in the specific pulmonary vein. With an increasingly distal catheter position (toward the source), the spike was recorded progressively later during sinus rhythm (left-hand panel, arrows) and correspondingly earlier during ectopic activity (arrowhead). Conversely, in a proximal position at its exit into the left atrium (right-hand panel), the spike was not as delayed during sinus rhythm (arrows) nor as precocious during ectopic activity (arrowhead).

Source: Haïssaguerre et al., 1998.

The application of radio-frequency energy at the source of ectopic activity eliminated the local spike during sinus rhythm and ectopic beats and atrial fibrillation on a short-term basis. The dotted lines mark the onset of the ectopic p wave, and 1-2 and 3-4 are bipolar recordings from the distal and proximal poles of the mapping catheter. A indicates near-field atrial activity. The radiograph (centre panel) shows the position of electrographic recordings inside the pulmonary vein at the source and exit.

4.6.2 Atrial electrical remodelling

Re-establishing and maintaining sinus rhythm in AF through either pharmacological or direct-current cardioversion is better achieved when AF has been present for 24 hours or less, while AF episodes sustained for longer periods make the restoration to sinus rhythm less likely and contribute to the truism that ‘atrial fibrillation begets atrial fibrillation’ (Allessie *et al.,* 2001; Alessie *et al.*, 2002; Haïssaguerre *et al.,* 1998). The increasing propensity to AF and the progressive shortening of effective refractory periods with increasing episode duration, result in a phenomenon known as ‘electrophysiological remodelling’. In addition to the remodelling and the changes in electrical refractoriness, episodes of prolonged AF are shown to affect the contractile function of the atria negatively. After successful restoration of sinus rhythm, subsequent to a period of persistent AF, the recovery of atrial contraction can be delayed for days or even up to weeks. This has important implications for the duration of anti-coagulation after cardioversion (Fuster *et al.,* 2006).

4.6.3 The pathophysiology of thrombus formation

After successful cardioversion by any method, i.e. spontaneous, electrical, or pharmacological, stunning of the left atrial appendage (LAA) may result. This stunning of the LAA may account for an increased risk of thromboembolic events. Atrial stunning has shown to be at maximum effectiveness immediately after cardioversion and progressive improvement of the atrial transport function occurs from within days to three to four weeks after cardioversion. The rate of improvement is dependent on, among other things, the duration of the episode of AF. Clinical evidence has shown that more than 80% of all thromboembolic events are likely to occur within the first three days after cardioversion and almost all such events occur within the first ten days after cardioversion. Data, including TEE studies, have not only shown evidence of LA/LAA dysfunction following conversion for AF but have also confirmed the tenacious nature of thrombus in a significant number of patients. These findings provide evidence for the need for anti-coagulants for patients both before and after successful cardioversion except where contra-indications may exist. In spite of the fact that stunning of the LAA may be negligible in some patients with certain associated conditions, or when the episode is of short duration, all patients with AF, including lone AF where the episode has lasted longer than 48 hours, should be anti-coagulated at the time of cardioversion and for at least four weeks afterwards (Fuster *et al.,* 2006).

Current clinical and therapy guidelines are founded on the hypothesis that, for thrombus formation to occur, the patient needs to be in AF for at least 48 hours. This was identified by Stoddard in 1995, but is not always the case (Lin et al., 2003). A study where echo was performed on 317 patients, indicated that thrombi may occur in patients within 48 hours of onset of AF (Stoddard et al., 1995; Manning et al., 1989). Reduced blood flow in the LAA/LA at the time of AF can often be recognisable on echo as “smoky” or “hazy” with variable echo density or spontaneous echo-contrast (SEC). SEC is associated with stasis and thrombus formation in AF (Agarwal & Venugopalan, 2001: 64), as noted in Figure 4.18.

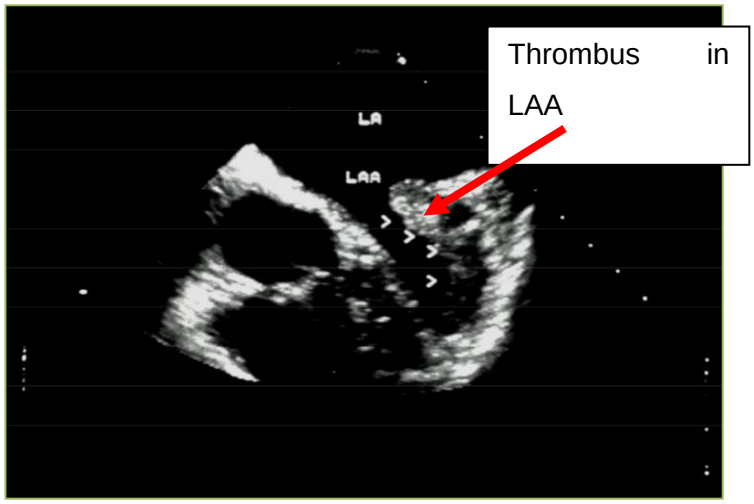


Figure 4.18: TEE of a mobile thrombus of approximately 2cm in diameter detected in the LAA

Source: medirec.ncvc.go.jp, 2008.

4.7 THROMBOEMBOLISM

Almost 50% of all elderly patients with AF suffer from hypertension, a key risk factor for the development of cerebrovascular disease. Almost 12% of these patients have carotid artery stenosis, although carotid atherosclerosis is not significantly more common in the patients who have AF and who have had a stroke, than in the patient group with no AF (Kanter *et al.,* 1994). Each year the risk of stroke as result of atrial fibrillation ranges from 3% to 8%, but may be as high as 10 to15%, depending on the patients' associated risk factors (Wolf *et al.*, 1991). AF is known to increase a patient's risk for stroke, but other factors, such as cardiac sources of embolism, atheromatous pathology in the proximal aorta and intrinsic cerebrovascular diseases cause up to 25% of strokes in patients. These data demonstrate that the pathogenesis of thromboembolic stroke is complicated (Miller *et al.,* 1993; Bogousslavsky *et al.,* 1990; Halperin & Hart, 1988).

Figures 4.18 to 4.21 demonstrate a series of TEE ultrasound examinations performed on a patient over a period of almost six weeks. Figure 4.18 shows a thrombus in the body of the left atrium, as indicated by the arrow, and is closely associated with the mitral annulus, in the posterior part of the atrium. The thrombus was measured at about 12mm in size and was mobile.

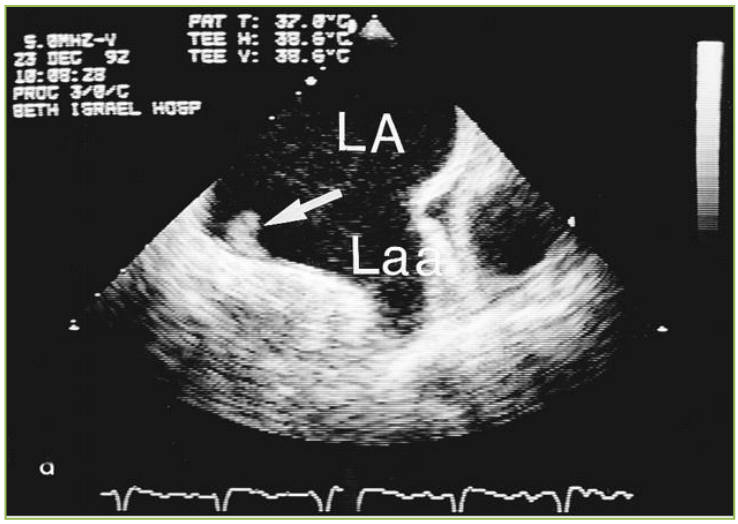


Figure 4.19: The first in a series of transoesophageal echocardiograms showing clot in the left atrium (LA)

Source: Adapted from Collins et al., 1995.

One week after the initiation of Warfarin therapy, TEE revealed that the thrombus persisted but had decreased in size (Figure 4.20).

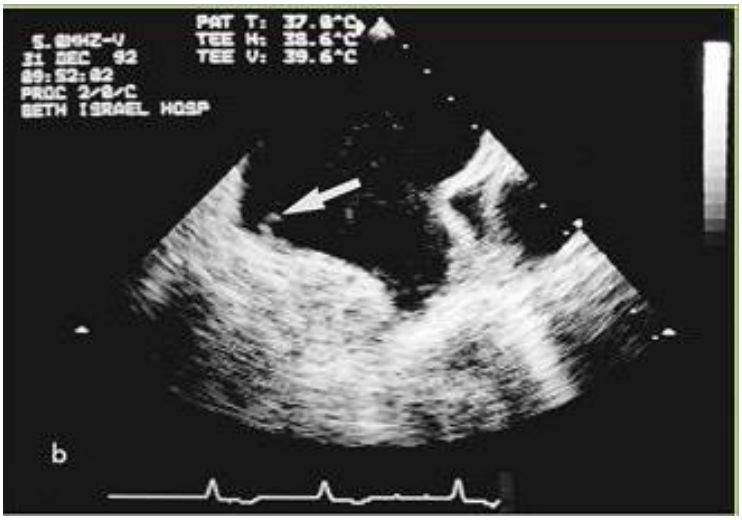


Figure 4.20: The second in a series of transoesophageal echocardiograms showing the left atrium (LA) and left atrial appendage (LAA) viewed with a TEE probe

Source: Adapted from Collins et al., 1995.

Three weeks after the commencement of Warfarin the thrombus continued to be seen, as indicated by the arrow in Figure 4.21.

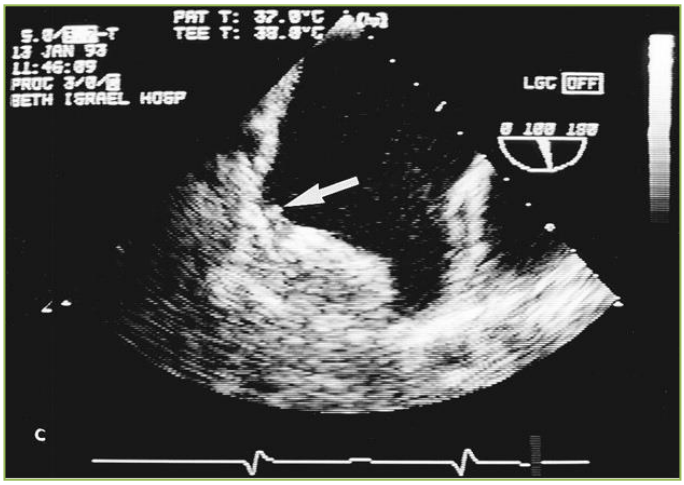


Figure 4.21: The third in a series of transoesophageal echocardiograms showing the left atrium (LA) and left atrial appendage (LAA) viewed with a TEE probe

Source: Adapted from Collins *et al.*, 1995.

Finally, after 5.5 weeks of Warfarin therapy, complete thrombus resolution was observed, as seen in Figure 4.22.

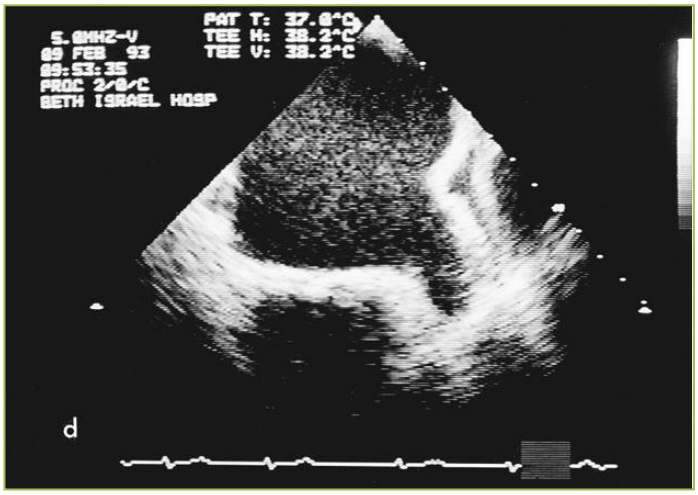


Figure 4.22: The fourth in a series of transoesophageal echocardiograms showing the left atrium (LA) and left atrial appendage (LAA) viewed with a TEE probe

Source: Adapted from Collins *et al.,* 1995.

4.8 ATRIAL FIBRILLATION AND MORTALITY

Benjamin *et al.* (1998) reported, after evaluating the original cohort of the Framingham study, that the mortality rate in both men and women was higher in those with AF when compared to those who did not suffer from the arrhythmia (P<0.0001) (Benjamin *et al.,* 1998). From 1980 to 1998, the age standardised death rate per 100 000 of the population in the USA who suffered from AF increased from 27.6 to 69.8 and by 1998, the number of patients with AF was almost double those patients who were in normal sinus rhythm (Fuster *et al.*, 2006).

The Kaplan-Meier mortality curves in Figures 4.23 and 4.24 identify the risk of death related to AF at the follow-up Framingham Heart Study in subjects 55-74 years old (Figure 4.23) and 74 to 95 years (Figure 4.24) (Benjamin *et al.*, 1998). The mortality rate, after adjustment for coexistent cardiovascular conditions and risk factors associated with AF, demonstrated a 1.5- to 1.9-fold increase in both men and women of various age groups. In addition, the first 30 days exhibited an increase in mortality which continued throughout the follow-up period.

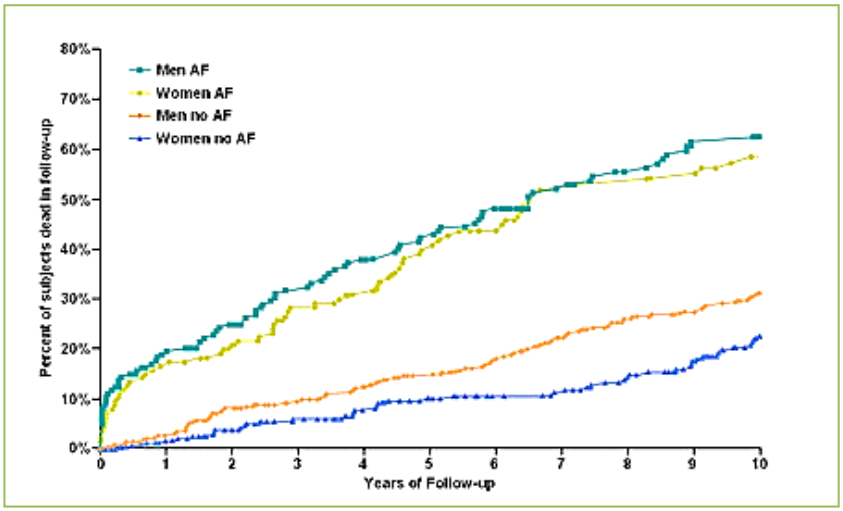


Figure 4.23: Kaplan-Meier mortality curve from follow-up Framingham Heart Study of subjects aged 55 to 74 years, with AF

Source: Benjamin et al., 1998.

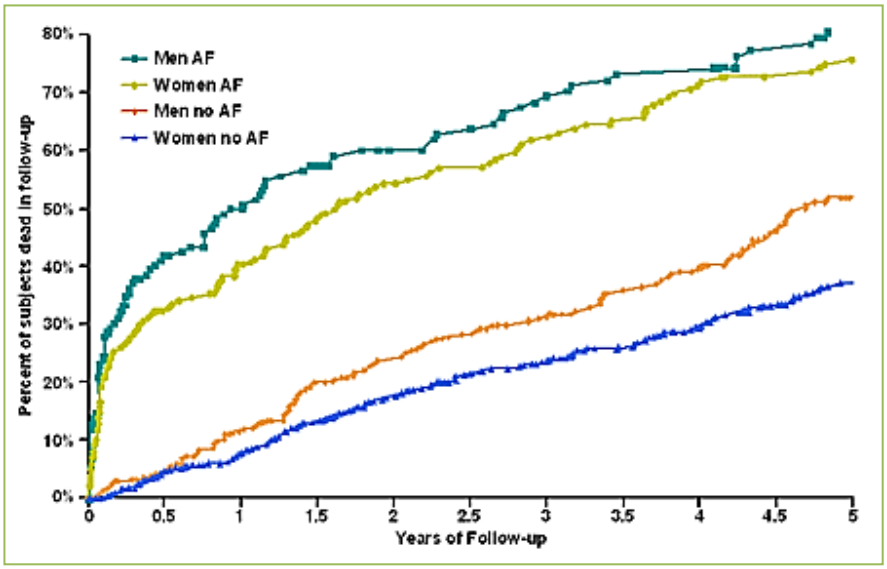


Figure 4.24: Kaplan-Meier mortality curve from follow-up Framingham Heart Study of subjects aged 74 to 95 years, with AF

Source: Benjamin et al., 1998.

A community-based cohort of 4618 adult residents of Olmsted County Minnesota (mean age 73.7 years for men and 76.4 years for women, range 18 to 95 years, 51% men), was studied and those patients who had AF confirmed on ECG, documented between 1980 and 2000, were followed up until 2004 or death. Miyasaka *et al.* (2006) reported that, after first AF diagnosis 3 085 patients had died during a mean follow-up time of 5.3 years. Of these deaths, 761 occurred within the first four months after diagnosis and the other 2 324 during the follow-up period (Miyasaka *et al.,* 2006). The Kaplan-Meier graph in Figure 4.24 demonstrates the early and increased mortality rate within four

months of 83% (95% CI 82% to 85%), compared to 77% (95% CI 76% to 78%) at one year, 63% (95% CI 62% to 65%) at three years, and 52% (95% CI 51% to 54%) at five years, respectively.

Relative to age- and gender-matched general Minnesota population, the mortality risk for AF patients was substantially higher (log rank p<0.0001). Of the early deaths (within four months), coronary artery disease (CAD) accounted for 22% of deaths, while congestive heart failure (CHF), and ischaemic stroke accounted 14%, and 10%, respectively. Of the deaths after four months CAD, CHF and ischaemic stroke accounted for 15%, 16%, and 7%, respectively (Benjamin *et al.*, 1998).

The most common non-cardiovascular cause of death was malignancy, which accounted for 18% of the early deaths and 14% of the late deaths. Figure 4.25 illustrates on the left graph the survival for the entire study population of patients diagnosed with first atrial fibrillation and on the right the subgroup of survivors who lived beyond the first four months after the initial AF diagnosis compared with the age- and gender-matched general Minnesota (MN) population.

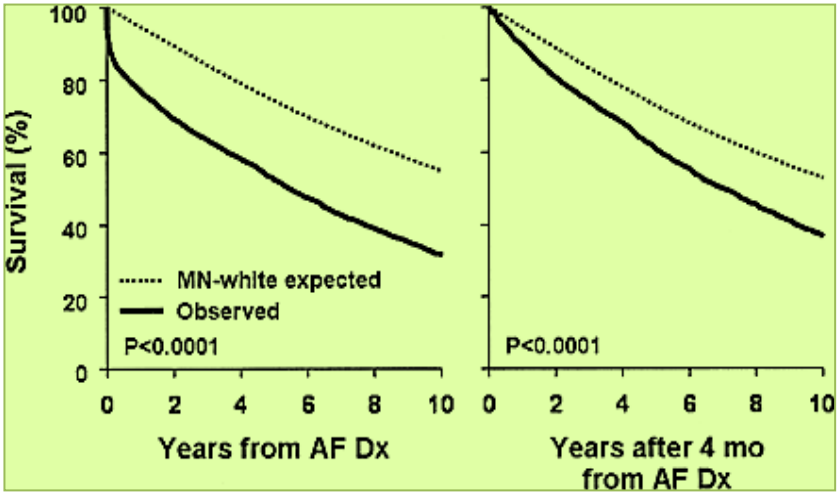


Figure 4.25: Survival for AF patients compared with the age- and gender-matched general Minnesota population

Source: Miyasaka et al., 2007.

In more recent data by Chugh *et al.* (2014), it was demonstrated that less than one percent of the deaths reported by the World Health Organisation was associated with atrial fibrillation. This is demonstrated in Figure 4.26. However, it was stressed that AF is often accompanied by other medical conditions, for example, heart failure and myocardial infarction, and that in these cases, the outcomes may be worse; in particular patients with new-onset AF in heart failure, the prognosis is very poor.

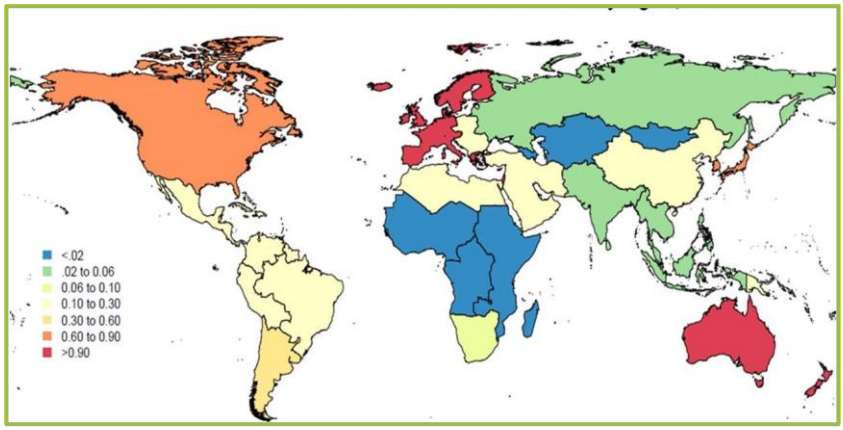


Figure 4.26: The percentage of deaths attributed to atrial fibrillation and flutter in 2010 by region

Source: Chugh et al. (2014).

Chugh *et al.* (2014) also illustrated that, in 1990, the age-adjusted mortality rate for AF as measured by 100 000 of the population was 0.8 (95% UI, 0.5–1.1) for men and 0.9 (95% UI, 0.7–1.2) for women. By 2010 there was an almost two-fold increase in the age-adjusted mortality rate, which was 1.6 in men (95% UI, 1.0–2.4) and 1.7 in women (95% UI, 1.4–2.2). Figure 4.27 shows that mortality in AF was higher for women than for men and, also, that the mortality rate increased between 1990 and 2005.

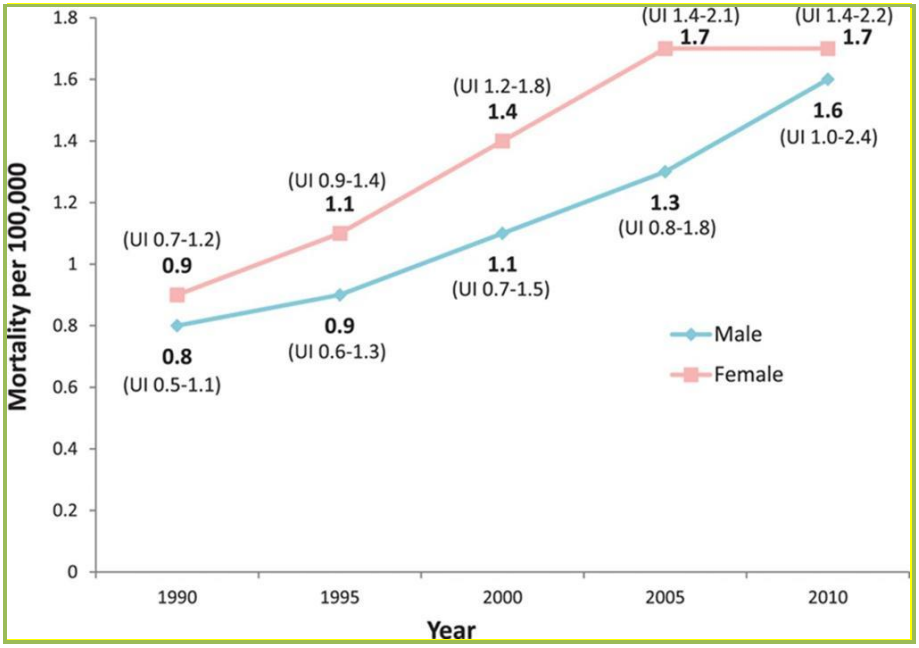


Figure 4.27: The mortality associated with AF per 100 000 of the population from 1990 to 2010

Source: Chugh et al. (2014).

4.9 THE CLINICAL IMPACT OF ATRIAL FIBRILLATION

Miller *et al.* (1993) found that, of 71 patients with non-rheumatic atrial fibrillation, who suffered ischaemic strokes, the cause of death was unknown in 17%; 18% were found to be non-cardio-embolic; and 65% were cardio-embolic (Miller *et al.*, 1993). This finding serves to confirm that the thromboembolic events at play in AF are complex and are related not only to atrial stasis, but also to systemic and local hypercoagulability, and may include endothelial dysfunction. There is a positive correlation between stroke in patients with AF and hypertension and it must be remembered that the risk of non-cardio-embolic strokes in patients with AF is further increased by hypertension.

Progressing age is cited as increasing the risk of stroke in patients with AF, but this is a highly complex situation as atherosclerotic disease and the presence of plaques in the aortic arch are also associated with aging and these are independent risk factors of stroke in AF (Blackshear *et al.,* 1999). Increasing age, especially over 75 years in women with AF, when pooled with risk factors like hypertension, have a significant bearing on the risk for stroke (Feng *et al.*, 2001).

4.9.1 Silent or asymptomatic atrial fibrillation (AF)

Silent or asymptomatic AF is believed to increase the risk of stroke in patients. In a study by Page *et al.* (2003), the investigators followed up patients in sinus rhythm who had a history of symptomatic AF. The double-blind study included 1 380 patients from the USA, 489 of whom received a placebo while the others received 35-125mg Azimilide daily for six to nine months. Within six months and before recurrence of symptomatic supra-ventricular arrhythmia, 17% of patients had experienced asymptomatic AF.

In the three trials evaluating Azimilide using therapeutic doses (100 and 125mg), asymptomatic atrial fibrillation occurred in 13% of patients receiving Azimilide, compared to 18% receiving the placebo. At least one asymptomatic atrial fibrillation event was recorded within the first four weeks in 12% of patients. The Kaplan-Meier curve in Figure 4.28 estimates the proportion of patients with at least one asymptomatic event within four weeks and 26 weeks to be 13% and 21% respectively.

After the evaluation of each of the four trials, the authors reported that asymptomatic atrial fibrillation was present in 10% to 20% of patients (Page *et al.*, 2003; Krahn *et al.,* 1995).

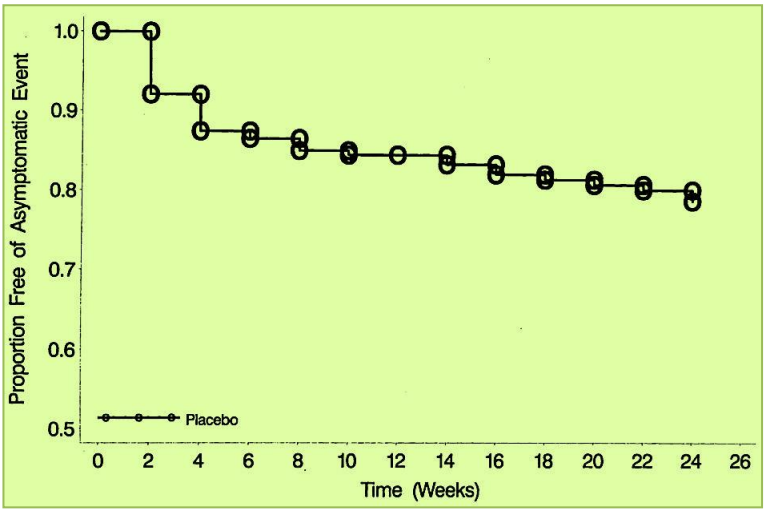


Figure 4.28: Kaplan-Meier plot for time to first documented occurrence of asymptomatic atrial fibrillation in all patients receiving placebo from the four trials (n=303 patients receiving placebo)

Source: Page et al., 2003.

Finally, Krahn et al. (1995) report that patients with AF had almost double the mortality rate compared to patients in sinus rhythm (Krahn et al., 1995). The ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation refers to large heart failure trials COMET and Val-HeFT, that cite AF as a strong independent risk factor for mortality and morbidity. Heart failure (HF) promotes AF, while AF aggravates HF, resulting in a poor prognosis in individuals with either condition who then go on to develop the alternate condition.

4.9.2 Atrial fibrillation and stroke

Current data widely accepts that the long-term risk of stroke, heart failure and all-cause mortality is increased in patients who suffer from AF (Adams *et al.,* 2008; Benjamin *et al.,* 1998; Go *et al.,* 2001) and that this risk is greater in women (Stewart *et al.,* 2002). Pooled data from five randomized trials were analysed comparing Warfarin only to Warfarin and aspirin. The mean age at time of randomization was 69 years and the mean blood pressure was 142/82mm Hg. The results showed that patients younger than 65 years with no other predictive factors (15% of all patients) had an annual rate of stroke of 1.0%, (95% CI, and 0.3% to 3.0%). However, the annual stroke rate in the patients on Warfarin was 1.4%, compared to the control group, 4.5%. This represents a 68% risk reduction (95% CI, and 50% to 79%) (Kanter *et al.,* 1994: 1449-57*)*.

Wolf *et al.* (1991) evaluated the effect which non-rheumatic atrial fibrillation, hypertension, coronary heart diseases, and cardiac failure had on the incidence of stroke in 5070 patients after 34 years of the Framingham study. The results were published in *Stroke* and the authors concluded that the age-adjusted incidence of stroke in the presence of coronary heart disease was more than doubled (p<001), while in the presence e of hypertension and heart failure, the risk more than trebled and,

where both heart failure and hypertension existed, the increase in risk was fourfold ($p<0.001$). Patients with AF had a fivefold increase in risk of stroke ($p<0.001$).

This landmark trial by Wolf *et al.* (1991) revealed that one in every six strokes occurs in a patient with atrial fibrillation and that, of all ischaemic strokes, 10% were as a result of emboli that originated as left atrial thrombi. When considering the patients who present with TIAs (transient ischaemic attack) or clinically “silent” stroke (detected by brain imaging), the rate of brain ischaemia accompanying non-valvular AF is observed to exceed 7% per year. Thus, the rate of ischaemic stroke among patients with non-valvular AF averages 5% per year; this is two to seven time that of people without AF (Wolf & Singer, 1997).

Clinical stroke is not a complication for all patients with atrial fibrillation, and the stroke rate may vary more than 20-fold, from 0.5% per year for young patients without organic heart disease or lone atrial fibrillation, to 12% per year in patients with atrial fibrillation that have had previous stroke (Fuster *et al.,* 2006). As noted, there is an increasing age-related risk of developing AF and it follows that the risk of stroke also increases with age. This was further demonstrated by Wolf *et al.* (1991) who reported that, in a study of participants aged 50 to 59 years old, the annual risk of stroke attributable to AF was 1.5%; this increased to 23.5% in those aged 80 to 89 years. Furthermore, in the Framingham Heart Study, in patients with rheumatic heart disease and AF, the risk of stroke was increased 17-fold compared with age-matched controls (Wolf *et al.,* 1978) and the attributable risk was five times greater than in those with non-rheumatic AF (Wolf *et al.,* 1991). The identification of risk factors for stroke in non-valvular atrial fibrillation is imperative, as it defends the need for individualised anti-thrombotic prophylaxis to be given according to stroke risk.

Founded on the data from the Framingham study, the investigators further researched the risk associated with stroke. This research was performed over a ten-year period and the population of interest was stroke-free individuals at baseline and between the ages of 55 and 84 years (D'Agostino *et al.,* 1994). The investigators established that the predictors for stroke were as follows:

- Age.
- Systolic blood pressure.
- Diabetes mellitus.
- Cigarette smoking.
- Prior cardiovascular disease.
- Atrial fibrillation.
- Left ventricular hypertrophy.
- Use of hypertensive medication.

Wang *et al.* (2004) went on to describe the risk of stroke or death in patients with new onset of AF and, based on this data, a new risk score was developed (Wang *et al.,* 2004), as shown in Table

4.18. For their study, the population of interest included 705 individuals between the ages of 55 and 94 years from the original and offspring cohorts of the Framingham Heart Study (Wang *et al.,* 2004).

Table 4.18: Step 1-5 of risk factors associated with risk of stroke in AF

Step 1	Risk Factor	Points		Risk Factor	Points
	Age				
	55-59	0		78-81	6
	60-62	1		82-85	7
	63-66	2		86-90	8
	67-71	3		90-93	9
	72-74	4		>93	10
	75-77	5			
Step 2	Gender				
	Male	0			
	Female	6			
Step 3	Systolic BP				
	<120	0			
	120-139	1			
	140-159	2			
	160-179	3			
	>179	4			
Step 4	Diabetes Mellitus				
	No	0			
	Yes	6			
Step 5	Prior stroke of TIA				
	No	0			
	Yes	6			
TOTAL SCORE FOR STEP 1 TO 5					

Source: Wang et al., 2004.

The inclusion criteria were the following:

- The patients had an occurrence of new-onset atrial fibrillation (AF).
- They were not treated with Warfarin at baseline.
- They had not had a stroke or transient ischaemic attack (TIA), or died within 30 days of AF diagnosis.
- They were without rheumatic mitral stenosis.

Wang *et al.* (2004) followed up these patients for a maximum of ten years (mean four years) and a five-year risk was estimated. To estimate five-year risk, a six-step scoring system was developed, as seen in Tables 4.18 and 4.19. For the purpose of the study, the investigators narrowed the predictors down from the previous scoring system and the following were included:

- Age.
- Gender.
- Systolic blood pressure.
- Diabetes mellitus.
- Prior stroke or ischaemic attack.

Table 4.19: Step 6: Predicted five-year risk of stroke with atrial fibrillation (AF)

Total points	5-year risk (%)	Total points	5-year risk (%)	Total points	5-year risk (%)
<1	*5%*	**13**	*18%*	**23**	*44%*
2-3	*6%*	**14**	*19%*	**24**	*48%*
4	*7%*	**15**	*21%*	**25**	*51%*
5	*8%*	**16**	*24%*	**26**	*55%*
6-7	*9%*	**17**	*26%*	**27**	*59%*
8	*11%*	**18**	*28%*	**28**	*63%*
9	*12%*	**19**	*31%*	**29**	*67%*
10	*13%*	**20**	*34%*	**30**	*71%*
11	*14%*	**21**	*37%*	**31**	*75%*
12	*16%*	**22**	*41%*		

Source: Wang et al., 2004.

4.9.3 Atrial fibrillation and heart failure

The first physician to describe an association between AF and heart failure, almost a century ago, was Paul Dudley who wrote:

> *Since auricular fibrillation so often complicates very serious heart disease, its occurrence may precipitate heart failure or even death, unless successful therapy is quickly instituted (Anter et al., 2009).*

Anter *et al*. (2009) describe heart failure and atrial fibrillation as the new cardiovascular epidemic of the last decade. The incidence of heart failure in the United States has remained stable over the past 50 years. Up to 2009, 550 000 new patients were diagnosed with heart failure each year in the United States. However, the prevalence of heart failure has steadily increased, and it is estimated that more than five million Americans are affected by heart failure (Anter *et al.,* 2009).

In modern heart failure studies, the reported prevalence of AF ranges from 13% to 27%. In the Framingham Heart Study, 1 470 participants developed either AF or heart failure between the years 1948 and 1995 and 26% of these participants developed both AF and heart failure (n=383). The investigators found that the prevalence of AF in patients with concomitant heart failure increased in parallel with the severity of the disease, ranging from as little as 5% in patients with mild heart failure to between 10% and 26% among patients with moderate heart failure and as much as 50% in patients with severe heart failure.

The pathophysiological connection between heart failure and AF is not fully understood, but it is believed that AF may facilitate the onset and or progression of heart failure by a number of mechanisms, as seen in Figure 4.29.

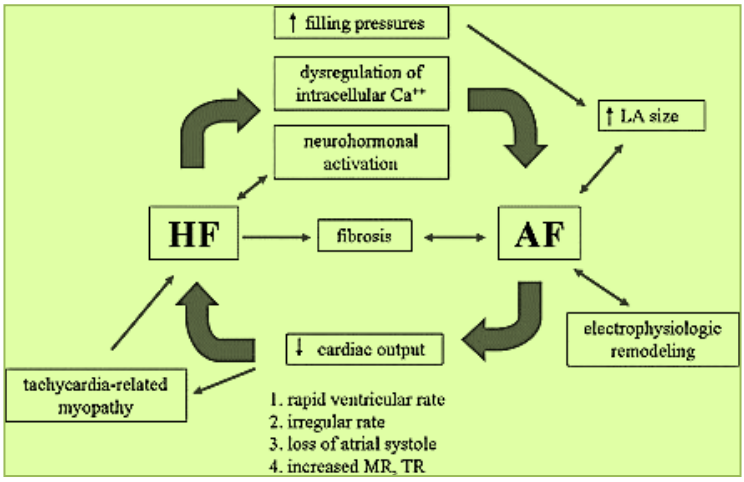


Figure 4.29: AF and heart failure (HF): A vicious pathophysiological cycle

Notes: LA indicates left atrial; MR, mitral regurgitation; and TR, tricuspid regurgitation.

Source: Anter *et al.,* 2009.

Despite the fact that the causative relationship between AF and heart failure has not been fully established, both conditions have common risk factors, including increasing age, diabetes, hypertension, valvular disease, ischaemic and non-ischaemic structural heart disease, and obesity. All of these risk factors are coupled with changes in myocardial cellular and extracellular function, alterations in electrophysiology, and neuro-hormonal modifications. These changes may all predispose the patient to both AF and heart failure.

In 1913 the first case of a tachycardia-mediated cardiomyopathy was described in a young man with atrial fibrillation with a rapid ventricular response, heart failure and inexplicable LV dilation. A similar case was again described in 1937. However, this case of heart failure was reversed after restoration of sinus rhythm as illustrated in Figure 4.30. The most common cause of tachycardia-induced cardiomyopathy is AF where the increase in resting heart rate as well as the heart rate during exercises results in decreased diastolic filling time, and a reduction in cardiac output. In patients with AF the decrease in left ventricular filling during a short R-R interval is not completely compensated for by increased filling during a longer R-R interval.

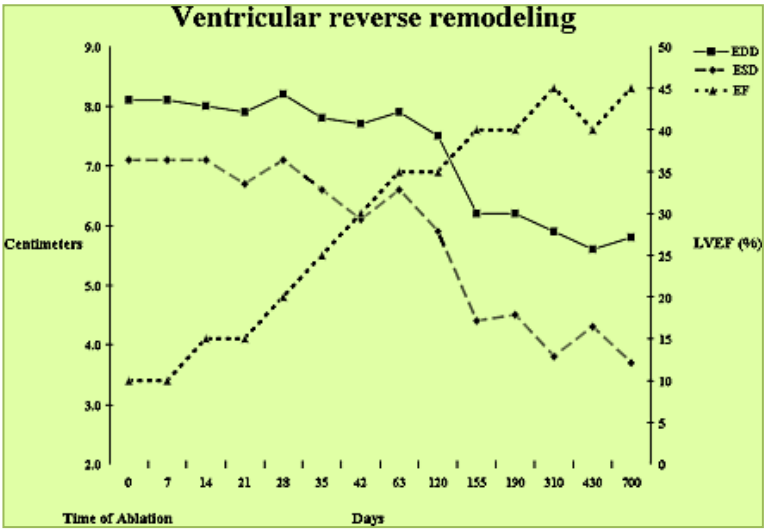


Figure 4.30: Ventricular reverse remodelling in an 18-year-old patient with unrecognised atrial tachycardia-induced cardiomyopathy

Notes: EDD= end diastolic diameter, ESD= end systolic diameter, EF= ejection fraction, LVEF=left ventricular ejection fraction.

Source: Anter et al., 2009.

Anter *et al.* (2009) discussed a prospective study that included 344 patients who were in sinus rhythm with heart failure where the onset of AF was linked with a significant deterioration of their New York Heart Association (NYHA) functional class, peak oxygen consumption, and cardiac indices, as well as increased mitral and tricuspid regurgitation. As illustrated in Figure 4.30 patients may experience an improvement in cardiac output, exercise capacity, and maximal oxygen consumption once sinus rhythm is restored.

Little consensus exists about the prognostic consequence of AF as an independent risk factor of adverse outcome in patients with coexisting heart failure, as demonstrated from the Framingham Heart Study which indicated that AF was associated with double the cardiovascular mortality when compared with patients who were in sinus rhythm. Table 4.20 highlights the lack of consensus on this topic.

Table 4.20: Prognostic significance of AF in patients with heart failure

Author/ sub study	Year	NYHA class	Patients, (n)	AF, %	Follow-up, y	Patients in SR, (n)	Patients with AF. (n)	*P-value*	Predictor
Carson *et al.*									
V-HeFT I	1993	II–III	632	15	2.5	64	54	0.86	No
V-HeFT II		II–III	795	13	2.0	52	46	0.68	
Dries *et al*. SOLVD	1998	I–IV	6517	6	2.8	23	34	<0.001	Yes
Mahoney *et al.*	1999	III–IV	234	27	1.1	16	23	0.21	No
Middlekauf *et al.*									
1985–1989	1998	III–IV	359	20	2.0	45	61	0.002	Yes
1990-1991	1991	III–IV	395	19	1.5	29	48	0.0013	Yes
1990–1993	1993	III–IV	391	24	2.0	25	34	0.09	No
Mathew/DIG[a]	2000	I–IV	7788	11	3.0	32	43	0.0001	Yes
Crijns/PRIME II[b]	2000	III–IV	409	84	3.4	47	60	NS*	No
Køber/VALIANT	2006	I–IV	14703	15	3.0	20	37	<0.0001	Yes
Swedberg *et al* COMET	2005	II–IV	3029	20	5.0	37	42	NS	No*

*Notes: SR indicates sinus rhythm; DIG, Digitalis Investigation Group; PRIME II, Prospective randomised study of Ibo amine on Mortality and Efficacy, *After adjustment for important prognostic variables.*

Source: Anter et al., 2009.

However, these trials may serve to highlight that AF may be a negative prognostic marker in patients with systolic heart failure, and that the independent effect of AF on mortality is inversely related to the severity of the heart failure. Ahmed & Perry, as cited by Anter *et al.* (2009), found that, of the 944 aged patients who were hospitalised with heart failure, those with onset of new AF had significantly higher mortality risk when compared with patients with no AF or those with chronic AF (HR, 1.41; 95% confidence interval, 1.08 to 1.83). More than 80% of patients who were hospitalised with heart failure and found to have new-onset AF died within four years of discharge, compared with only 61% to 66% in those without AF or with persistent AF (Anter *et al.,* 2009).

4.9.4 Other clinical consequences of atrial fibrillation

Haemodynamic function during an episode of AF is affected by, among other things, loss of synchronous atrial mechanical activity within the ventricles. This may cause an irregular ventricular response (R-R interval), rapid heart rate, and impaired coronary arterial blood flow. Cardiac output may be markedly decreased through the loss of atrial contraction, particularly when the diastolic filling of the ventricles is impaired by other co-morbidities such as mitral stenosis, hypertension, hypertrophic cardiomyopathy (HCM), or restrictive cardiomyopathy.

A persistently elevated ventricular rate during AF may adversely affect mitral regurgitation, resulting in a dilated ventricular cardiomyopathy (tachycardia-induced cardiomyopathy). In this instance, the cause of the cardiomyopathy is due to the heart failure rather than the AF, therefore the ability to control the ventricular rate may initiate the reversal of the myopathic process (Tracey, 1998).

4.10 CONCLUSION

Atrial fibrillation is a complex disease that affects millions of people around the globe. Data indicate that the number of people affected by the disease is increasing as the world's population lives longer. Stroke, TIA, CHF and a myriad of other co-morbidities are associated with AF, some with deleterious outcomes for the patient. Early diagnosis may help to prevent some of the risks associated with AF and improve the outcome for the patient as it has been shown that there is an increased four-year mortality rate in patients with new onset AF.

Management of this disease should focus not only on reducing symptoms but also on preventing complications linked with AF. Unfortunately, the management of the disease is in many instances as complex as the disease itself. This has prompted numerous approaches to treat and manage the disease, all with varying degrees of success. Chapter 5 explores these management options, in order to determine the risk associated with each, as well as the documented success rates and complications. This is important to ensure that the proposed model is a relevant option challenging the current standard of care for the treatment of AF.

CHAPTER 5: THE MANAGEMENT OF ATRIAL FIBRILLATION

5.1 INTRODUCTION

The management of atrial fibrillation is, at times, as complex as the disease itself. Each management option yields varying degrees of success. The standard of care for treating AF remains drug therapy which, in spite of a considerable number of drug trials, remains only marginally effective, with a large number of patients returning to AF.

Chapter 5 is again a descriptive chapter which focuses on the treatment options for AF that are found in peer-reviewed journals, all with varying degrees of success and also with different risks attached. This chapter is not only of value to the non-medical reader, but also the medical reader who is not involved in the treatment of AF on a daily basis. The importance of this chapter is that it explores all the options that are available and narrows the choice down to two options, which can be used to build a cost effectiveness model with appropriate therapies.

The topics covered in this chapter include the following:

- Pharmacological treatment options.
- Non-pharmacological options.
- Surgery.
- Various types of permanent pacemakers.
- Radiofrequency ablation.
- Cryoablation.

5.2 BACKGROUND

The management of patients with atrial fibrillation involves three therapeutic goals, namely, to control the heart rate (rate control), maintain sinus rhythm, and prevent thromboembolism. These goals are not mutually exclusive, and the risks and benefits of each treatment must be considered for each individual patient. The initial management decision involves primarily a rate control or rhythm control strategy. Under the rate control strategy, the ventricular rate is controlled with no commitment to restore or maintain sinus rhythm. On the other hand, the rhythm control strategy attempts restoration and/or maintenance of sinus rhythm. The latter strategy also requires attention to rate control. Depending on the patient's course, the strategy initially chosen may prove unsuccessful and an alternate strategy is then adopted. Regardless of whether a rate control or a rhythm control strategy is pursued, attention must also be directed to anti-thrombotic therapy for the prevention of thromboembolism (Prystowsky, 2008; Fuster *et al.,* 2006).

5.3 TREATMENT OPTIONS FOR PATIENTS WITH ATRIAL FIBRILLATION

The therapeutic choice of the physician depends on how symptomatic each individual patient is, as well as the specific symptoms each patient experiences. For example, where a patient with AF has a rapid ventricular response, the symptoms are often described as palpitations and treatment may be directed at the AV-nodal conduction system so as to decrease the rate. This can be achieved either through the use of drugs or, if this fails, through the implementation of non-pharmacological methods.

In contrast, a patient with a controlled ventricular response during AF, who experiences shortness of breath and or fatigue, often benefits from the restoration and maintenance of sinus rhythm. Depending on the circumstances, an asymptomatic patient and, in particular, one with good rate control, may not need any further therapy other than the consideration for anti-coagulation (Prystowsky, 2008).

Both drugs and catheter ablation are effective for rate and rhythm control strategies, but in some special circumstances surgery may be the preferred option. Regardless of the approach, the need for anti-coagulation is based on the risk of stroke and not on whether sinus rhythm is maintained. For rhythm control, drugs are typically the first choice and left atrial ablation is a second-line choice, especially in patients with symptomatic lone AF. In some patients, especially young people with very symptomatic AF, in whom sinus rhythm is preferable, radiofrequency ablation may be preferred over years of drug therapy. Patients with pre-operative AF undergoing cardiac surgery face a unique opportunity to undergo a Maze procedure at the time of surgery as there are otherwise only a few candidates for a stand-alone surgical procedure to treat AF by means of the Maze or LA ablation techniques. These approaches can, however, be an effective adjunct to coronary bypass or valve repair surgery to prevent recurrent post-operative AF. Because more than 95% of detected thrombi are found in the LAA, this structure is commonly removed from the circulation during cardiac surgery for patients who are at risk of developing post-operative AF, although this has not been proven to prevent stroke (Healey *et al.,* 2005b).

5.3.1 Primary prevention

In spite of the fact that AF is a disease with an incidence of up to 10% per annum, there are no landmark primary prevention studies as there has been with, for example, cholesterol management. Young-Xu *et al.* (2004) report, in a study of 449 patients with CAD who were on statins for five years, that there was a reduction in the incidence of AF, while other studies have suggested that statins may also protect one against AF (Young-Xu *et al.,* 2004; Siu *et al.,* 2003). While this has not been observed with the use of other lipid-lowering drugs, the data is deemed inadequate to recommend statins for primary prevention of AF in populations at risk (Ashburn *et al.,* 2003; Mozaffarian *et al.,* 2004).

The use of angiotensin receptor antagonists in the CHARM and LIFE studies showed that the incidence of AF was reduced in patients who were hypertensive with left ventricular hypertrophy (LVH) and who had symptomatic HF (Wachtell *et al.,* 2005; Maggioni *et al.,* 2005; Olsson *et al.,* 2006).

Similar results were found during the secondary analysis of placebo-controlled trials using Angiotensin Converting Enzyme (ACE) inhibitors for treatment (Pedersen *et al.,* 1999; Alsheikh-Ali *et al.,* 2004). Data from eleven clinical trials, which included more than 56 000 patients with various cardiovascular diseases, suggested that the use of Angiotensin Receptor Blockers (ARBs) and or ACE inhibitors has the propensity to diminish the episodes and re-emergence of AF (Healey *et al.,* 2005a).

5.3.2 Rate vs. rhythm control

While the long-term goal for patients with symptomatic AF, lasting many weeks, may be the restoration of sinus rhythm, the initial treatment is often anti-coagulation and rate control. When the duration of AF exceeds 48 hours or is not known and the patient requires electrical cardioversion, the guidelines suggest that they may benefit from short-term anti-coagulation even if long-term anti-coagulation is not required. Where rate control does not offer adequate symptomatic relief for the patient, the restoration of sinus rhythm becomes the long-term goal. Patients who suffer from hypotension or whose heart failure is worsened due to episodes of AF often require early cardioversion. In contrast, older patients whose symptoms improve through rate control may not require attempts to restore sinus rhythm. There are situations such as thyrotoxicosis or post-cardiac surgery, when the initiating pathophysiology of AF is reversible and, under these conditions, no long-term therapy may be necessary (Fuster *et al.,* 2006: 25).

Large randomized trials investigating both rhythm and rate control in AF have shown similar findings, as seen in Table 5.1. In the RACE trial (Rate Control *vs*. Electrical cardioversion for persistent AF) the investigators did not find rate control inferior to rhythm control for the prevention of death and morbidity in patients with AF, while the AFFIRM trial (Atrial Fibrillation Follow-up Investigation of Rhythm Management) showed no difference in stroke or mortality rate between patients assigned to either rate or rhythm control. It is thought that clinically silent recurrences of AF in asymptomatic patients who are treated with anti-arrhythmic drugs, but in whom anti-coagulation therapy is withdrawn, may be responsible for thromboembolic events after the withdrawal of the anti-coagulation, and that patients who are at high risk for stroke may require anti-coagulation regardless of whether the rate control or rhythm control strategy is chosen. It is important to remember that the AFFIRM study was not designed to address this question (Sherman *et al.,* 2005: 194).

Patients with similar health status, for example AF, may experience an entirely different quality of life while affected by the same disease and data from many of the above studies has led clinicians to

agree that treatment must be tailored to each individual, depending on the nature, intensity, and frequency of symptoms, patient preferences, co-morbid conditions, and the ongoing response to treatment in many patients, medications that use both anti-arrhythmic and rate-controlling effects may be necessary. A further option to be considered in order to maintain sinus rhythm in selected patients who failed to respond to anti-arrhythmic drug therapy may be catheter ablation (Oral *et al.,* 2006).

Table 5.1: Trials comparing rate control and rhythm control strategies in AF

Trial	Patients (n)	AF Duration	Follow-up (y)	Age (mean y ± SD)	Patients in SR	Clinical Events			
						Stroke/ Emboli		Death	
						Rate	Rhythm	Rate	Rhythm
AFFIRM (2002)	4 060	NR	3.5	70±9	35% *vs*. 63% at 5 yrs.	88/2027	93/2033	310/2027	355/2033
RACE (2002)	522	1 to 399 days	2.3	68±9	10% *vs*. 39% at 2.3 yrs.	7/256	16/266	18/256	18/266
PIAF (2000)	252	7 to 360 days	1	61±1	10% *vs*. 56% at 1y	0/125	2/127	2/125	2/127
STAF (2003)	200	6±3m	1.6	66±8	11% *vs*. 26% at 2yrs.	2/100	5/100	8/100	4/100
HOT CAFE (2004)	205	7 to 730 days	1.7	61±11	NR *vs*. 64%	1/101	1/104	1/101	3/104

Notes: Comparison between rate and rhythm control groups. Approximately one third of patients were enrolled with first episode of Atrial fibrillation (AF).AFFIRM indicates Atrial fibrillation Follow-Up Investigation of Rhythm Management; ECV, internal or external electrical cardioversion; HOT CAFÉ, How to Treat Chronic Atrial fibrillation; IA, quinidine, procainamide; IC, propafenone and/or Flecainide; NR, not reported; PIAF, Pharmacological Intervention in Atrial fibrillation; RACE, Rate Control Versus Electrical Cardioversion for Persistent Atrial fibrillation; SR, sinus rhythm; STAF, Strategies of Treatment of Atrial fibrillation; and TE, thromboembolism.

Source: Sherman et al., 2005.

5.3.3 Pharmacological rate control during atrial fibrillation

It has been demonstrated that drugs with a mode of action aimed at prolonging the refractory period of the AV node are by and large effective in rate control. This is because the functional refractory period of the AV node during AF is inversely correlated with the ventricular rate. No evidence exists to prove that controlling the rate pharmacologically results in any unfavorable effect on LV function. It is important to note that ensuing bradycardia and heart block, unwelcome side effects of beta blockers, Amiodarone, *digitalis glycosides*, or non-dihydropyridine calcium channel antagonists, may

be present specifically in patients with paroxysmal AF, and more particularly in the elderly. Combinations of drugs from different pharmacological classes may be required to achieve rate control in both acute and chronic situations. Patients who develop symptomatic bradycardia may require permanent pacing as discussed in section 5.10. When optimal pharmacological measures fail to control the patient's symptoms, non-pharmacological treatment options should be considered.

5.3.4 Pharmacological cardioversion

While a sizeable segment of patients with recent-onset AF revert spontaneously to sinus rhythm within 24 to 48 hours, it is less likely to occur in patients whose AF has been present for longer than seven days (Azpitarte *et al.,* 1997). Cardioversion may be achieved through the use of pharmacological agents, and current data suggests that this is most effective when the drug therapy is initiated within seven days after the onset of an episode of AF (Suttorp *et al.,* 1990). Thereafter, the efficaciousness of pharmacological cardioversion is noticeably diminished in these patients (Kochiadakas *et al.,* 1999).

The use of beta blockade or non-dihydropyridine calcium channel blockers may be encouraged in patients with atrial flutter to prevent rapid AV conduction (Feld*,* 1990; Leitch *et al.,* 1990). When deciding whether to initiate anti-arrhythmic drug therapy in hospital or on an outpatient basis for the pharmacological cardioversion of AF the potential for serious adverse effects, including torsade's de pointes exists and must be considered. Fuster *et al.* (2006) state that a large majority of studies examining pharmacological cardioversion of patients with AF, except those involving low-dose oral Amiodarone, were conducted on hospitalised patients. It should be considered that frequent and repeated hospitalisation not only has a financial impact for the patient but also an effect on the quality of life for the patient (Alboni *et al*., 2001).

5.3.5 Prevention of thromboembolism

The risk of stroke in atrial fibrillation has been discussed in Section 4.8.2. In the SPAF trial (Stroke Prevention in Atrial fibrillation III) the yearly incidence of ischaemic stroke in patients with paroxysmal AF, who were treated with aspirin, was comparable with those who were in permanent AF (3.2%:3.3%) (Hart *et al*., 2000). The annual stroke rate in patients with a previous history of TIA or stroke, when treated with aspirin, had subsequent stroke rates of 10% to 12% per year. Moreover, it is now accepted that prior thromboembolism, increasing age, diabetes mellitus, hypertension and heart failure are recognized as independent risk factors for ischaemic stroke associated in non-valvular AF (Hart *et al*., 1999). These patients benefit substantially from adjusted-dose oral anti-coagulation (Blackshear *et al.,* 1996). It has been argued that prior TIA or stroke remains the greatest independent predictor of stroke, and that all patients with prior TIA or stroke should be anti-coagulated save those in whom contra-indications exist. Despite the fact that patient age, too, is an independent predictor of stroke, older

people are at increased risk of bleeding associated with anti-coagulant use and to err on the side of caution with older patients constitutes effective stroke prophylaxis (Landefeld & Goldman, 1989; Moulton *et al.,* 1991).

The goal of anti-coagulation therapy with Warfarin is to achieve a therapeutic international normalized ratio (INR) range of between two and three, and this is a suitable target for most patients with atrial fibrillation. These are tabulated in Table 5.2. Values of less than 2.0 are associated with an increased incidence of thromboembolic events while INR values exceeding 4.0 are linked to an increased risk of bleeding complications (Cox *et al.,* 1996). A meta-analysis by Cox el al demonstrates the outcomes for patients who received Warfarin had a better outcome than the control group (Figure 5.1).

Table 5.2: ACC/AHA/ESC guide to anti-thrombotic therapy for patients with AF

Risk category	Recommended therapy
No risk factors	Aspirin, 81 to 325mg daily
One moderate-risk factor	Aspirin, 81 to 325mg daily, or Warfarin (INR 2.0 to 3.0, target 2.5)
Any high-risk factor or more than 1 moderate-risk factor	Warfarin (INR 2.0 to 3.0, target 2.5)

Source: Fuster et al., 2006.

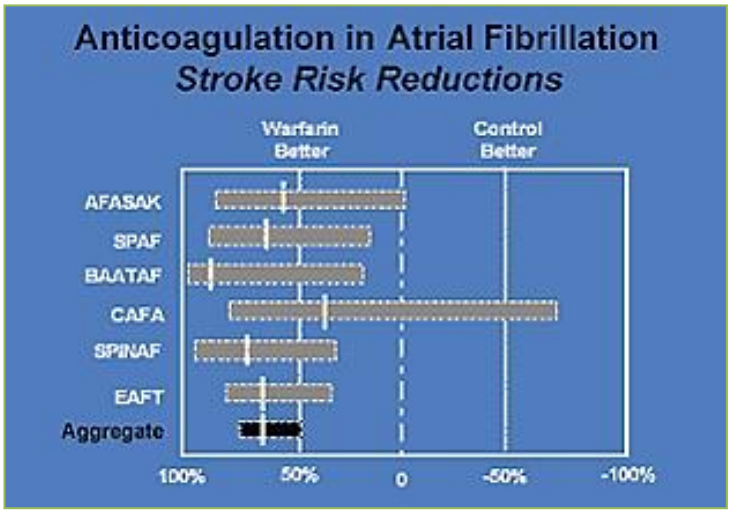


Figure 5.1: A comparison of studies demonstrating the use of Warfarin in AF for stroke risk reduction

Source: Cox et al., 1996.

5.4 THE NON-PHARMACOLOGICAL TREATMENT OF ATRIAL FIBRILLATION

The unpredictability of the efficacy, as well as the potential toxicity and side effects associated with the use of anti-arrhythmic drugs has, over the past decades, resulted in investigations into various

alternatives to pharmacological therapies for the prevention and control of AF. These therapies are discussed below.

5.4.1 Direct current (DC) cardioversion

Cardioversion (also known as electrical cardioversion, "direct-current" or DC cardioversion), is a short procedure where a timed electrical shock is delivered to the heart through the chest wall in an attempt to convert an abnormal heart rhythm back to a normal rhythm. This can be achieved by using either paddles or special electrodes placed on the front and back of the chest. The procedure is usually performed in a hospital environment with a cardiologist, a nurse and/or an anesthesiologist present. The aim of DC shock as shown in Figure 5.2 is to disrupt the abnormal electrical circuit(s) in the heart and to restore to sinus rhythm.

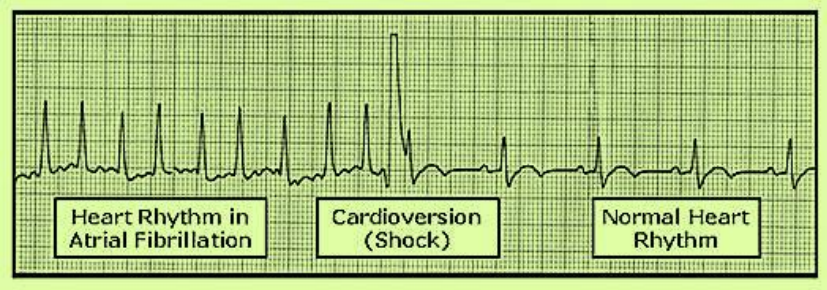


Figure 5.2: ECG of patient undergoing DC shock for atrial fibrillation

Source: Shilling, 2009a.

The shock is believed to cause all the heart cells to contract simultaneously, thereby interrupting and terminating the abnormal electrical rhythm (typically fibrillation of the atria) without damaging the heart.

If a patient presenting with AF is not on anti-coagulants such as Warfarin, and the episode of AF is less than 48 hours, cardioversion may take place after an echo has established that there are no evident thrombi in the LAA. Patients in whom the episode is longer than 48 hours, or who don't know when the onset was, or where a clot is seen on echo, should first be anti-coagulated for a few weeks before attempting cardioversion.

For new-onset AF, electrical cardioversion is usually effective at converting the heart back into normal sinus rhythm, but it may have a low success rate in keeping it there, and reversion to AF after cardioversion is common, with 50% of patients being in AF only six weeks after cardioversion. The number of patients reverting to AF after cardioversion increases as time goes by, which may necessitate multiple attempts to electrically cardiovert the patient. The most common problem after a DC cardioversion is painful skin burns. The procedure itself is safe, but it is associated with between 1% and 7% of complications of stroke in patients who are not adequately anti-coagulated (Arnold *et al.,* 1992; Fuster *et al.,* 2006). Cardioversion does not alter the underlying causes of AF,

nor is it a cure for AF. The benefit of performing cardioversion is that it is a relatively simple and easy procedure to perform which is successful in restoring sinus rhythm in 60-95% of patients, and particularly in patients where the AF has been induced by a reversible cause such as a chest infection (Shilling, 2009b; Russo, 2006).

5.4.2 Surgery

Based on the hypothesis that the chief mechanism for AF is a re-entry circuit in the LA, the first surgical procedure for the treatment of AF, known as the Cox Maze, was performed at the St. Louis' Barnes Hospital in 1987 (Cox *et al.*, 1996).

The purpose of the surgical approach is to eradicate macro re-entrant circuits in the atria (see Figure 5.3) while conserving the function of the sinus node and maintaining atrial transport functions. This is achieved through creating transmural lesions in the atria to create barriers to these macro re-entrant circuits and thereby preventing sustained AF (Cox, 2004).

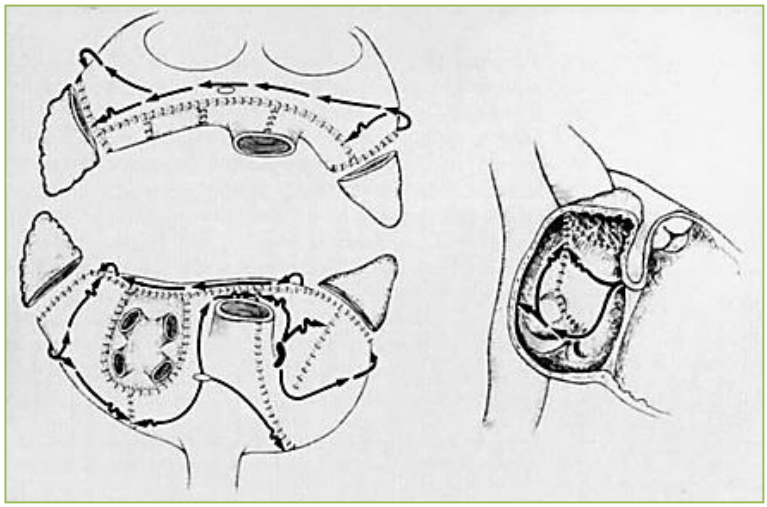


Figure 5.3: Two-dimensional representation of the original Maze I procedure for atrial fibrillation

Source: Cox *et al.*, 1996.

The evolution of the surgical technique has resulted in an accepted theory which purports that creating transmural lesions to isolate the pulmonary veins and then joining the scar lines to the mitral valve annulus results in electrical barriers in the atria which prohibit macro re-entrant circuits from developing. These macro re-entry circuits are responsible for atrial flutter or AF becoming sustained (Cox *et al*., 1995).

The long-term success rates of the Maze procedure are reported at between 70% and 95% over a 10 to 15-year follow-up period in patients undergoing mitral valve surgery (Damiano *et al*., 2003; Gillinov & McCarthy, 2004). These studies indicate that the atrial transport function is preserved and

that when, at the time of surgery, the LAA is eliminated, the risk of thromboembolism post-surgery is significantly reduced.

The Cox-Maze procedure has a very high success rate and the associated adverse events, namely death (less than 1% when performed as an isolated procedure), bleeding, atrial-oesophageal fistula, complete heart block (requiring permanent pacing), and other arrhythmia is low, but the need for cardiopulmonary bypass means that the Maze operation has not been widely accepted and is not performed routinely for patients undergoing cardiac surgery. While not commonly performed, the Maze procedure has promoted investigation into less invasive procedures and, in particular, catheter-based procedures (Gillinov & McCarthy, 2004).

5.4.3 Regulation of atrio-ventricular nodal conduction by pacing

5.4.3.1 The case for right ventricle (RV) apex pacing

Some patients with AF who are on medication develop bradycardia at rest while others are particularly sensitive to the variability of R-R interval, which increases their symptoms. Both of these groups of patients may benefit from ventricular pacing, which prolongs the AV nodal refractory period as a result of concealed retrograde penetration, thus reducing the longer ventricular cycles which may reduce the number of short ventricular cycles related to rapid AV conduction during AF. By pacing at roughly the mean ventricular rate during spontaneous AV conduction, the ventricular rhythm during AF is regulated (Wittkampf *et al.,* 1988).

5.4.3.2 The case for atrial-based pacing or dual-chamber pacing

Other studies have concluded that atrial or dual chamber pacing rather than RV apex pacing may be the preferred method of pacing in patients with sinus node dysfunction and normal AV conduction with AF (Connolly *et al.*, 2000: 1998). The rationale underpinning atrial pacing as opposed to ventricular only pacing is that atrial pacing thwarts bradycardia-induced dispersion of repolarisation and suppresses atrial premature beats and is supported by both the electrical and mechanical theory in preventing the onset of AF. Atrial pacing prevents potential triggers for AF such as bradycardic episodes and ectopic atrial beats. Atrial and dual-chamber pacing promote AV synchrony, thus preventing retrograde VA conduction. Atrial-based pacing prevaricates the stretching of the atria, which is as a result of increased atrial pressure associated with atrioventricular AV desynchrony (Lamas *et al.,* 2002).

Knight *et al.* (2005) report on five prospective randomized trials which compare single chamber pacing, either atrial or ventricular to dual-chamber pacing for evidence on AF in patients with symptomatic bradycardia, the results of which demonstrate superiority for atrial- based pacing for preventing AF. Other observational studies indicate that the annual incidence of AF in patients with

dual-chamber pacemakers is ≤3% when compared to an incidence of between 6% and 15% per year in patients with single-chamber ventricular pacemakers (VVI) (Knight *et al*., 2005).

In the presence of SA node dysfunction and concomitant disease of the AV conduction system and where dual-chamber pacing is unavoidable, the evidence is less clear that atrial-based pacing is superior. Andersen *et al.* (1997) reported on a study with a mean follow-up time of 3.3 years in patients with sick sinus node disease, who were randomized to receive either a single-chamber atrial pacemaker (AAI) or single-chamber ventricular pacemaker (VVI), which found that the atrial-based pacing was linked with a lower risk of AF and stroke than ventricular-based pacing, although there was no difference in mortality or CHF (Andersen *et al.,* 1997). They continued to follow-up with the patients for eight years, at which time their findings showed that the cumulative incidences of atrial fibrillation and chronic atrial fibrillation were significantly lower in the atrial group compared with the ventricular group (0·54 [0·33-0·89], p0·012 and 0·35 [0·16-0·76], p0·004, respectively). While thromboembolic events occurred in thirteen patients in the atrial group, this was half the occurrence in the ventricular group (0·47 [0·24-0·92], p0·023). The heart failure was less severe in the atrial group compared with the ventricular group (p<0·05). In spite of these data, Andersen *et al.* (1997) concluded that the value of pacing as a primary therapy for prevention of recurrent AF had not been proven (Wozakowska-Kaplon *et al.,* 2004).

5.4.3.3 The case for bi-ventricular pacing (cardiac resynchronisation therapy)

Leon *et al.* (2002) describe distinct improvement in patients with impaired LV function not due to tachycardia, who had a bi-ventricular pacemaker implanted. The results of the study conducted on 20 patients showed an improvement in the NYHA functional classification of 29% (p=0.001), as seen in Figure 5.4.

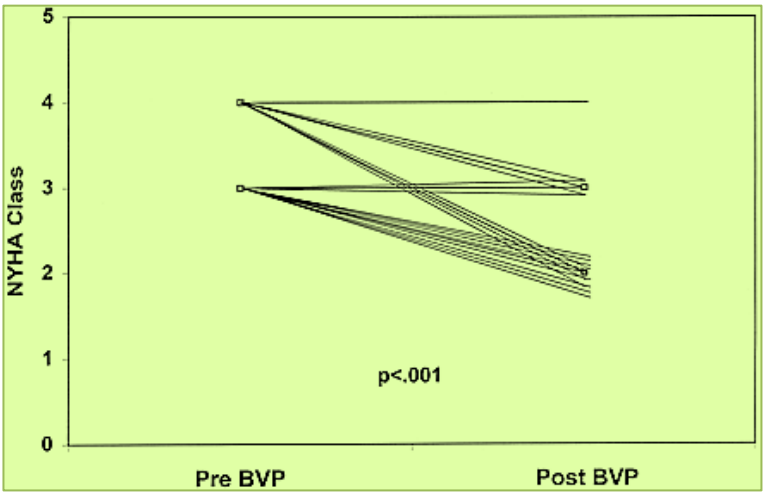


Figure 5.4: Improvement in New York Heart Association (NYHA) functional class after upgrade from a RV pacemaker to a biventricular pacemaker (BVP)

Source: Leon et al., 2002.

The left ventricular ejection fraction (LVEF) improved by 44% (p=0.001), with a simultaneous reduction in the end-systolic diameter of 8.5% (p=0.01) and a decrease in the LV diastolic diameter of 6.5% (p=0.003). The number of hospitalisations also showed a decrease of 81% (p=0.001), while the Minnesota Living with Heart Failure survey scores showed an improvement of 33% (p=0.01).

The current recommendations from the ACC/AHA/ESC guidelines are that for these patients bi-ventricular pacing with or without defibrillator capability should be considered. It should also be considered that patients with HF and a right ventricular pacing system that have undergone an AV node ablation should be upgraded to a bi-ventricular device (Fuster *et al.,* 2006; Leon *et al.,* 2002).

Data presented at the Late Breaking Clinical Trials at the 32nd Heart Rhythm annual scientific sessions in San Francisco in May 2011, showed that there was indeed clinical benefit of cardiac resynchronization therapy compared with right ventricular apex pacing for improving heart failure in patients with AF who were undergoing atrioventricular junction ablation.

The study, known as the APAF study, was a prospective, multi-centre study which included 186 patients. All patients had successfully undergone an AV node ablation and were randomized to receive either the traditional RV apex pacing (n=89) or echo-guided CRT (n=97). The median follow-up was 20 months and the CRT group had 26% reduction in primary endpoints for heart failure, worsening of heart failure and hospitalisation for heart failure. Total mortality was similar in both groups. The CRT mode was the only independent predictor of absence of clinical failure during follow-up (Brignole*,* 2011).

5.4.3.4 The case for internal atrial defibrillators

As discussed in Section 5.3.1, performing electrical cardioversion in patients with AF is highly effective for restoring sinus rhythm, but, as previously discussed, maintaining sinus rhythm remains a challenge in spite of the use of anti-arrhythmic drugs and often the patient requires multiple shocks over a period of time. The time from onset of AF to cardioversion is important, especially in patients who are not adequately anti-coagulated to reduce the risk of thromboembolism (Geller *et al.,* 2003).

The use of implantable cardioverter defibrillators (ICD) have, since first human implant in February 1980, shown success in treating ventricular tachycardia. This resulted in an interest in internal cardioversion for AF (Geller *et al.,* 2003).

An implantable defibrillator consists of two parts: Firstly, the implantable atrial defibrillator/generator, which keeps track of the heart rhythm and sends out electrical pulses and shocks when needed and, secondly, a set of wires called leads or electrodes that are placed inside the heart and are connected to a generator. The power source or generator is implanted subcutaneously in the chest or abdomen (see Figure 5.5).

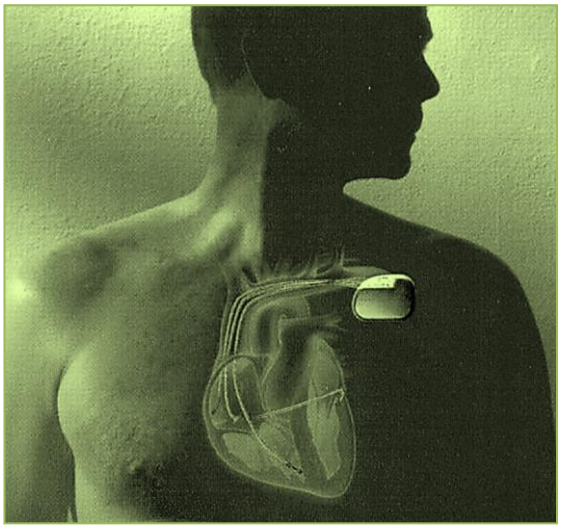


Figure 5.5: A schematic view of the implanted METRIX device, showing the two atrial shock leads, one in the right atrium and one in the coronary sinus, and the right ventricular lead for shock synchronisation and pacing

Source: Geller *et al.,* 2003.

A number of different types of implantable defibrillators are available at present. The greatest number are used for the treatment of ventricular arrhythmia, but dual-purpose defibrillators exist, and these can treat either atrial or ventricular fibrillation by means of anti-tachy pacing (ATP) before delivering either a low or high energy shock as programmed.

The programming of an internal cardioverter defibrillator is specific and tailored to each individual patient's underlying disease and takes into account the type of arrhythmia, the cycle length or rate of the arrhythmia and the defibrillation threshold of the patient. The aim of the ICD, which is implanted for ventricular arrhythmia, is to prevent life-threatening arrhythmia, where ATP is unable to stop the arrhythmia. After a predetermined number of ATP attempts, the device is set to deliver a shock or shocks until sinus rhythm is restored.

Atrial fibrillation is not a fatal arrhythmia and the programming of an ICD for AF allows for greater flexibility. The different modes are as follows: the *off mode*, *monitor only*, *pacing only*, *patient-activated mode* and *automatic mode*. In general, the implantable devices constantly monitor the heart rate and, when programmed to monitor only, the devices monitor all episodes of AF. This valuable information can be downloaded to a disk or printed out for evaluation by the patient's physician. When programmed in automatic mode, the device continues to monitor the episodes of AF, but will deliver a defibrillation shock when AF is confirmed, based on what the device has been programmed to deliver, unless interrupted by a conventional pacemaker magnet which will prevent the shock from being delivered. In the pacing-only mode, the device paces the atria as programmed by the physician but will not deliver any defibrillation therapy. Finally, the patient-activated mode allows the patients greater control of the management of their AF and, with the use of a pacemaker magnet, they are able to activate the device to deliver a shock.

If the patient activator confirms the presence of AF, it will deliver a shock to terminate the arrhythmia. The benefit of this mode is that the patients can time their own shock so as not to occur at an inopportune moment. The downside to this device is that when the patients are cardioverted in a hospital setting by a physician, they are generally given a form of sedation to tolerate the discomfort of the shock. With the use of an ICD, they do not have this benefit.

For patients who suffer from paroxysmal AF, the device offers a degree of control over their arrhythmia and this may result in fewer emergency room visits and hospitalisations. However, the limitations associated with this approach include not only the significant discomfort of the DC shock, but also the likelihood of concomitant anti-arrhythmic drugs to prevent excessive shocks.

Lévy *et al*. (1997) in a prospective, multi-centre trial investigated the efficacy and safety of low energy shocks during atrial fibrillation in a diverse cohort of patients by delivering synchronized shocks between two electrode catheters, one placed in the right atrium and the other in the coronary sinus. The defibrillation protocol started with a test shock of 20V (volts), and the shocks increased in 40V increments with a maximum of 400V or until sinus rhythm was restored. The greatest success (92%) was achieved in the patients in whom AF was paroxysmal, requiring a mean of 2.0 joules of energy (229V) to restore sinus rhythm, while only 70% of the patients with chronic AF were cardioverted with an average of 3.6 joules of energy required to achieve cardioversion (Lévy *et al.,* 1997).

A prospective trial was conducted by Daoud *et al.* (2000: 1407) to evaluate the safety, efficacy, and patient acceptance of the Metrix Atrioverter in 105 patients (75 men, 30 women; mean age 59 years) in an ambulatory setting. All patients had recurrent AF and were symptomatic and medically refractory. Of the 105 patients, 27 had no structural heart disease, while the other 78 patients had a combination of congenital heart disease, valvular disease, CHF, CAD or cardiomyopathy. The mean LVEF was 57% (±8) and the mean follow-up period was 11.7 months.

The treatment efficacy was measured as 85% and the atrial defibrillators delivered 5 523 shocks, of which the majority (4 261) were delivered for AF induction and defibrillation testing. The remaining shocks were as follows: 365 shocks were delivered during ambulatory treatment and a further 897 were delivered before the patient's transition to ambulatory treatment to treat episodes of AF.

Out of the 105 patients enrolled in the study, fifteen had their devices explanted for the following reasons: three patients experienced lead complications; one patient had pacemaker site infection; and eleven other patients' devices were explanted for the inadequate control of AF. It is reported that, in spite of the fact that some patients reported moderate discomfort, the overall satisfaction among patients was high (Mekel *et al.,* 2006). At one-year follow-up, efficacy of the defibrillator in 48 patients was 90% and 70% of the AF episodes were successfully treated with a single shock.

Timmermans *et al.* (1999a) propose that the use of a low energy shock during internal atrial defibrillation may lead to a decrease in the need for sedation when compared with external

cardioversion, as demonstrated by a group of twelve patients who experienced 213 episodes of AF of which 92% were successfully treated without the use of intravenous sedation (Timmermans *et al.,* 1999b).

In another study, Geller *et al.* (2003) reviewed the outcome of implantable atrial defibrillators in 106 patients for a period of seven to 66 months (median 40 months) after implantation. The results indicated that in 13% (n=14) of patients the device was used to monitor the arrhythmia, but no shocks were delivered, while in 50% of patients (n=53) the devices were either explanted or turned off and only 37% of the patients (n=39) received therapy from the devices. The most significant reasons for the discontinuation of the therapy were the patient intolerance of multiple cardioversion shock (n=15), the increase in defibrillation thresholds (n=7), bradycardia requiring pacing (n=12) and early depletion of the devices' battery. The investigators concluded that a critical limitation of the implantable atrial defibrillators, which was unrelated to the efficacy of the device, was the one Joule discharge from the device, which was not well tolerated by most patients and that technical improvements were required to assure long-term use (Geller *et al.,* 2003).

The investigators suggested that implanted devices had limited utility, with the exception of patients with LV dysfunction, who are candidates for implantable ventricular defibrillators. The use of implantable atrial defibrillators is feasible, but the patient selection criterion remains crucial. Finally, the investigators commented that for patients who were possible candidates for atrial cardioverters because of infrequent episodes of poorly tolerated AF, the option for catheter ablation was an alternative treatment option.

5.4.3.5 The case for atrioventricular nodal ablation

A further way to treat patients with AF is to use radiofrequency ablation to render the AV node ineffective. This procedure results in complete heart block for the patients, i.e. it prevents conduction of impulses from the atria to the ventricles. A permanent pacemaker is implanted, either as a single chamber with a single lead in the ATP apex (VVI), or as a bi-ventricular pacemaker with a second lead that is passed down the coronary sinus to the surface of the left ventricle, via the great cardiac vein.

Wood *et al.* (2000) describe the meta-analysis of 21 studies that included 1 181 patients with medically refractory atrial tachyarrhythmia's, where 97% of these were primary atrial fibrillation. The focus of the study was to measure nineteen clinical outcomes including quality of life, ventricular function, exercise duration, and healthcare use in patients who had undergone AV node ablation and permanent pacemaker implantation (Wood *et al.,* 2000). Wood *et al.* (2000) demonstrated improved quality of life and left ventricular function after AV nodal ablation and insertion of a permanent pacemaker for patients with AF who were refractory to medical therapy and for whom their AF was extremely symptomatic. Table 5.3 is a summary of the meta-analysis.

Table 5.3: Summary of findings from the 21 studies included in the meta-analysis on AV node ablation and pace in patients with medically refractory atrial tachyarrhythmia

Author	No Patients	Mean follow-up	Exercise duration	LVEF	QOL	Healthcare	Total Mortality n (%)	SCD n (%)
Olgin	54	24 months	-	-	Improved	Improved	4 (7)	2 (4)
Geelen	235	20 months	-	-	-	-	0	6 (2)
Wong	11	3 months	-	-	-	-	0	0
Jackman	17	8 months	-	-	-	-	3(18)	1(6)
Heinz	10	48 days	-	Improved	-	-		
Bubien	44	6 months	-	-	Improved	-		
Twidale	14	9 months	-	Improved	-	-	1(7)	
Brignole	22	3 months	Improved	-	Improved	-	1(4)	
Darpo	220	31months	-	-	-	-	31(14)	11(5)
Natale	14	12 months	-	Improved	Improved	-		
Kay	156	12 months	-	-	Improved	Improved	23(15)	5(3)
Brignole	43	6 months	-	-	Improved	-	0(0)	0(0)
Fitzpatrick	107	2.3 years	-	-	Improved	Improved	17(16)	2(2)
Jensen	50	17 months	-	-	Improved	Improved	6(12)	2(4)
Morady	20	12 months	-	-	-	-	0(0)	0(0)
Edner	29	216 days	-	-	-	-		
Geelen	11	6 months	-	Improved	Improved	-	0(0)	0(0)
Buys	25	7 months	-	-	-	-	0(0)	0(0)
Lee	30	6 months	Improved	Improved	Improved	Improved	0(0)	0(0)
Twidale	22	14 months	Improved	Improved	Improved	Improved	2(23)	2(9)
Jordaens	47	25 months	-	-	-	-		0(0)

Notes: QOL= quality of life; Sx= symptoms; improvement = improvements or favourable change after ablation and pacing; = no change after ablation and pacing.

Source: Wood et al., 2000.

Anter *et al.* (2009), in reference to a paper by Manolis *et al.* (1998), described 46 patients who underwent radiofrequency ablation of the AV node and subsequent permanent pacemaker implantation (Anter *et al.,* 2009). All of these patients were refractory to medical therapy and had a rapid ventricular response to their atrial tachyarrhythmias. At the start of the study the mean left ventricular ejection fraction (LVEF) was measured at 42% (±16%). The patients were followed up for two years and the LVEF improved to a mean of 50% (±14%). The improvement of the LVEF was significantly better in the sub-group of patients with heart failure, who had a mean LVEF at the start of the study of only 32% (±9%) which, after two years, had improved to a mean of 48% (±8%), with

a concurrent improvement in NYHA functional class from 2.7(±0.6) to 1.4(±0.8) (p<0.001) (Manolis *et al.,* 1998).

The ACC/AHA/ESC guidelines indicate that patients with symptoms or tachycardia-mediated cardiomyopathy related to rapid ventricular rate during AF that cannot be controlled adequately with anti-arrhythmic drugs or negative chronotropic medications, are most likely to benefit from the ablate and pace strategy (Fuster *et al.,* 2006).

While the symptomatic benefits of AV node ablation and pacemaker implantation are accepted, it must be noted that several limitations exist with this treatment regime, including but not limited to irreversible complete AV block with lifelong pacemaker dependency, a tendency of ventricular rate to rise over the six month period following ablation, lifelong anti-coagulation, and a finite risk of sudden death due to Torsade's de pointes or ventricular fibrillation and the loss of AV synchrony.

While some patients are not adversely affected by the loss of AV synchrony, patients with anomalies of diastolic ventricular functions, such as those with hypertrophic cardiomyopathy (HCM) or hypertensive heart disease that rely on AV synchrony to maintain cardiac output, may experience persistent symptoms even after AV nodal ablation and pacemaker implantation (Brignole *et al.,* 1997).

A study of 71 patients suggested that, in some patients, the long-term outcome for heart failure may be less favourable when undergoing AV nodal ablation and permanent pacing. In a study by Tan *et al.* (2008: 460), where 71 patients over the age of 65 years with pharmacologically refractory AF, who were assigned to either AV nodal ablation and pacing or ablation for AF for a period of five years' follow-up, the patients assigned to AV nodal "ablate and pace therapy" demonstrated a higher incidence of new heart failure when compared with those who underwent AF ablation (53% *vs.* 24%). Table 5.4 illustrates this as well as other indices where differences were seen in favour of AF ablation.

Table 5.4: Comparison of five-year outcome between AV-node ablation and permanent pacing therapy (ablate and pace) *vs*. AF ablation in 71 patients over 65 years of age

	Group 1	Group 2
	Ablate and Pace	AF Ablation
Development of new CHF	53%	24%
LVEF	44% (±8%)	51% (±10%)
NYHA functional class	1.7(±0.9)	1.4± (0.7)

Source: Tan et al., 2008.

Data from the APAF study, presented at the HRS Congress in May 2011 reveal the results of the prospective, multi-centre study which included 186 patients who had successfully undergone AV

junction ablation and randomized to receive echo-guided CRT (97 patients) or RV apical pacing (89 patients). During a median follow-up of 20 months, the CRT group had fewer worsening HF symptoms and hospitalisation for heart failure; however, the total mortality was similar in both groups. Additionally, only the CRT mode remained an independent predictor of absence of clinical failure (defined as death due to HF, hospitalisation due to HF or worsening HF) during the follow-up period.

5.5 CATHETER ABLATION

The surgical approach for the treatment of refractory tachycardia was the mainstay of non-pharmacologic therapy until the late 1960s, when the first intra-cardiac catheters were used to stimulate the heart and record rhythms. Initially, direct current (DC) from an external defibrillator was used as the energy source. This form of high voltage energy was not ideal as it was difficult to control and resulted in widespread tissue damage.

Catheter ablation is a minimally invasive procedure whereby catheters are inserted in the body via veins in the groin or neck and directed with X-ray up into the heart. The ablation may be in the form of RF energy or cryoablation and the application of the energy is dependent on the site of ablation. Each catheter has between four and 20 electrodes which, when placed in the heart, collect electrical measurements from the heart. This data helps determine where the arrhythmia foci are and, once determined, RF energy is delivered to the site to obliterate a small amount of tissue, the result being that the abnormal electrical impulses are disrupted, and the normal heart rhythm is restored.

5.5.1 Types of ablation for atrial fibrillation

There are two main types of ablation that are utilised for the treatment of atrial fibrillation, namely radiofrequency ablation and cryoablation.

5.5.1.1 Radiofrequency ablation

The introduction of radiofrequency catheter ablation transformed the way that tachyarrhythmia is treated, and this has become first-line therapy for many types of tachycardia. Radiofrequency (RF) energy uses energy that is high-frequency but low-voltage. The RF energy causes the tissue to heat up and a small uniform lesion is created. The size of the lesion is determined by the length of the distal ablation electrode as well as the type of catheter (irrigated or non-irrigated.) used. Other factors that affect the size of the lesion include the amount of power delivered to the tissue and the contact the catheter has with the tissue. RF ablation lesions will typically measure about five to seven millimetres in diameter and three to five millimetres in depth. Success rates for catheter ablation are highest in patients with common forms of supra-ventricular tachycardia (SVT), for example atrioventricular nodal re-entrant tachycardia (AVNRT) and orthodromic reciprocating tachycardia (ORT).

5.5.1.2 Cryoablation

Catheter or balloon-based cryoablation is an alternative source of energy that requires pressurized liquid nitrous oxide to be injected into closed catheter tip or balloon. The result is the rapid evaporation of the nitrous oxide which cools the underlying tissue to about minus 75ºC. An ice ball or hemispherical block is formed at the catheter tip, and the underlying tissue is frozen. As the tissue thaws out, tissue injury results, which may include haemorrhaging and inflammation and the end result is a fibrotic lesion in the heart. There is minimal risk of permanent total heart block when ablation is near the AV node. This is due to the fact that the rapid warming of tissue results in the reversing of the electrophysiological outcome. Cryoablation has a number of potential advantages over RF ablation and these include the following:

- The ice ball creates excellent stability of the catheter during ablation;
- The patient does not experience any pain during energy delivery, and
- There is less risk of damaging vascular structures such as the coronary arteries and pulmonary veins.

In spite of this, cryoablation has been shown to be less effective clinically than RF ablation. It may be useful in specific clinical circumstances, in particular when the ablation site is close to the AV node. Radiofrequency catheter ablation remains the dominant and most useful energy source in clinical practice (Prystowsky, 2000).

5.5.2 Indications for radiofrequency catheter ablation

Catheter ablation may be indicated for patients with arrhythmia which are not controlled by either medication or lifestyle management. In some circumstances, certain medications may be contra-indicated for some patients, or the patients express the desire not to take life-long anti-arrhythmic medications, because of side effects that interfere with their quality of life. The following are class 1 indications for catheter ablation:

- Symptomatic supra-ventricular tachycardia (SVT), for example, atrioventricular nodal re-entrant tachycardia (AVNRT).
- Wolff-Parkinson-White syndrome, unifocal atrial tachycardia, and atrial flutter.
- Atrial fibrillation with lifestyle-impairing symptoms, after inefficacy or intolerance of at least one anti-arrhythmic agent.
- Symptomatic ventricular tachycardia in structural heart disease.
- Drug inefficacy or intolerance.

5.5.3 Complications of radiofrequency catheter ablation

As fluoroscopy is used for the procedure, there is a risk of radiation, which is higher than the risk from common radiologic procedures. However, this risk remains low. The average risk for genetic defects is one case per million births, while the average risk for fatal malignancies ranges from 0.3-2.3 deaths per 1 000 cases for every 60 minutes of fluoroscopy. The time required per procedure is dependent on factors that include complexity of the arrhythmia and skill of the operator but seldom requires more than 60 minutes of fluoroscopy for simple cases. Major complications are reported to affect approximately 3% of patients who undergo ablation procedures. The risk of death is less than 0.3% and thromboembolism occurs in less than 1% (although this is higher in some atrial fibrillation ablation data). The list below describes reported complications, most of which are rare or uncommon:

- Death (0.1-0.2% of all procedures)
- Cardiac complications (incidence varies based on site and type of ablation)
    - AV block
    - Cardiac tamponade (highest in atrial fibrillation ablation, up to 6%)
    - Coronary artery spasm/thrombosis
    - Pericarditis
    - Valve trauma
    - Vascular complications (~2-4%)
- Retroperitoneal bleeding
    - Hematoma
    - Vascular Injury
    - Transient ischaemic attack/stroke
    - Hypotension
    - Thromboembolism or air embolism
- Pulmonary complications
    - Pulmonary hypertension with and without Haemoptysis (secondary to pulmonary vein stenosis)
    - Pneumothorax
    - Miscellaneous
- Left atrial-oesophageal fistula
- Acute pyloric spasm/gastric hypomotility
- Phrenic nerve paralysis
- Radiation or electrically induced skin damage
- Infection at access site
- Inappropriate sinus tachycardia
- Proarrhythmia.

5.5.4 Results of radiofrequency catheter ablation

The success rate of RF catheter ablation for many of the common supra-ventricular tachycardia such as atrioventricular nodal re-entrant tachycardia (AVNRT), or Wolff-Parkinson-White syndrome, is typically between 90% and 95% with a single procedure. The success rates for right atrial flutter and other unifocal atrial tachycardia is in the region of 90%. Some tachyarrhythmia may recur in the first few months following ablation and success may only be achieved after the second procedure (Greenberg *et al.,* 2008).

The ablation for AF is complicated and it is now accepted that AF is a progressive disease that is unlikely to be cured (Kuck, 2010). Success rates for terminating atrial fibrillation with RF ablation in patients with paroxysmal atrial fibrillation and in the absence of structural heart disease was reported in 2006 as 87%. The patient group with persistent atrial fibrillation in the presence of structural heart disease and left atrial enlargement had a success rate of 50% or less, and a repeat procedure was needed in more than 25% of patients.

To deal with the complexities of RF catheter ablation for atrial fibrillation, new techniques such as 3D mapping systems (Carto and Ensite) are evolving (see Figure 5.6). These 3D mapping systems can be merged with MRI or CT scan images of the left atrium, enabling the navigation of the ablation catheter, mapping of ectopic foci and atrial scars, and finally the evaluation of the transmurality of ablation lines. Intra-cardiac echocardiography (ICE) offers the physician the ability to avoid collateral damage to the pulmonary veins or oesophagus and ensures adequate endocardial contact. The use of robotic catheter navigation (Hansen or Stereotaxis) is now available to assist in delivering radiofrequency catheter ablation (RFCA) (Greenberg *et al.,* 2008).

At the 2011 Heart Rhythm Society's 32nd annual scientific sessions in San Francisco, findings from the DISCERN AF trial were announced. The DISCERN AF trial utilised the Medtronic Reveal XT, which is an implantable loop recorder to monitor the incidence of symptomatic *vs*. asymptomatic AF, on a long-term basis. All the patients had undergone RF ablation.

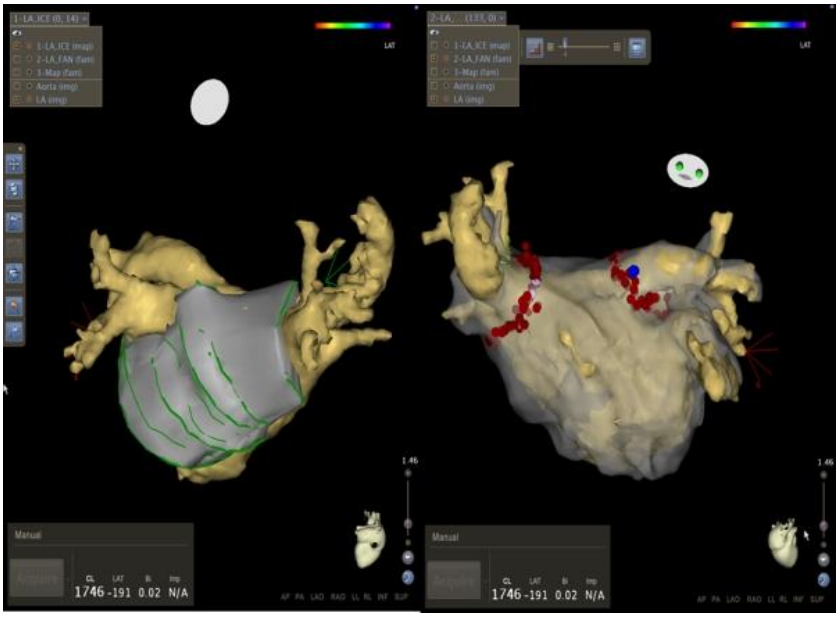


Figure 5.6: Carto 3D map of left atrium, illustrating the pulmonary veins

Notes: Right superior pulmonary vein (RSPV), right inferior pulmonary vein (RIPV), left superior pulmonary vein (LSPV), and left inferior pulmonary vein (LIPV). The red circles represent actual discrete radiofrequency applications, predominantly delivered in a circumferential pattern around the pulmonary veins. This ablation strategy can isolate pulmonary vein foci that initiate atrial fibrillation, and/or alter the substrate of the left atrium to inhibit fibrillatory activity due to re-entry.

Source: Kabra & Singh, 2010.

The DISCERN study was a prospective, multi-centre study of 50 patients with symptomatic AF. All the patients had the Reveal XT, with an automated detection algorithm, implanted at least three months prior to the RF ablation and all patients were monitored for 18 months after the ablation procedure.

The study showed an 86% decrease in burden of AF, (i.e. the total amount of time the patient was in AF). The burden of AF decreased from a pre-ablation period of 2.0 hours per day (±0.5 hours) to a post ablation time of 0.3 hours (±0.2 hours) (p=0.005). It was also found that 56% of the entire AF burden was asymptomatic. It is important to note that, when analysing symptoms only, 58% of patients were free of AF, suggesting that symptoms alone underestimate the overall burden of disease in these patients and this may impact the treatment regimens of patients in the future (Verma, 2011).

5.6 ABLATION FOR ATRIAL FIBRILLATION

Nademanee *et al.* (2004) argue that, despite the advancements made in the treatment of cardiovascular diseases, the management of AF has remained a frustrating dilemma for physicians. The publication of studies like the AFFIRM (Atrial Fibrillation Follow-up Investigation of Rhythm Management) as well as several other randomized trials, which compared the two main strategies of AF treatment, i.e. rate *vs*. rhythm control, leave the arrhythmia society with the knowledge that, besides

the addition of anti-coagulants to the therapeutic regime, the use of anti-arrhythmic drugs to maintain sinus rhythm offers no benefit to reduce mortality or stroke in AF patients when compared with the use of drugs for rate control (Nademanee *et al.,* 2004; Wilber *et al*., 2010).

Nademanee (2004) recognises that the use of rate-control treatment is acceptable as a pharmacological approach. However, he states that physicians are unsatisfied with the fact that many of their high-risk patients remain in AF. Nademanee cites the AFFIRM investigators, who suggest that the unwanted effects of anti-arrhythmic drugs might offset the benefits of being in sinus rhythm (Nademanee, 2008). Wilber *et al.* (2010) submit that the effectiveness of drugs remains inconsistent and that the likelihood of AF recurrence within six to 12 months is almost 50% with most drugs therapies (Wilber *et al*., 2010).

Catheter ablation of atrial tissue to treat atrial fibrillation is still evolving (Greenberg *et al*., 2008). The procedure is technically demanding, riskier, and less successful than the other ablation procedures described above. Early radiofrequency catheter ablation for AF emulated the surgical Maze procedure by introducing linear scars in the atrial endocardium (Fuster *et al.*, 2006). It was Haïssaguerre *et al.* (1998) who, in the mid-1990s, observed that pulmonary vein foci triggered atrial fibrillation resulting in scientific enthusiasm that this tachyarrhythmia, which affected millions of people, could be amenable to catheter ablation (see Figures 5.7 and 5.8).

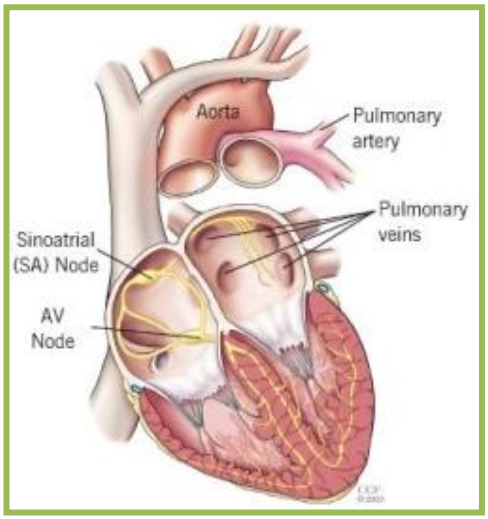


Figure 5.7: Diagram illustrating the site of the four pulmonary veins in the left atrial body

Source: Greenberg, et al., 2008.

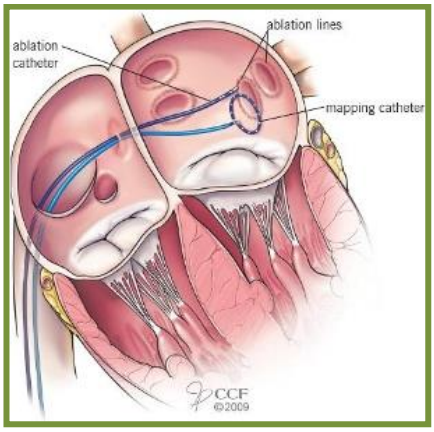


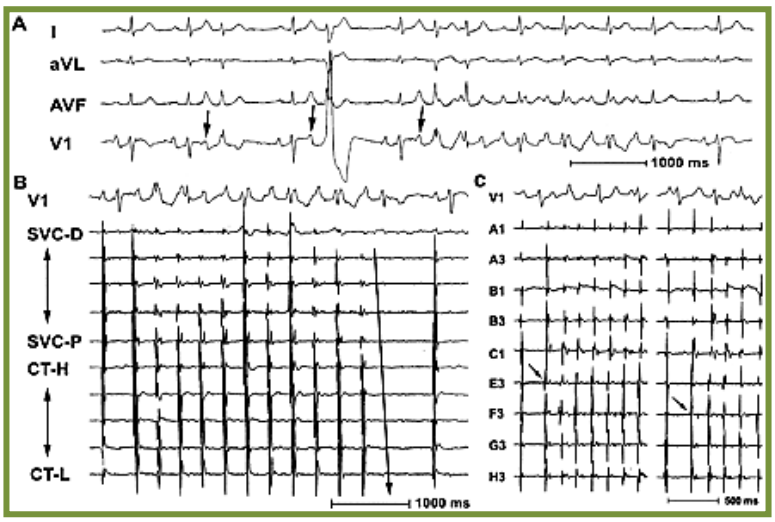
Figure 5.8: Diagram illustrating the Lasso mapping catheter across the intra-atrial septum and mapping electrograms at the left inferior pulmonary vein

Note: Ablation catheter performing RF ablation circumferentially around the veins.

Source: Greenberg et al., 2008.

The initial success rate for this procedure was between 40% and 50% and had relatively high complication rates. It did, however, encourage observations which indicated that the electrical potentials which arose in or near the ostia of the pulmonary veins often provoked AF and it further demonstrated that when these foci were eradicated the AF terminated. At the outset, it was only areas in the pulmonary veins where automaticity was found that were targeted. Jaïs *et al.* (1997) later demonstrated over a follow-up period of eight months, in a series of 45 patients, all of whom had paroxysmal AF, that 62% were free of symptomatic AF, but 70% of these patients required multiple procedures (Jaïs *et al.,* 1997). It was Chen *et al.* (1999) who then established a success rate over a six months' follow-up period of 86% (Chen *et al.,* 1999).

Figure 5.9 illustrates one of the mechanisms apparent to start an episode of AF as a single ectopic foci and, in a study of 240 patients, Lin *et al.* (2003) described that, of the 358 ectopic foci that started paroxysmal atrial fibrillation (PAF), 28% of patients' AF was initiated by an ectopic foci, while 20% were from non-pulmonary vein areas and included the left atrial free wall in 38.3%, the superior vena cavae (SVC) in 37% of patients, the crista terminalis in 3.7% of patients, the ligament of Marshall in 8.2%of patients, the coronary sinus ostium in 1.4% of patients and a further 1.4% from the intra-atrial septum (Lin *et al.,* 2003).



Notes: (A) Bigeminal ectopic beats (arrow) followed by initiation of tachycardia in the surface ECG. (B), Ectopic foci initiating tachycardia from SVC-D (distal) and conducting to SVC-P (proximal). (C), Ectopic beats initiating AF from SVC after isoproterenol infusion (basket catheter recording inside SVC, with the earliest ectopic beat from E3 and F3).

Figure 5.9: The initiation of AF from superior vena cava (SVC)

Source: Lin et al., 2003.

When catheter ablation was performed to terminate the AF, the acute success rates varied according to the site of the initiation of the AF and were as follows: 63% in left atrial posterior free wall, 96% in the superior vena cava, 100% at the crista terminalis, 50% at the ligament of Marshall, 100% in the coronary sinus ostium, and 0% at the intra-atrial septum respectively. The patients were followed up for 22(±11) months and 43 patients or 63.2% were found to be free of AF and no longer on anti-arrhythmic drugs (Chen *et al.,* 1999).

Subsequent research by Hocini *et al*. (2004) from the Bordeaux group in France confirmed that potentials arise in a number of different regions in both the right atrium and the left atrium and include, among others, the SVC, intra-atrial septum, the LA posterior wall, the coronary sinus, ligament of Marshall, and the crista terminalis. Modifications, as seen in Figure 5.10, were made to the procedure of pulmonary vein isolation, which now includes linear ablation in the left atrium and/or mitral isthmus ablation in selected patients (Hocini *et al.,* 2004; Lin *et al.,* 2003; Anter *et al.,* 2009).

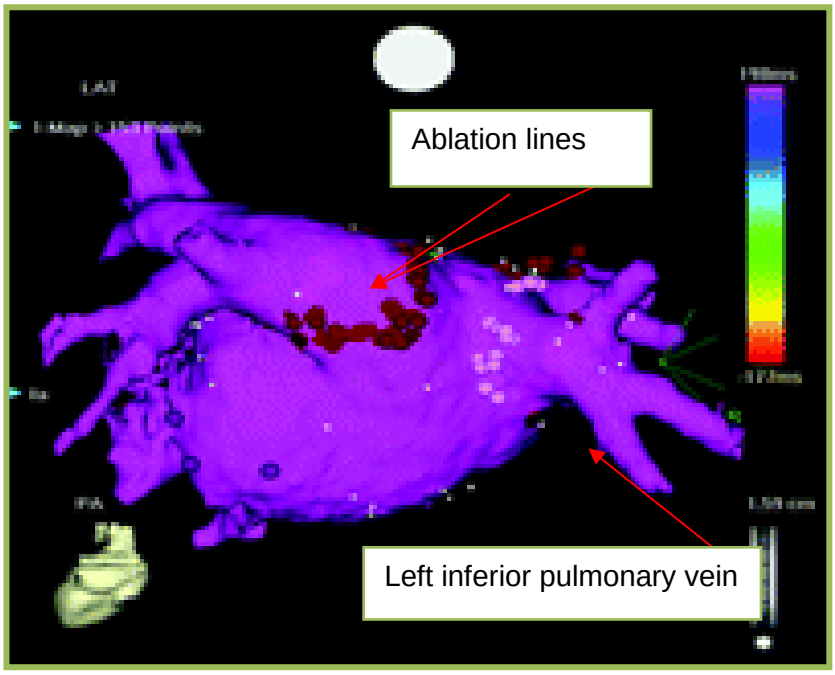


Figure 5.10: Pulmonary vein isolation using advanced imaging techniques

Notes: A CT scan is shown of the left atrium which has been merged with a 3-dimensional mapping system (Carto Merge). Individual ablation lesions are represented by red and pink icons; the pink icons represent low-power lesions over the area where the oesophagus is in close contact with the posterior wall of the left atrium. The pulmonary veins are completely surrounded by ablation lesions, electrically isolating the pulmonary vein myocardial sleeves that provide the trigger beats that initiate episodes of atrial fibrillation.

Source: Adapted from Anter et al., 2009.

5.6.1 Results of ablation for atrial fibrillation (AF)

Despite these advances, the long-term efficacy of catheter ablation to prevent recurrent AF requires further study. Available data demonstrates one or more years free from recurrent AF in most (albeit carefully selected) patients (Hindricks *et al.*, 2005; Karch *et al.,* 2005). Of importance is the fact that AF can recur without symptoms and may therefore not be recognised by either the patient or the physician. Hindricks *et al.* (2005) concluded in their study that, if centring the success of AF ablation on symptoms only, the success rate of the procedure may be substantially overestimated.

Therefore, it remains uncertain whether apparent cures represent elimination of AF or transformation into an asymptomatic form of paroxysmal AF. The distinction has important implications for the duration of anti-coagulation therapy in patients who are at risk of stroke associated with AF. In addition, little information is available about the late success of ablation in patients with HF and other advanced structural heart disease, who may be less likely to enjoy freedom from AF recurrence (Hindricks *et al.,* 2005).

A study evaluating the outcome of catheter ablation in high risk patients was published in the *Journal of American College of Cardiology* (*JACC)* in 2008. The investigators evaluated 2 356 patients with symptomatic and refractory AF. Of these patients, 771 met the inclusion criteria, as they all had a

high risk of stroke and were similar to the patients studied in the AFFIRM trial. Of these 771 patients, 674 underwent catheter ablation for AF. Of the 97 patients who were not treated, 27 were excluded because of a left atrial thrombus, while the other 70 patients declined to undergo the procedure.

In total, 1065 ablations were performed, with 53% (329) patients requiring only one procedure, 32% (204) undergoing two procedures, 12.6% (80) requiring a third procedure, and 2.5% (22) patients requiring a total of four procedures.

The mean follow-up period was 836 days (±605) from the last ablation procedure, and 517 of the 635 patients, or 81.4%, remained in sinus rhythm. The remaining 118 patients (18.6%) still had atrial tachyarrhythmia and of the 517 patients who remained in sinus rhythm (SR), only 13% required anti-arrhythmic agents to maintain SR. Table 5.5 illustrates that AF ablations are significantly more effective in maintaining sinus rhythm in patients with paroxysmal or persistent AF when compared with those with permanent AF.

Table 5.5: Comparison of baseline clinical characteristics of patients maintaining SR vs. patients remaining in AF after ablation

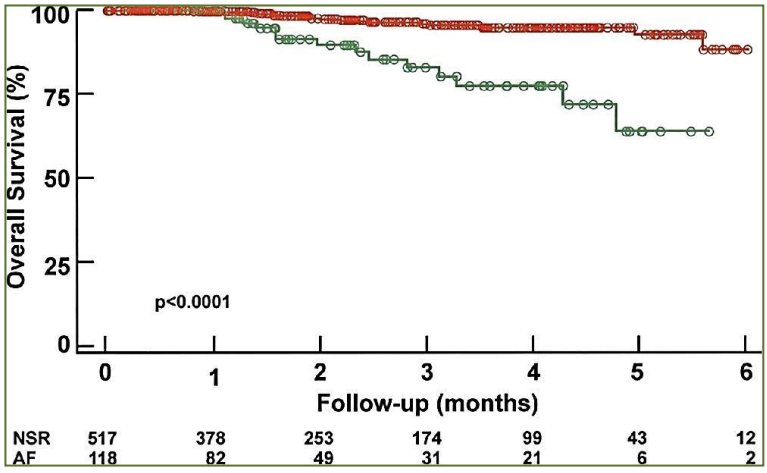
	SR (n=517)	AF (n=118)	P value
Age (years)	67 ±12	67 ±12	0.9
Duration of AF (months)	36±	57±79	0.008
Ejection fraction	51±14	51±12	0.97
LA size (mm)	45±6	48±7	<0.0001
Types of AF			
Paroxysmal (n=254)	226	28	
Persistent (n=146)	124	22	<0.0001
Permanent (n=235)	167	68	

Source: Nademanee et al., 2008.

When evaluating the effects of sinus rhythm on mortality, Nademanee *et al*. (2008) described that 29 deaths occurred over the follow-up period. Of the 517 patients who remained in SR, fifteen died (2.9%), four from CHF, one from sudden death, and ten from non-cardiac death. In comparison, fourteen of the 118 patients with recurrent AF died (11.9%), eight from CHF, two from sudden death, two from non-cardiac death, two from stroke, including one patient with a spontaneous intracranial haemorrhage on Warfarin). This showed that the cardiac death rate was lower in the patient cohort who remained in sinus rhythm (0.96% vs. 8%; p<0.0001) (Nademanee *et al*., 2008).

Further to this, the investigators showed that the five-year mortality rate was lower where AF ablation was effective in maintaining SR. Figure 5.11 illustrates that the five-year mortality rate was 8% for those in sinus rhythm after ablation compared with 36% for those with recurring AF after the ablation

(p<0.0001). Sinus rhythm was shown to be the strongest independent factor associated with a lower mortality (HR 0.14, 95% CI 0.06 to 0.36, s<0.0001) (Nademanee *et al.,* 2008).



Notes: Kaplan-Meier curve demonstrating improved survival in patients who remained in normal sinus rhythm (NSR) (red circles) from all-cause mortality compared with patients who remained in atrial fibrillation (AF) (green circles).

Figure 5.11: Survival effect of maintaining normal sinus rhythm (NSR) after AF ablation

Source: Nademanee et al., 2008

This study systematically evaluated the safety and effectiveness of catheter-based substrate ablation in high-risk patients with AF. The mean follow-up period was 836 days (±605) and the patient population had a median age of 69 years. In spite of this high-risk patient profile, the data supported the fact that ablation of AF substrate with complex fractionated atrial electrograms (CFAE) mapping was effective in maintaining sinus rhythm and that, at 2.3-year mean follow-up, the highest success rates of 89% and 85%, respectively, were the patient group with paroxysmal or persistent AF while the success rate of the patients with permanent AF was only 71% (p<0.0001).

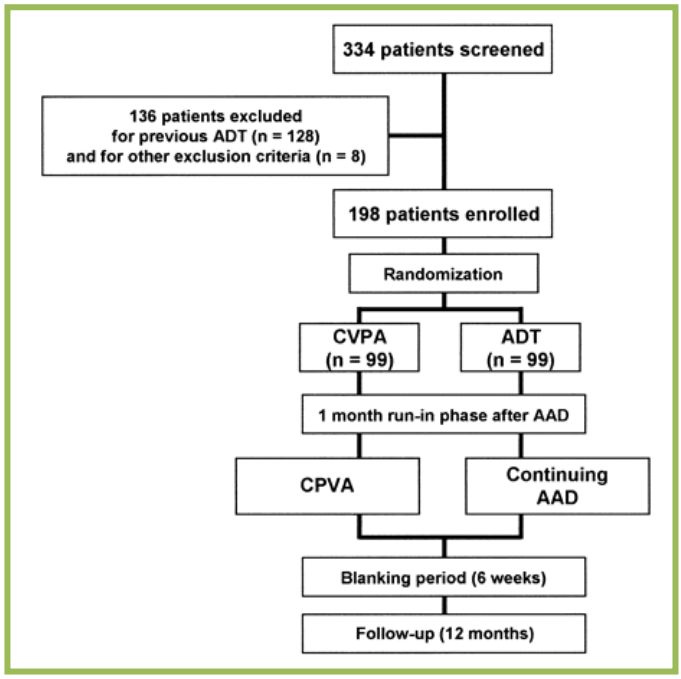
In spite of the fact that a large majority of the patients who remained in sinus rhythm stopped their anti-coagulants, their rate for both stroke and embolic complications were low. The annual stroke rate among the successfully treated patients who discontinued anti-coagulation was 0.4%, compared with 2% in the patients with recurrent AF. The Kaplan-Meier curve derived a five-year stroke incidence of 3% compared with 23% for patients who required ongoing Warfarin therapy (p = 0.04). For the patients who remained in sinus rhythm and, as result of their age, were not ideal candidates for anti-coagulation, the benefits were remarkable with respect to stroke and mortality reduction (Nademanee *et al.,* 2008).

5.6.2 Results for RF ablation for AF vs. anti-arrhythmic drugs for AF

Anti-arrhythmic drug therapy (ADT) is at present considered the first line of therapy to prevent symptomatic and recurrent atrial fibrillation (AF). However, many of the anti-arrhythmic drugs (AADs) are cited as being not only ineffective but also often associated with serious adverse effects (Fuster *et al.,* 2006). Little data exist to compare RF ablation to anti-arrhythmic drugs for AF but where data exists, they exhibit a positive trend in favour of RF ablation. Ablation for atrial fibrillation is an effective alternative to chronic ADT in patients with AF (Haïssaguerre *et al.,* 2000; Nademanee *et al.,* 2008). Three randomized trials by Wazni *et al.* (2005), Stabile *et al.* (2006) and Oral *et al.* (2006) demonstrated superiority of AF ablation strategy over ADT. The first study, by Wazni *et al.* (2005), evaluated the recurrence of AF, hospitalisation, and the quality of life scores in 70 patients between the ages of 18 and 75 years, all of whom had an initial history of paroxysmal AF (PAF) and were untreated. The second study, by Stabile *et al.* (2006), reported that ablation therapy, combined with AAD, was superior to AAD on its own for patients with paroxysmal or persistent AF.

Oral *et al.* (2006) demonstrated that, at one-year, pulmonary vein isolation by means of circumferential pulmonary vein ablation was more effective than Amiodarone in maintaining sinus rhythm. The APAF (ablation for paroxysmal atrial fibrillation) trial was conducted to establish whether circumferential pulmonary vein ablation was superior to ADT for maintaining SR at one year in patients with a long history of PAF.

In the randomized control study by Pappone *et al.* (2006) a total of 334 patients were screened and 198 were enrolled in the study. Figure 5.12 demonstrates that 198 patients were enrolled either to receive ADT or undergo an ablation. All patients received a one-month period of AAD, after which they either had the ablation procedure or stayed on medication. Of the 99 patients assigned to the drug group, 42 underwent ablation after a mean of 5.8 months and, after a mean of 6.2 months of follow-up after crossover, 36 were free of recurrent AF in the absence of ADT, compared with 6 in whom AF was present (14%).



Notes: Circumferential pulmonary vein ablation (CPVA) (n = 99), anti-arrhythmic drug therapy (ADT) (n = 99). After four weeks of anti-arrhythmic therapy (run-in phase), patients proceeded to the randomized treatment (i.e., catheter ablation or solely continuing ADT). AAD = anti-arrhythmic drug.

Figure 5.12: Randomisation of patients to either circumferential pulmonary vein ablation or anti-arrhythmic drug therapy

Source: Pappone et al., 2006: 2341.

As noted in Figure 5.13 the Kaplan-Meier analysis showed that 86% of patients who were randomized to the ablation arm were free of all atrial tachycardia at the end of the follow-up period, compared with only 22% of patients randomized to receive ADT ($p<0.001$).

Of further interest in this trial were the numbers of hospital admissions in each group. Among patients assigned to ablation, nine patients had a total of 24 hospital admissions for cardiovascular causes, which included repeat procedures. In contrast, in the ADT group, there were 167 cardiovascular event-related hospital admissions. These hospitalisations did not include the hospitalisations for crossover to ablation.

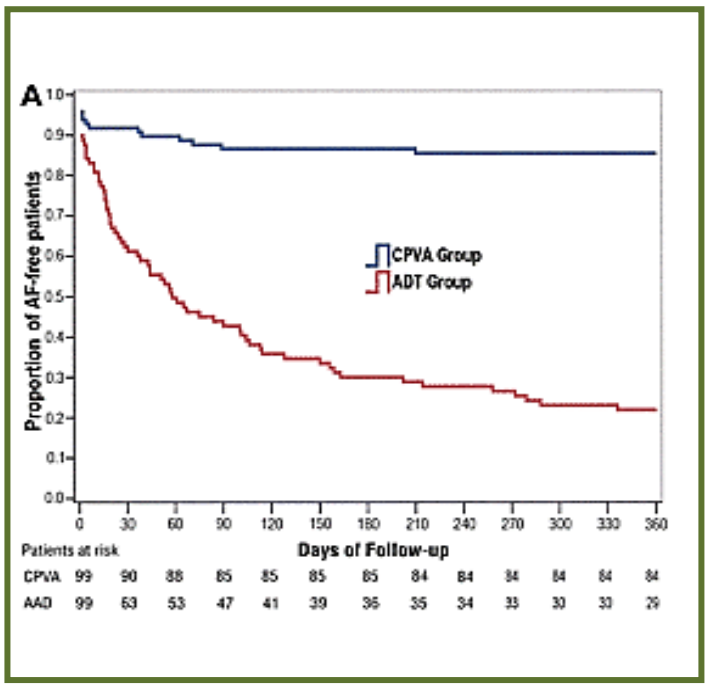


Figure 5.13: Outcomes in the APAF (ablation for paroxysmal atrial fibrillation) trial

Source: Pappone et al., 2006: 2345.

The main findings of this study demonstrated that a single circumferential pulmonary vein ablation procedure was more effective in preventing relapses of AF in selected patients with paroxysmal AF, than ADT and that ablation resulted in the maintenance of sinus rhythm at one year without the need for ADT in 86% of patients.

This finding is significantly different from the patients in the ADT group, where only 22% of the patients remained in sinus rhythm at one year. The authors purport that the maintenance of sinus rhythm after ablation could be associated with reverse left atrial remodelling, fewer adverse events and less hospital admissions due to cardiovascular causes.

Of interest was the fact that, in the ablation arm of the study, the patients who underwent ablation with an irrigated-tip catheter were less likely to have AF recurrences compared with those ablated with an 8-mm catheter. The findings also confirmed that, by including additional posterior lines, the incidence of atrial tachycardia was decreased to 3.9%.

In January 2010, the *Journal of the American Medical Association* (*JAMA)* published a prospective, multi-centre, randomized study designed to compare catheter ablation with ADT in patients with symptomatic AF, who had not shown clinical improvement on at least one drug. The primary goal of the study was to evaluate freedom from symptomatic AF recurrence after treatment (Wilber *et al.,* 2010).

Randomisation sequences were generated by the sponsor statistician, and patients were randomly assigned on a 2:1 basis to receive either ablation or a previously unused anti-arrhythmic drug (classes I or III) (see Figure 5.14).

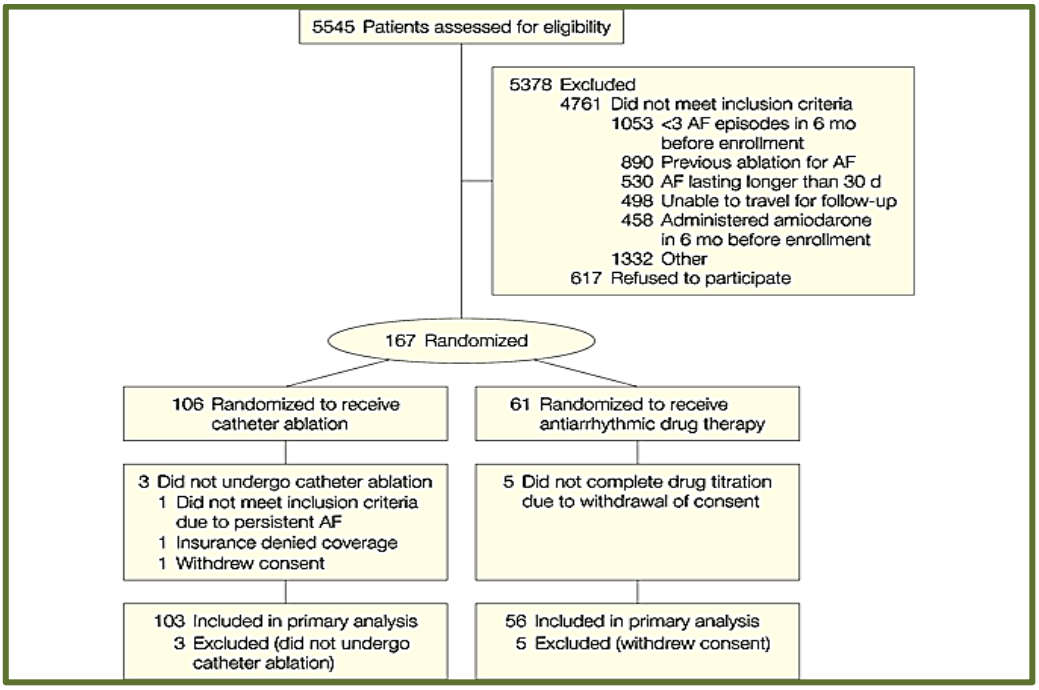


Figure 5.14: Patient flow diagram for selection and randomisation

Source: Wilber et al., 2010.

These patients were followed up for comparable nine-month effectiveness evaluation period. ECGs were done at all follow-up visits and trans-telephonic monitoring was performed during the nine-month period for patients in both groups. Patients from both groups were required to transmit all symptomatic cardiac episodes and, for those patients undergoing ablation therapy, a CT scan or MRI was performed within 30 days before the procedure and then at intervals of three months and 12 months after the procedure, in order to identify pulmonary vein stenosis. This was defined as at least 70% reduction of the PV diameter when compared with the baseline scan.

For the cohort of patients randomized to drug therapy, drugs were administered only if the patient had not previously received that drug and a choice of dofetilide, Flecainide, propafenone, Sotalol, or quinidine were prescribed at the discretion of the investigator. The patients who underwent PVI all did so with the use of a Navistar Thermocool Irrigated Tip Catheter (Biosense Webster, Diamond Bar, California) and Carto (Biosense Webster). Circumferential lesions were performed and additional ablation for CFAE, left atrial linear lesions, and cavo-tricuspid isthmus were at the discretion of the investigator. Up to two repeat ablations were considered acceptable within 80 days.

The Kaplan-Meier curves for the effectiveness outcomes are illustrated in Figure 5.15. It can be noted that, after the nine months' effectiveness evaluation period, 70% of patients treated with catheter ablation were free of symptomatic and recurrent atrial tachycardia *vs*. 19% of patients treated with medication (HR, 0.24; 95% CI, 0.15-0.39; $p<0.001$). A total of 66% of patients in the catheter ablation group were free from protocol-defined treatment failure compared to only 16% of patients who received drug therapy (HR, 0.30; 95% CI, 0.19-0.47; $p<0.001$). In addition to this, 63%

of the patients treated in the ablation cohort were free of any recurrent atrial arrhythmia *vs*. 17% of patients treated with medication (HR, 0.29; 95% CI, 0.18-0.45; *p*<0.001)

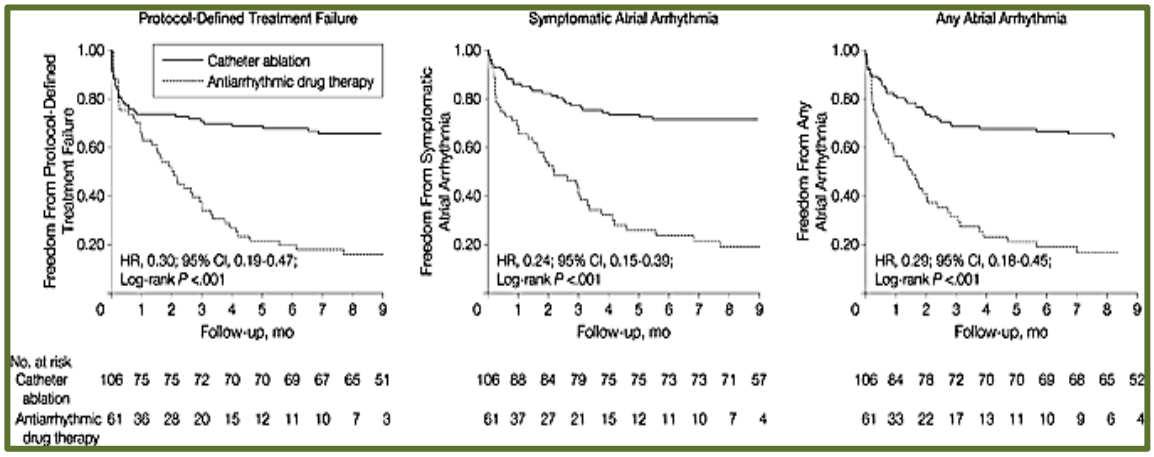


Figure 5.15: Kaplan-Meier curves of time to protocol-defined treatment failure, recurrence of symptomatic atrial arrhythmia, and recurrence of any atrial arrhythmia by treatment group

Source: Wilber et al., 2010.

In the study, the baseline measure for the two treatment groups for quality of life (QoL) were similar. As early as three months into the effectiveness evaluation period, the mean SF-36 physical and SF-36 mental summary scores in the patient group who had undergone AF ablation had improved compared with the scores of patients treated with medication. As illustrated in Table 5.6, the patients who underwent ablation reported significantly lower (improved) frequency and severity of symptoms after only three months.

Table 5.6: Quality of life assessment with change from baseline to three months

Absolute change from baseline						
	Catheter ablation		**Anti-arrhythmic drug therapy**			
	No. of patients	Mean change (95% CI)	No. of patient	Mean change (95% CI)	Mean difference between groups (95% CI)	*P* value
SF-36 mental	90	8.5 (5.9 to 11.1)	39	1.6 (-1,1 to 4.3)	6.9 (2,6 to 11.2)	*p*<0.001
SF-36 physical	90	6.9 (5.2 to 8.6)	39	0.4 (-1.7 to 2.6)	6.6 (3.6 to 9.4)	*p*<0.001
Symptom frequency	82	-11.1 (-12.9 to -9.3)	29	0.7 (-2.4 to 3.9)	-11.8 (-15.4 to -8.3)	*p*<0.001
Symptom severity	65	-9.4 (-10.9 to 07.9)	39	0.0 (-3.3 to 3.4)	-9.9 (-12.6 to 06.3)	*p*<0.001

Notes on abbreviations: CI = confidence interval; SF 36 = short form health survey.

Source: Wilber et al., 2010.

The results of this study demonstrate that radiofrequency catheter ablation had significantly better outcomes for patients with frequent symptomatic paroxysmal AF who were unresponsive to drug therapy versus rhythm control with alternative drug therapy. The results also showed that there was

a substantial reduction in the risk of recurrent atrial arrhythmias and clinically meaningful improvement in symptoms and QoL and that catheter ablation was associated with a favourable safety profile. No major adverse events, i.e. thromboembolic events, atrial oesophageal fistula, cardiac perforation, phrenic nerve paralysis, or death occurred in this study, while major adverse events or drug intolerance requiring early withdrawal of the assigned drug occurred in approximately 10% of study patients. This is comparable with other studies.

5.6.3 Results for cryoablation for AF vs. anti-arrhythmic drugs for AF

Little data exist on the use of cryoablation for AF in comparison with RF ablation techniques. Weerasooriya *et al.* (2008) reported that there is an inherent risk with the use of radiofrequency energy because of the relatively thin-walled left atrium. The risks cited were the risk of cardiac tamponade due to the steam pop phenomenon, and risk of injury to adjacent structures such as the pulmonary veins and oesophagus, nerve-plexi, the aorta, bronchi, pericardium, as well as phrenic nerve and lungs. In addition to these potential complications, it was observed that the procedure is extremely demanding in terms of operator competency and dexterity and has a steep learning curve.

At the time of publication, the investigators reported that the use of cryo-energy as an alternative energy source in the clinical setting may be less likely to cause pulmonary vein stenosis or oesophageal damage, but they did comment on the fact that studies of cryoablation for slow and accessory pathways demonstrated a higher recurrence rate than RF ablation.

In theory, balloon technology offers the advantage of being simpler, faster, and a more widely applicable means of achieving pulmonary vein isolation. One major drawback of this type of technology is the highly variable anatomy of pulmonary veins. It is estimated that as many as 70% of people have abnormal pulmonary veins. In practical terms, it means that one size balloon does not fit all different types of anatomies and the physical effect of oversizing the balloon in the right superior pulmonary vein may result in a higher rate of phrenic nerve palsy (Weerasooriya *et al.,* 2008).

Weerasooriya *et al.* (2008) referred to a study by Van Belle *et al.* (2008) and reported that the mean procedure times for AF ablation in 138 patients with cryoablation was 207min, while the fluoroscopic duration was 57min. These times were from an experienced group who were very early adopters of this new platform, and used it exclusively, suggesting that this is not as simple a procedure as alleged. It was also noted that 40% of patients also required extra ‘touch up’ ablation using an additional point-by-point ablation catheter illustrating that the technique did not reduce the requirements of manual dexterity or understanding of pulmonary vein electrograms.

While cryo-technology was considered a safe alternative to RF ablation, the rate of serious complication was high, at 8.6% of patients, and these included phrenic nerve palsy in four patients and pulmonary vein rupture in one patient.

Weerasooriya *et al.* (2008) finally commented that, until better alternatives are available, the use of balloon-based cryoablation offers only a modestly effective alternative to radiofrequency ablation for patients with paroxysmal atrial fibrillation in whom pulmonary vein isolation was planned (Weerasooriya *et al.* 2008).

During the recent American College of Cardiology meeting held in Atlanta from 14 to 16 March 2010, the results of the STOP-AF trial were announced.

A total of 245 patients with paroxysmal AF from 26 centres were enrolled for the STOP-AF trial. Patients were randomized to receive either cryoablation or anti-arrhythmic drug therapy. The randomisation was done as 2:1 (163 Cryoablation and 82 AAD). Inclusion criterion was two or more episodes of AF within two months, documented on electrocardiogram, or the failure of at least one anti-arrhythmic drug. As described by Packer, the patients were relatively young, with little documented heart disease and, based on their $CHADS_2$ score, were a low risk cohort of patients. However, they all had frequent, highly symptomatic AF, failing, on average, 1.2 anti-arrhythmic drugs (Packer, 2010).

After one year (three-month blanking period and nine-month follow-up) 69.9% of patients treated with cryoablation were free from AF, compared with 7.3% of patients treated with anti-arrhythmic drug therapy. Of the successfully ablated patients, 58% were free from AF at one year without the use of anti-arrhythmic drug therapy, and 60% were free from AF after a single ablation procedure.

While the study met both primary safety outcomes of less than 14.8%, it should be noted that slightly more than 3% of patients treated with cryoablation experienced serious complications requiring intervention. Of the complications in the cryoablation cohort, phrenic nerve paralysis occurred in 29 (11%) patients and five (3.1%) had pulmonary vein stenosis with two requiring intervention. In the cryoablation group, the stroke rate was 2.5% *vs*. 1.2% for the AAD group and myocardial infarction was 1.2% in the cryoablation group *vs*. 0% in the AAD group. Newly diagnosed atrial flutter was found in 3.7% of the cryoablation group *vs*.15.9% in the AAD group, and the death rate was 0.6% in the cryoablation group *vs*. 0 in the AAD group. This death occurred at 288 days and was due to a myocardial infarction. The mean procedural duration was 371 minutes, involving a cryoablation time of 65.7min and fluoroscopy time of 62.8min (Cox, 2010; Packer, 2010; Raible *et al.,* 2010).

Finally, it may be noted that, while cryoballoon technology could potentially represent a very quick, simple and safe approach to the treatment of paroxysmal atrial fibrillation, the data does not yet indicate this, nor does the single freeze approach support data that show the increased success rate of AF ablation when also ablating the posterior wall, SVC, mitral valve annulus or CFAE, in which case additional “touch up” is required with a traditional ablation catheter at additional costs (Day, 2010).

5.7 CLINICAL EFFECTIVENESS OF CATHETER ABLATION

A study published in *Journal of Cardiovascular Electrophysiology* (Bunch *et al*., 2011) compared the outcome of rates of death, stroke and dementia in patients with AF. A total of 37 908 patients were enrolled in the trial, with 4 212 patients undergoing AF ablation. These patients were compared in a 1:4 analysis with 16 848 AF patients who were age- and gender-matched but not treated with ablation, and a further 16 848 age- and gender-matched patients who did not suffer from AF (Bunch *et al.,* 2011: 839).

The patients were enrolled in the prospective AF study and were followed-up for at least three years for myocardial infarction, dementia, Alzheimer's disease, heart failure, cardiovascular hospitalisation and death. Death included all-cause mortality and coronary artery disease- related mortality. Approximately 55% of the patients had paroxysmal AF, while 27% were considered to have persistent AF, and a further 18% permanent. The actual follow-up period by cohort was as follows: The patients with no AF had a mean follow-up period of six years (±4.6 years); the AF patients who did not undergo ablation were followed up for a mean of 5.1 years (±4.7 years); and the AF patients who underwent catheter ablation were followed up for 3.1 years (±2.4years). Table 5.7 illustrates the baseline demographics of the patients who were enrolled in the study.

As indicated in Table 5.7, the main difference between the three cohorts was that there was a lower incidence of hypertension, CHF, CVA, or TIA and renal failure in the patients without AF compared to those with AF. Among the two cohorts of patients with AF, there was a higher rate of diabetes and TIA in the group who did not undergo ablation. The cohort who received catheter ablation was found to have a higher rate of hypertension, CHF and valvular heart disease.

Table 5.7: Baseline demographics of patients who underwent AF ablation, patients with AF who did not receive AF ablation, and control population age- and sex-matched with patients, who did not have AF

Characteristic	No AF n=16 848	AF (no ablation) n=16 848	AF (ablation) n=4 212	p-Value
Age (years)	64.1 ± 13.0	66.0± 13.3	64.8±12.7	<0.0001
Sex (male)	60.8%	60.8%	60.8%	1
Diabetes	19%	21.1%	16.3%	<0.0001
Hypertension	41.2%	45.3%	47.8%	<0.0001
Hyperlipidaemia	58.4%	37.3%	44%	<0.0001
CHF	14.5%	23.6%	29.5%	<0.0001
Renal Failure	5.6%	7.8%	7.5%	<0.0001
TIA history	4%	4.2%	4.6%	0.16
CVA history	4.4%	6.3%	4.5%	<0.0001
MI history	10%	6.4%	6.4%	<0.0001

Source: Bunch et al., 2011: 841.

Cranial computed tomography (CT) scans were performed in the patients with dementia (5.7%) and an additional 3.7% of the study patients with dementia underwent an MRI scan. Table 5.8 illustrates the outcomes, with regard to dementia and Alzheimer's disease.

Table 5.8: Alzheimer's rate and rate of dementia at three years

Outcome	No AF n=16 848	AF (no ablation) n=17 848	AF (ablation) n=4 212
Alzheimer's dementia	0.5%	0.9%	0.2%
Other dementias	0.7%	1.9%	0.4%

Source: Bunch et al., 2011: 841.

Specific mortality rates for the three groups at one year, three years and five years is illustrated in Table 5.9. The one-year, three-year and five-year mortality rate was significantly lower in patients who underwent ablation, compared with the patients with AF who did not receive catheter ablation. They also had lower rates of mortality than the control group, who did not have AF.

Table 5.9: Mortality rates at one year, three years and five years

Outcome	No AF n=16848	AF (no ablation) n=17848	AF (ablation) n=4212
1-year mortality	4.7%	16.2%	3.0%
3-year mortality	8.7%	23.5%	6%
5-year mortality	11.4%	27.9%	7.6%

Source: Bunch et al., 2011: 841.

Bunch *et al.* (2011) reported that, at three-year follow-up, 64.4% of patients who underwent AF ablation had no documented episodes of AF. Finally, a multivariate analysis was performed which compared, among others, the outcomes of patients with AF and ablation *vs*. AF and no ablation (Table 5.10). In the following categories of total mortality, CVA, total dementia, Alzheimer's dementia and senile dementia, the odds ratio was in favour of the AF ablation cohort with a p value <0.00001. With regard to heart failure and vascular dementia, the odds ratio was in favour of the AF ablation group, but it was not found to be statistically significant.

Table 5.10: Long-term multivariate outcomes comparing patients with AF and ablation *vs*. AF no ablation

	OR/HR	P value
Total mortality 1 year	OR=6.45	<0.0001
Total mortality 3 years	OR=5.16	<0.0001
Total mortality long-term	HR= 2.81	<0.0001
CVA 1 year	OR=2.12	<0.0001
CVA 3 years	OR=1.9	<0.0001
CVA long-term	HR=1.68	<0.0001
Total Dementia 1 year	OR=8.27	<0.0001
Total Dementia 3 years	OR=4.00	<0.0001
Total Dementia long-term	HR=2.88	<0.0001
Senile Dementia 1 year	OR=8.07	<0.0001
Senile Dementia 3 years	OR=4.12	<0.0001
Senile Dementia long-term	HR=3.32	<0.0001
Heart failure 1 year	OR=1.03	0.81
Heart failure 3 years	OR=1.06	0.55
Heart failure long-term	HR=0.77	0.001
Vascular Dementia 1 year	OR=4.91	0.03
Vascular Dementia 3 years	OR=2.12	0.08
Vascular Dementia long-term	HR=1.35	0.37

Source: Bunch et al., 2011: 844.

Complication rates as result of the ablation procedures were recorded as follows: 0.6% (n=25) had pericardiocentesis; 0.2% (n=7) had AV fistulas which required surgical intervention; and 0.4% (n=16) suffered TIAs. There were two documented oesophageal perforations; one of these patients died from multi-system failure. Four (0.1%) patients had pulmonary vein stenosis and a total of 27.6% (n=1162) patients required a second AF ablation over the long-term.

5.8 CONCLUSION

The management of atrial fibrillation is complex. The risks of thromboembolism and stroke remain a real issue for both the patient and the physician. Large-scale community-based studies have shown that patients with AF have high rates of both morbidity and mortality. Drug therapy has failed many of these patients and, even with new generations of drugs, the ability to control rhythm pharmacologically has shown no mortality or morbidity benefits over rate control strategies in major studies (Van Gelder *et al.,* 2002: 1840). Bunch *et al.* (2011) have shown in an epidemiological study that patients who achieved sinus rhythm after AF ablation have clinical outcomes similar to patients who do not have AF. At present, drugs seem inferior to catheter ablation for achieving and maintaining sinus rhythm and the long-term outcome of catheter ablation should be investigated with regard to safety, efficacy and cost-effectiveness.

Chapter 5 has thoroughly investigated all the treatment options that are available for patients with AF. Based on this information it is evident that building a cost-effectiveness model using both anti-arrhythmic drugs and radiofrequency ablation is appropriate.

Chapter 6 delves deeper into the literature about both of these therapies and probes and challenges all the data required to construct such a cost-effectiveness model.

Both Radiofrequency ablation and Cryoablation are used extensively to treat Paroxysmal Atrial Fibrillation. There are a number of reviews that compare the two. An overview of systemic reviews comparing RF ablation with Cryoablation can be found in Annexure A.

CHAPTER 6: TOWARDS THE DEVELOPMENT OF A MODEL TO EXPLORE THE COST-EFFECTIVENESS OF CATHETER ABLATION

6.1 INTRODUCTION

Chapter 2 investigated the relevance of health economic studies, described the various techniques that are available to examine costs associated with medical treatment and settled on the alternative of cost effectiveness analysis as the choice of models to use. Chapter 3 contained detailed information about South Africa from a demographic, economic and healthcare point of view. This was to highlight some of the issues that pertain to a country like South Africa, which is an emerging market with a medium-sized GDP and an advanced private healthcare sector, but also a country with high inequality, unemployment, death rate and disease entities like HIV/AIDS and its co-morbid diseases. The reason for this in-depth analysis was to ensure that the need for treatment of non-rheumatic AF was appropriate within this society. Chapters 4 and 5 introduced the reader to the disease of AF by describing the disease and investigating all the various treatment options available to patients. All of these earlier chapters have built the foundation for Chapters 6 and 7.

Chapter 6 researches all the factors that are required to build a cost effectiveness model, including the following:

The economic burden of AF.
Literature comparing anti-arrhythmic drugs and RF ablation.
Literature review on the cost effectiveness of catheter ablation.
Literature review on the quality of life associated with AF.
Finally, an in-depth review of the APAF study which forms the framework of the model.

6.2 BACKGROUND

Atrial fibrillation is the most commonly occurring and sustained arrhythmia and poses a major public health burden. The lifetime risk of developing AF after the age of 40 is about one in four for both men and women. Large-scale, population-based studies have estimated that the prevalence of AF in the US population is 0.9%, with similar estimates for the UK. The prevalence of AF increases with age, from around 3 to5% in people over the age of 65, increasing to 10% in people over the age of 80 years (Bajpai *et al.,* 2007).

Bajpai *et al.* (2007:15) and Reynolds *et al.* (2007: 628) predict that the population of patients with AF will increase between twofold and fourfold by 2050. There are two reasons for this increase, cited by Stewart *et al.* (2004). Firstly, the population is ageing, meaning that there is a larger pool of patients who are at risk of AF each year and, secondly, the co-morbid conditions associated with AF, like hypertension, congestive heart failure and coronary artery disease are also increasing as more patients with these conditions survive. Furthermore, Bajpai *et al.* (2007) suggest that these

projections may be conservative, as AF is often silent and the prevalence of sustained silent AF in people over the age of 65 years may, in fact, be as high as 25 to 30%.

Congestive heart failure and thromboembolic stroke are the most severe and debilitating complications of AF. A number of large-scale studies in AF have shown increased risk of death from all causes and cardiovascular causes ranging from 1.3 to 2.8-fold for men and women. Thromboembolism and stroke are increased in patients with AF with the Framingham study reporting an annual risk of 1.5% in patients aged 50 to 59 years and up to 23.5% in those patients over 80 years old. Stroke in patients with AF is often more severe and disabling than in those without it (Fuster *et al.,* 2006).

The *Central Intelligence Agency World Factbook* indicates that the 2011 population of the world is 6.9 billion. Of these, close to 8% or close to 552 million are over the age of 65 years (Central Intelligence Agency, 2011). If one makes a simple extrapolation using population-based studies, one could estimate that as many as 55 million people in the world may currently be affected by AF. A crude estimate suggests that approximately 387 000 South Africans are affected by AF, or 8% of the total number of patients living with HIV/AIDS.

Anti-arrhythmic drug therapy (ADT) is used widely for the treatment of AF but continues to show limited efficacy, even in large, controlled trials. Many of these drugs are known to cause toxic side effects and may, in some cases, be arrhythmogenic. Some trials have shown that rhythm control strategy has little or no benefit over a rate control strategy for the management of AF (Van Gelder *et al.,* 2002). Evidence supporting the fact that patients who achieve sinus rhythm have better survival highlights the lack of efficiency in the treatment of AF with ADT (Noheria *et al.,* 2008: 581). Pulmonary vein isolation (PVI) by means of radiofrequency ablation is becoming more widely accepted as a treatment option for the treatment of AF in patients who are symptomatic (Camm *et al.,* 2010: 2409).

6.3 THE ECONOMIC BURDEN OF AF

AF undoubtedly imposes a significant economic burden on a country's healthcare system, mainly owing to the severity of the co-morbid diseases. However, there has not been much research into the actual costs of managing patients with atrial fibrillation. Two studies published in 2004 and 2007 attempted to demonstrate the economic burden of AF. The first study, published in *Heart* in 2004, was a UK-based survey that showed that the direct cost of managing AF in 1995 accounted for between 0.6 and 1.2% of the total National Health Service (NHS) budget. This increased to between 0.9 and 2.4% in 2000 (Bajpai *et al.,* 2007: 15).

The results of the study indicate that, in 1995, 534 000 patients in the UK were treated for AF as a primary diagnosis. This accounted for 0.9% of the entire population and 5% of the population over the age of 65 years. This is congruent with data from the Framingham study. There was a total of 1.5

million GP consultations by these patients in 1995 or three GP consultations per patient per year for AF. Figure 6.1 demonstrates the components of healthcare expenditure related to AF in the UK in 1995.

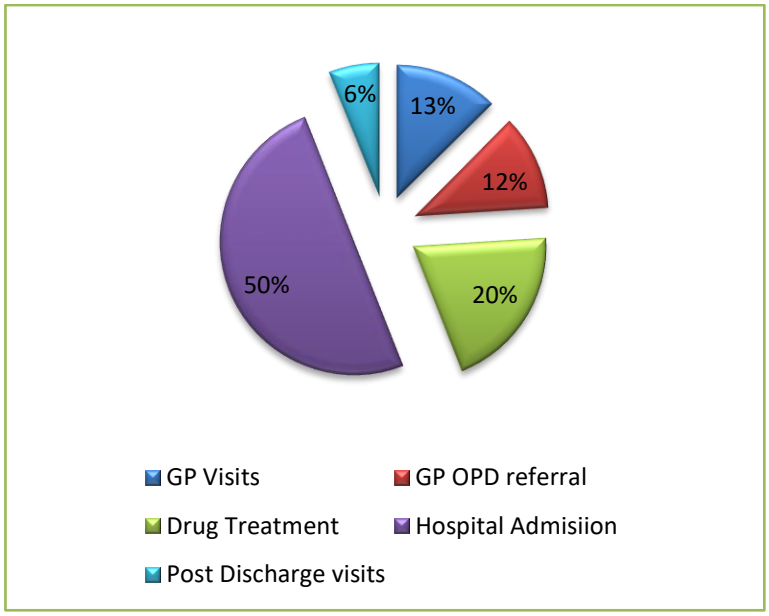


Figure 6.1: Component of healthcare expenditure related to AF in the UK, 1995

Source: Stewart et al., 2004.

In addition to these 58 700 hospital admissions for AF as a primary diagnosis, a further 101,000 admissions occurred in 1995, where AF was the secondary diagnosis. The total number of hospital days was 89 000, which accounted for seven hospital days per admission. The cost of AF to the NHS in 1995, excluding hospitalisations where AF was a secondary diagnosis and excluding the cost of nursing home care after discharge, amounted to £243.9 million out of the total NHS budget of £39 118 million. This means that, in 1995, where AF was the primary diagnosis, excluding post discharge nursing home care for patients, the cost of managing AF accounted for 0.62% of all NHS expenditure for the year. The greatest portion of this was spent on hospitalisation, which accounted for 0.31% of the total NHS budget (Stewart *et al.,* 2004: 289).

The authors again examined costs in 2000, five years after the first measurement. Their findings included the fact that the prevalence of AF had increased from 0, 9% to over 1% of the population, a growth in total number of patients of 13%. The total number of admissions where AF was the primary diagnosis had increased from 58 700 admissions in 1995 to 109 000 admissions, with an average of 6.1 days per patient per admission (2% growth in days in hospital and an 86% increase in the number of hospital admissions). The total cost for AF in 1995, where AF was the primary diagnosis and including the admissions to hospital where AF was the secondary diagnosis, was £484.9 million. This increased by 49.8% to £726.6 million in 2000 (Stewart *et al.,* 2004: 289).

A study by Reynolds *et al.* (2007) published in *Journal of Cardiovascular Electrophysiology* examined the costs of treating new-onset AF in the USA. This US-based study, known as the FRACTUAL Registry, was an inception cohort study of 973 patients with AF who were followed up at three- and six-month intervals for a mean of 24 months (±9 months). The treatment options for AF, as well as the clinical outcomes, and in-patient and out-patient resource utilisation were tracked at each follow-up interval. The patients in the registry were managed primarily with anti-arrhythmic drugs and cardioversion. Table 6.1 tabulates the reason for hospitalisation that were associated with the primary diagnosis of AF.

Table 6.1: Profile of hospitalisations associated with the principal diagnosis of atrial fibrillation in 1995 and subsequent outcomes

	Men	Women	Total
Admissions	31 200	27 500	58 700
Alive at discharge	30 500	26 400	56 900
% admissions alive at discharge	98	96	97
Age over 65 years	17 160	15 125	32 285
% over 65 years	55	55	55
First Diagnosis	22 152	20 350	42 502
% patients in whom first diagnosis	71	74	72
Admitted to specialised units	7 176	6 050	13 226
% of admissions to specialised units	23	22	22.5
Subsequent outcomes			
Heart failure	4 992	3 850	8 842
% of heart failure	16	14	15
Stroke	2 496	3 025	5 521
% of stroke	8	11	9.4
Acute myocardial infarction (AMI)	2 184	1 650	3 834
% of AMI	7	6	7
Readmission at 1 year	5 795	3 696	9 491
% readmissions at 1 year	19	14	17

Source: Adapted from Stewart et al., 2004: 288.

Reynolds *et al.* (2007) estimated that more than 400 000 hospital admissions occur each year for atrial fibrillation. These costs were for the management of AF and excluded any out-of-pocket expenditure, patient time spent on care, lost productivity, as well as non-acute nursing home care or rehabilitation. All hospitalisations were recorded, but only those related to cardiovascular disease or AF and its complications, including stroke, were included in the analysis. Hospital costs were

assigned in 2002 $US. Of the 1 005 patients enrolled in the study, only 973 completed at least three months' follow-up. Of these, 3.5% (n=34) were considered to have chronic AF, 503 patients had paroxysmal AF (51.7%) and, in 436 (44.8%), the AF was terminated by electrical cardioversion. During the follow-up period, a further 31 patients progressed to chronic AF (3.19%). No patients received pulmonary vein isolation (PVI) or underwent surgery for their AF (MAZE procedure).

During the follow-up period, 319 patients (33%) had more than one recurrent episode of AF. It is important to note that the majority of patients in whom AF became permanent were from the older group of patients and that there were more women than men in this group. In those who developed permanent AF, the prevalence of heart failure and valvular disease was higher.

During the follow-up period, 259 patients (27%) were admitted to hospital a total of 395 times. This is an average of 1.5 admissions per patient admitted, but the data show that the range was between 1-9 admissions per patient.

A total of 190 admissions (48%) were for arrhythmia and a further 75 admissions were for heart failure. The average length of stay was 4.4 days (±7.2 days). This is lower than the data from the UK where the average hospital stay was six days in 1995 and seven days in 2000. The average hospital cost was US$9 358 (±9 670) per admission. By using the data in Figure 6.2 and the average cost associated with treating AF, it is possible to estimate the total cost for managing AF, as tabulated in Table 6.2.

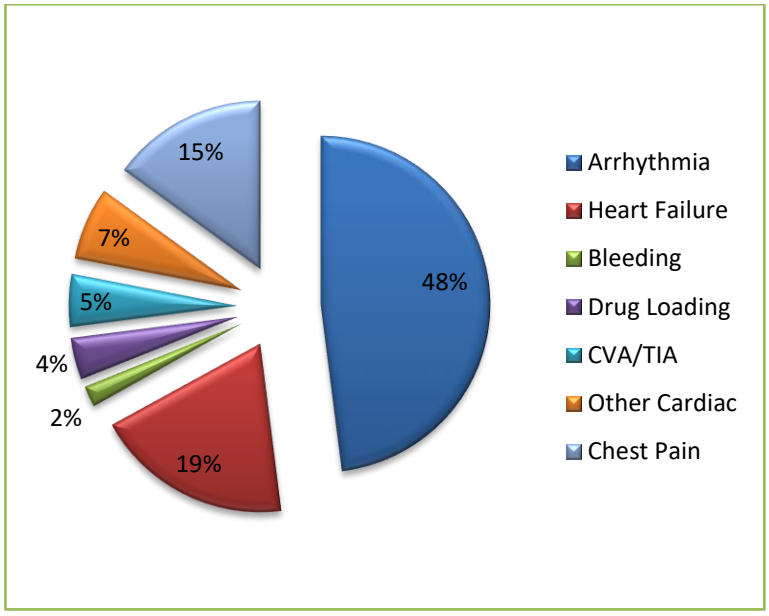


Figure 6.2: Principal diagnoses for hospital admission related to cardiovascular disease, AF, AF therapy or complication in the FRACTUAL registry

Source: Reynolds et al., 2007: 630.

Table 6.2: The total estimated cost of AF using mean and median for hospital costs

	Cost at Median value US$ (2002)	Cost at Mean value US$ (2002)
Hospitalisation	2. 5 Billion	3.7 Billion
Drug costs including INR	1.8 Billion	2.78 Billion
Outpatient visits	958 million	1.4 Billion
Total costs	5.37 Billion	8 Billion

Source: Adapted from Reynolds et al., 2007: 630.

Given the mean cost of hospitalisation of US$9 358 per admission, with an estimated number of admissions in the US of 400 000 per year for AF, the cost of hospitalisation only for AF could be US$3.7 billion. On the other hand, by using a more conservative estimate of the median cost of hospitalisation, while still utilising the 400 000 admissions each year, the cost of hospitalisation would be US$2.5 billion.

The data reveal that, for the nearly 1 000 patients included in the study, the average healthcare cost was almost $4 700 per year during the first year following diagnosis. Of note was the fact that patients who accepted permanent AF had lower costs than those patients who did not accept the symptoms. Approximately half of all the costs in AF are attributed to hospitalisations. The study demonstrated that each recurrence of AF increased the average cost by about $1 600, which represents 34% of the initial cost. Table 6.3 demonstrates resource utilisation by group over the full follow-up period.

Table 6.3: Resource utilisation by group over entire follow-up period measured per 100 patients

AF Recurrences				
Procedures per 100 patients	**Permanent AF n= 34**	**None n= 620**	**1-2 n= 286**	**>3 n=33**
Cardioversion	2.9	8.1	49.3	160.6
AF related hospital admissions	0.21	0.24	0.64	1.61
Total hospital days	0.32	1.3	2.7	4.5
AF emergency room visits	2.9	10	25.2	54.5
Trans-oesophageal ECHO	0	12.9	30.8	45.4
Trans thoracic ECHO	14.7	33.1	44.4	60.6
Ambulatory monitors	14.7	25.2	35	54.5

Source: Adapted from Reynolds et al., 2007: 631.

Reynolds *et al*. suggests that, given the limited effectiveness of anti-arrhythmic drugs, it may be conceivable that, for highly symptomatic patients, other alternatives including catheter ablation, may provide benefits in terms of symptoms and quality of life.

6.4 STUDIES COMPARING CATHETER ABLATION WITH DRUGS FOR AF

The ACC/AHA/ESC guidelines indicate that catheter ablation is a reasonable alternative to drug therapy for the treatment of atrial fibrillation and the prevention of the recurrence of AF. Numerous studies show that pulmonary vein isolation is superior to drugs at one year with regard to maintaining sinus rhythm.

There are a number of randomized clinical trials designed to evaluate catheter ablation vs. drug therapy, but, because of the small number of patients in each trial and the fact that many are single centre studies, the clinically relevant efficacy of catheter ablation for patients with AF remains in question. Therefore, in the absence of large, randomized, multi-centre clinical trials comparing catheter ablation to drug therapy, the author examined the rationale and results of three systematic reviews and meta-analysis published in 2008 and 2009 for efficacy of catheter ablation vs. anti-arrhythmic drugs for the maintenance of sinus rhythm at one-year follow-up.

6.4.1 The Calkins *et al.* study

The first study by Calkins *et al.* (2009) included studies that focussed on the ablation of the pulmonary veins but may also have included additional ablation lines like roof lines, flutter ablation and lines around the superior vena cavae.

Of the 537 studies that were identified, 142 met the inclusion criteria, but only 63 studies were included in the final selection. Studies were considered eligible for inclusion irrespective of whether the design was prospective or retrospective. Studies were excluded if they were done in animals or in vitro. Studies in any language other than English, French, German, Italian, Portuguese or Spanish were also excluded. Any studies performed before 1990 or after January 2007 were also excluded. Finally, paediatric studies and studies with less than 40 patients, or more than one type of catheter ablation, were also excluded.

In the systematic review of the drug therapy arm, a total of 3 383 abstracts were reviewed, but only 44 of the studies met the inclusion criteria and only 34 were finally analysed. The review on the drug arm focussed on five specific anti-arrhythmic drugs, namely Amiodarone, propafenone, dofetilide, Flecainide and Sotalol. In the drug therapy arm, any studies in any language other than English were excluded as were studies before 1990 and after 1 January 2007. Again, animal or in vitro studies, paediatric studies or studies with fewer than 40 patients were excluded. Studies with less than a 30-day follow-up period were also excluded (Calkins *et al.,* 2009: 351).

Of the 63 eligible studies in the radiofrequency ablation (PVI) dataset, nine were randomized controlled, 11 were prospective comparative, 31 were single arm prospective studies and 12 were retrospective studies. Two-thirds of the studies were published after 2004. Of the 34 studies included in the drug therapy arm, only four had been published after 2004. Of these, 24 were randomized

control studies, there was one non-randomized, comparative study, and nine studies were single arm trials. Some of the characteristics of the two patient groups are tabulated in Tables 6.4 and 6.5.

Table 6.4: Characteristic of patients undergoing either catheter ablation or receiving anti-arrhythmic drugs

	Catheter ablation		AAD	
	Mean	**Range**	**Mean**	**Range**
Age (y)	55.5	42-67	62.6	38-80
Mean no of drugs refractory	2.6	1-5	1.7	0-3
Mean duration of AF (y)	6.0	1-9	3.1	0-1
Mean LA size (mm)	42.6	35-50	43.7	33-49
Mean LV ejection fraction (%)	57.5	49-71	49	25-67

Source: Calkins et al., 2009: 353.

Table 6.5: Baselines characteristic of patients with AF undergoing catheter ablation or receiving anti-arrhythmic drugs measured as percentage

	Catheter ablation	AAD
Sex (male)	72	64.6
Paroxysmal AF	69.8	56.4
Persistent	14.9	35.1
Permanent (long standing)	13.9	7.5
Previous ablation	4.2	0
Ischaemic heart disease	10	18.2
Valvular heart disease	5.6	16
CHF	15.7	24.6
Stroke	3.3	0
Diabetes	4.8	12.1
Hypertension	30.3	38.4
Previous anti- arrhythmic	95	36.3
Anti-coagulants	100	100

Source: Calkins et al., 2009: 353.

What can be noted from the baseline characteristics of the two groups is that the average age of patients in the PVI group was lower (mean age 55 years *vs*. 62 years). The PVI group had all failed a greater number of drugs prior to receiving ablation (2.6 drugs *vs*. 1.7) and 70% of the patients in

the PVI groups were reported to have paroxysmal AF, compared to the 56% in the drug therapy group. Finally, the patients in the PVI cohort had a longer duration of AF (6 years *vs*. 3.1 years).

In the drug therapy cohort there were sixteen Propafenone treatment groups, eleven Amiodarone treatment groups, nine groups treated with Sotalol, seven with Flecainide and two groups with Dofetilide.

Calkins *et al.* (2009) report that almost half of the procedures performed in the PVI studies were done using a catheter navigation system, the use of which increased markedly from 2002. The use of irrigated catheters also increased over this period.

The efficacy of the outcomes for the PVI cohort (where efficacy was defined as a lack of recurrence of AF during the follow-up period), with an average follow-up period of 14 months, is illustrated in Table 6.6.

Table 6.6: Efficacy outcomes for radiofrequency ablation

	Number of patients	Mean (%)	Range (%)
Single ablation, no AAD	2 800	57	50 to 64
More than one ablation with no AAD	3 481	77	65 to 77
More than one procedure on AAD	3 562	77	73 to 81
Single ablation on AAD	4 782	72	Not stated

Source: Calkins et al., 2009: 354.

In the drug therapy cohort, Amiodarone showed the greatest success over placebo; however, the overall success rate of all drugs was 52% (47% to 57%) in 3 180 patients.

Complications associated with catheter ablation are well documented and Calkins *et al.* (2009) report a total of 28 adverse events (4.9%). The most common complication associated with the PVI procedure is pulmonary vein stenosis (1.6%), cardiac tamponade (0.7%), pericardial effusion (0.6%), peri-procedural stroke (0.3%) and peri-operative TIAs (0.2%). The overall mortality rate in all treatment groups was 0.7%.

While the types of adverse events differ in the drug therapy group, the following were reported from the Calkins *et al.* (2009) publication:

- Overall mortality rate was 2.8%.
- The total number of adverse events in the drug therapy arm was 24 or 29.8% (Calkins *et al.,* 2009: 354).
- Adverse events caused 10.4% of patients to discontinue their drugs while another 13.5% discontinued their drugs due to failure of the therapy.

Calkins *et al.* (2009) state, in their concluding remarks, that catheter ablation is associated with a higher efficacy than AAD, even though most of the patients who were enrolled had already failed more than one AAD. They also remarked that modification of the ablation procedure did not make an impact on the data, but that more difficult and older patients were being treated in the later studies.

It may be relevant to question the fact that this study was published in 2009, when the cut off for inclusion of studies was January 2007. Ablation for AF is a relatively new procedure which requires skill and has a steep learning curve. As noted in the Calkins study, two-thirds of the trials were published after 2004 while only 12% of the studies on ADT were published at the same time. There was also an increase in the adoption of both catheter navigational technologies and irrigation technologies, which not only improve the accuracy (and implying, thereby, the efficacy) but also the safety of the procedure. Is this a fair comparison?

6.4.2 The Noheria et al. review

A second systematic review employed a methodology similar to that used in the Calkins *et al.,* review described above. Success in both the ADT cohort and the PVI cohort was described as free of recurrent atrial tachycardia. This study differed in that it looked only at studies where both drugs and PVI were compared (Noheria *et al.,* 2008: 581). Figure 6.3 illustrates the flow diagram of the literature review of the systematic review of studies.

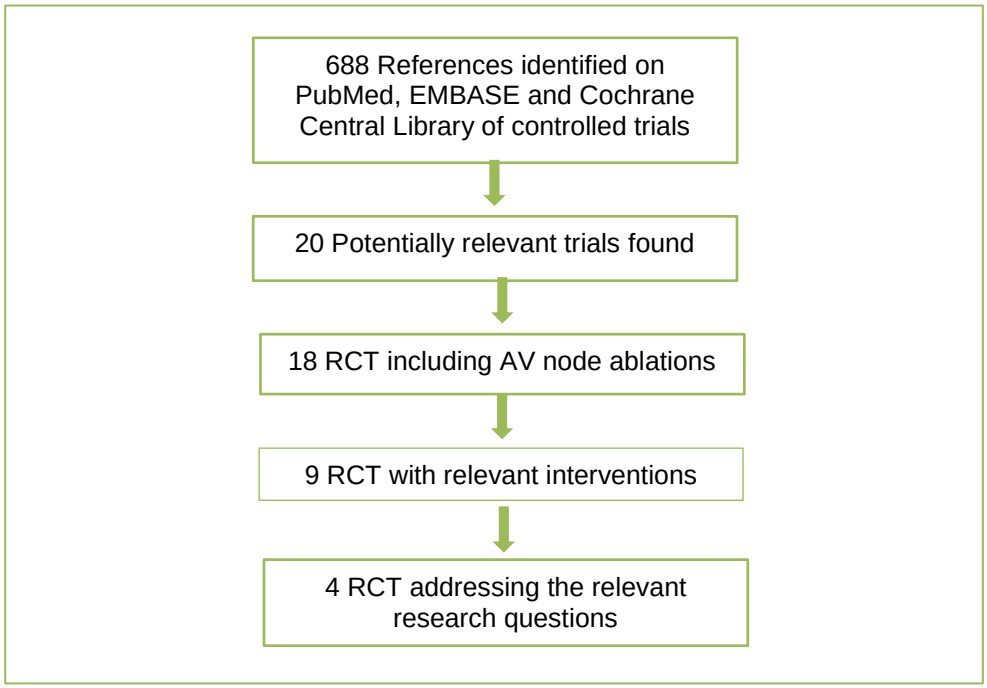


Figure: 6.3: Flow diagram of the stages of the literature search to find relevant randomized control trials (RCT)

Source: Noheria et al., 2008: 581.

The following five criteria were important for inclusion:

- Appropriate allocation sequence of generation.
- That no exclusions occurred after randomization.
- The attrition rate was less than 15%.
- The assessments were blinded.
- There was an intention to treat analysis.

Those that did not meet at least three of these criteria were excluded.

The four trials reviewed in the meta-analysis are Krittayaphong *et al.* (2003), Wazni *et al.* (2005), Stabile *et al.* (2006) and Pappone *et al.* (2006). The characteristics of the four trials are tabulated in Table 6.7.

Table 6.7: Characteristics of the trials reviewed in the meta-analysis comparing catheter ablation *vs*. ADT for AF

Author	Year	N	Age	Type	Previous ADT	Repeat	Cross over
						%	
Krittayaphong	2003	30	PVI 55±10 ADT 47±15	PAF & persistent	≥1	Not stated	Not stated
Wazni	2005	70	PVI 53±8 ADT 54±8	PAF	Naïve to ADT	12	49
Stabile	2005	137	PVI 62±9 ADT 62±10	PAF & persistent	≥2	No	57
Pappone	2006	198	PVI 55±10 ADT 57±19	PAF	≥2	AF 6 AT 3	42

*Note: *These 44% of "failures" included 4 patients who had atrial flutter.*

Source: Adapted from Noheria et al., 2008: 582.

A total of 432 patients were included in this analysis: 218 received ADT while the other 214 underwent catheter ablation. At the end of the follow-up period, a total of 75.7% of patients from the catheter ablation cohort were considered free from AF, while only 18.8% of those in the ADT cohort were free of AF. Table 6.8 demonstrates the results of each study as well as the number of adverse events.

Table 6.8: Results from individual trials

	PVI Arm			Control Arm			
Source	**Total**	**Recurrence free survival**	**Adverse events**	**Total**	**Recurrence free survival**	**Adverse events**	**RR for AT (95% CI)**
Krittayaphong *et al.* (2003)	15	12	5	15	6	7	3.73 (2.47-5.63)
Wazni *et al.* (2005)	32	27	4	35	7	4	2.00 (1.02-3.91)
Stabile *et al.* (2006)	68	38	3	69	6	4	6.43 (2.91-14.21)
Pappone *et al.* (2006)	99	85	5	99	22	23	3.86 (2.65-5.63)
Total	214	162 (76%)	17 (8%)	218	41 (19%)	38 (17%)	

Source: Noheria et al., 2008: 582.

The Forest plot illustrated in Figure 6.4 shows that, in each of the four studies, the evidence is in favour of PVI. What makes this analysis different from the previous meta-analysis by Calkins *et al.* (2009) is the fact that all four studies in the Noheria study had Holter monitors at three, six and 12 months follow-up, while fewer than 50% of the studies in the Calkins trial used Holter monitors to evaluate whether or not patients were free of AF recurrence.

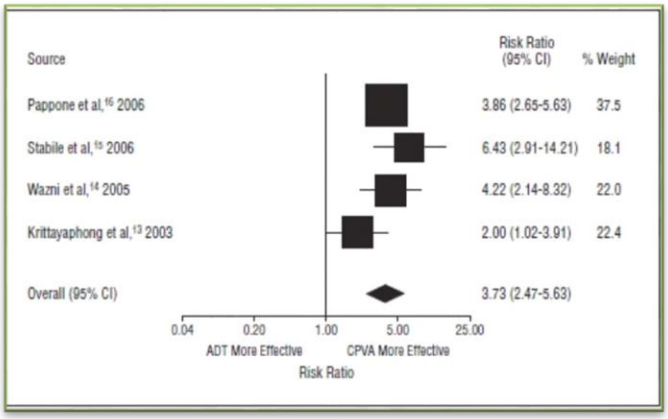


Figure 6.4: Forest plot of four randomized controlled trials evaluating PVI *vs*. ADT for recurrence free survival during the follow-up periods. Width of diamond represents 95% confidence interval

Source: Noheria *et al.,* 2008: 584.

The authors reported on the Beg and Egger tests for publication bias and showed that there was no statistically significant publication bias. They acknowledge that there were only a small number of studies included in the analysis, which made the meta-analysis underpowered to detect publication bias. They did, however, state that there was little evidence to suspect any such bias. This is shown in Figure 6.5 (Noheria *et al.,* 2008: 583).

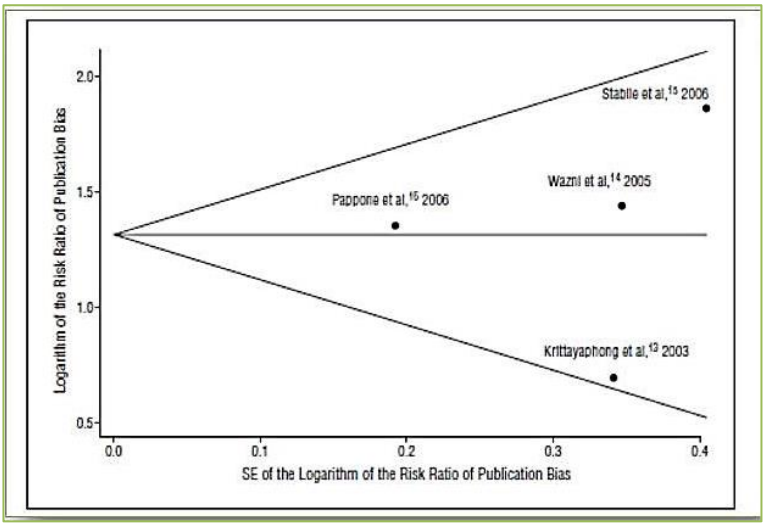


Figure 6.5: Funnel plot with 95% CI for assessing for publication bias

Source: Noheria *et al.,* 2008: 584.

6.4.3 The Piccini et al. meta-analysis

The final meta-analysis evaluated was that by Piccini *et al.* (2009). The goal of their meta-analysis was to determine whether PVI was more efficacious than ADT and to evaluate the adverse events and safety of the two comparators. To do this, the authors analysed studies in which patients were randomly assigned to either catheter ablation or anti-arrhythmic drugs.

Studies were excluded from the analysis based on any of the criteria below:

- If catheter ablation was used in both treatment arms.
- If the follow-up period was <12 months.
- If the control arm had <10 patients.
- If surgical ablation was included.
- If only patients with atrial flutter were included.
- If patients were in a previously reported publication (e.g., a sub-study).

The primary endpoint was freedom from AF at 12 months with all recurrences after the blanking periods considered, regardless of anti-arrhythmic drug status. Secondary outcomes included the number of repeat catheter ablations, cross-over from the drug arm to the catheter ablation, hospitalisation for cardiovascular causes, pulmonary vein stenosis, oesophageal injury, thromboembolic events (including stroke/transient-ischaemic attacks) and, finally, all-cause mortality. All outcomes were analysed according to the intention-to-treat principle.

After reviewing 102 abstracts for inclusion and exclusion criteria the authors excluded 96 studies. The six remaining studies were reviewed and included in the analysis. The reasons for the exclusion of the other 96 studies include the following:

- Studies comparing two catheter ablation or surgical techniques without a medical therapy only arm.
- Trials of imaging or mapping techniques.
- Observational studies.
- Studies of medical therapy only (e.g., rate *vs*. rhythm control).
- Trials of pacing strategies or atrioventricular nodal ablation.
- Studies of supraventricular tachycardia or atrial flutter only.

The six randomized, controlled trials incorporated in this meta-analysis included a total of 693 enrolled patients. Only one trial was in a single centre study, whereas all the others were multi-centre studies. The baseline patient characteristics of these 693 patients are presented in Table 6.9. Most of the patients in the meta-analysis had paroxysmal AF (70%). In five of the studies that included information on the sex of the patients, it was found that 73% of the patients were male. The mean age was 55 years, the mean left ventricular ejection fraction was 60% (±4%) and the mean left atrial diameter among patients randomly assigned to ablation was 42mm (±3 mm). In the trials that specifically looked at pre-trial enrolment drug failure, the average number of drugs which were ineffective before enrolment was two.

Table 6.9: Patients characteristics in randomised trials of catheter ablation vs. ADT

Source	Mean age years	% Male	Paroxysmal AF %	Persistent AF %	Mean LEVF %	Mean LA diameter mm	Mean no of prior ineffective AADs
Krittayaphong *et al.* (2003)	52	63	67	33	63	39	Not stated
Wazni *et al.* (2005)	54	Not stated	96	4	54	42	0
Stabile *et al.* (2006)	62	59	67	33	59	46	Not stated
Oral *et al.* (2006)	57	88	0	100	456	45	2
Pappone *et al.* (2006)	56	67	100	0	61	39	2
Jaïs *et al.* (2008)	51	84	100	0	64	40	≥1

Source: Piccini et al., 2009: 628 & 629.

The primary endpoint in all six trials was freedom from AF at 12 months of follow-up. It is important to note that catheter ablation was decidedly more successful than drugs (77% *vs*. 29%). When, because of heterogeneity, the trial that enrolled only patients with persistent AF was removed from the analysis, catheter ablation was associated with even greater odds of AF-free survival (15.78; 95% CI) compared with the odds ratio when this study was included (9.74; CI 95%). With respect to freedom from both AF and anti-arrhythmic drug therapy, only two trials reported the number of subjects free from AF without anti-arrhythmic medications at 12 months. In those trials, 86%

(n=131/152) of those randomly assigned to catheter ablation were free from AF without an anti-arrhythmic therapy at 12 months.

Three of the trials in the analysis reported on hospitalisations. The total number of hospitalisations was significantly lower in the catheter ablation groups with only 14 hospitalisations per 100 person years in the catheter ablations groups compared with 93 in the ADT group. In four of the trials that reported on repeat catheter ablation, a total of 17% of the patients randomised to the catheter ablation arm underwent another catheter ablation. In the trials where cross-over was allowed, a total of 51% of patients in the drug therapy arm underwent catheter ablation. While the authors were interested in the left atrial diameter as well as left ventricular ejection fraction, they concluded that, due to the significant differences in how these were reported in the studies, it would not have been possible to obtain an unbiased summary on these measures and, as such, they were not reported on in this meta-analysis.

The rate of serious complications is often cited as a reason why catheter ablation should not be considered as a first-line option. However, Piccini *et al.* (2009) found that the major complication rate for catheter ablation was only 2.6%. These complications included the following:

- Cardiac tamponade, n=2 (<0.6%)
- Symptomatic pulmonary vein stenosis, n=1 (<0.3%)
- Pericardial effusion, n=2 (<0.6%)
- Phrenic nerve paralysis, n=1 (<0.3%)
- Thromboembolic events, n=3 (<0.9%)
- Total n=9 (2.6%)

Of those patients who were randomized to ADT, the reported adverse event rate was 8% (n=29). This is lower than that reported in other studies like Noheria *et al.* (2008) who reported adverse events at 17%. The following adverse events were reported by Piccini *et al.* (2009):

- Cases of pro-arrhythmia with Flecainide, n=3 (<0.9%)
- Cases of thyroid dysfunction secondary to Amiodarone, n=9 (2.6%)
- Cases of sexual impairment caused by Sotalol, n=11 (3.18%)
- Gastroenterological adverse event, n=1 (<0.3%)
- Corneal micro deposits, n=2 (<0.6%)
- Abnormal liver function tests, n=2 (<0.6%)
- Case of sinus node dysfunction caused by Amiodarone. n=1 (<0.3%)
- Total n=29 (8%)

Similar to the Noheria meta-analysis, Piccini *et al.* (2009) evaluated the impact of potential publication bias and, as in the Noheria meta-analysis, they found that the funnel plot demonstrated

no publication bias among the five studies which were included in the determination of treatment effect. The three main findings in this meta-analysis were as follows:

- Catheter ablation had more than a twofold greater efficacy at 12 months for maintaining sinus rhythm than did ADT and was measured across the studies at 75%.

- Patients treated with catheter ablation had two-thirds reduction in hospitalisation for cardio-vascular causes.

- Catheter ablation had a procedural complication rate less than major complication rates associated with high risk percutaneous coronary interventions at 2.6%.

The authors concluded that, when catheter ablation was compared with an ADT strategy, the catheter ablation results showed a significantly increased freedom from AF at one year and that catheter ablation appeared to be associated with significantly decreased hospitalisations for cardiovascular causes. Although the procedure is associated with major complications, including stroke, cardiac perforation, and pulmonary vein stenosis, these events appear to be rare. Finally, the authors stated that the current American College of Cardiology/American Heart Association/Heart Rhythm Society guidelines recommend catheter ablation as a class IIa indication as an alternative to pharmacological treatment to prevent recurrent AF in those with symptoms and little to no left atrial enlargement. It can be argued that catheter ablation should be elevated to a class I recommendation for the prevention of recurrent AF.

6.5 COST-EFFECTIVENESS ANALYSIS OF CATHETER ABLATION

Research by Stewart *et al.* (2004) showed that the cost of treating AF in the UK rose by 49% in the five years between 1995 and 2000. This was due to the increase in prevalence of AF and the resultant increase in hospitalisations. A number of studies have indicated that catheter ablation is more effective at preventing the recurrence of AF at one year than ADTs. ADTs are also associated with more hospitalisations and significantly more, but often less severe, side effects (Piccini *et al.,* 2009; Noheria *et al.,* 2008). When evaluating the costs associated with treating patients with AF, both the costs associated with catheter ablation and the cost of treating patients with medication must be considered (Martin-Doyle & Reynolds, 2010: 727). AF is also associated with a negative quality of life and Reynolds *et al.* (2008) reported that several studies showed that achieving and maintaining sinus rhythm resulted in improved quality of life scores. Based on a number of studies with AF cohorts, the baseline utility value has been reported as 0.725 for patients in AF and the change in utility associated with achieving and maintaining sinus rhythm was 0.065 (Martin-Doyle *et al*., 2010).

6.5.1 Costs associated with ADT

The FRACTUAL study revealed that almost half of all costs associated with treating AF with ADTs were related to hospitalisation. In some instances, the cost of using a rhythm control strategy is associated with higher costs than a rate control strategy as, in some countries, patients are admitted to hospital when drug dosing needs to be changed. These are not the only reasons for hospitalisation of AF patients, as many patients may be admitted in order to undergo cardioversion or require hospitalisation for heart failure or stroke. Piccini *et al.* (2009) state that in patients treated with catheter ablation for AF, the cost of hospitalisation decreased by two-thirds when compared to the patients treated with ADT alone. Other costs associated with treating patients with ADTs include the costs associated with INRs if patients are required to take anti-coagulants. This may, however, affect both the catheter ablation group and the ADT group.

6.5.2 Costs associated with catheter ablation

A literature review found several studies that have investigated both cost and cost-effectiveness of catheter ablation *vs*. ADT.

1. The first study was published in *Pacing Clinical Electrophysiology* in 2003. The authors were Weerasooriya *et al.* (2003). The study was titled 'Cost Analysis of catheter ablation for paroxysmal atrial fibrillation'. This was a single-centre study in Bordeaux, France, comprising 188 consecutive patients who underwent catheter ablation. The patients had, on average, 1.52 ablations, but ranged from one to four procedures. Their findings were based on the fact that 72% of the patients were free from AF at the end of the study. Their findings, calculated at 2001 Euros were as follows: The authors estimated that over a five-year period, the total cost of the ablation strategy was €6 730 compared with a five-year cost of ADT of €7 194. They concluded that the upfront costs of ablation were significantly more than those of ADT, but that the patients on ADT had higher annual costs. They stated that, after five years, the costs continued to diverge, implying that catheter ablation was not only better from an efficacy point of view, but also from a cost point of view at five years. Of note was that in 2011 this group published a study which evaluated the same group of patients. This cohort of patients required an average of 1.75 catheter ablations to remain free of AF recurrence at five years. With the additional ablation, the number of patients who were free of AF recurrence was 87%, 81%, and 63% at one, two, and five years, with major complications occurring in less than 3% of patients (Weerasooriya *et al.*, 2003).

2. The second study was published in the *Journal of the American College of Cardiology* in 2006. The authors were Chan *et al.* (2006). The study was titled 'Cost-Effectiveness of Radiofrequency Catheter Ablation for Atrial Fibrillation'. The study used a Markov model to

assess the cost-effectiveness of catheter ablation with rate control or Amiodarone. The authors looked at hypothetical cohorts with AF at low or moderate risk of stroke and evaluated short and long-term outcomes like stroke, haemorrhage procedural complications and drug toxicity. The authors state that their model was conservative and biased against catheter ablation (Chan *et al.*, 2006: 2516). The costs were measured in 2004 US$ and the authors reported that the lifetime costs for patients undergoing ablation ranged from between $43 036 to $59 380 for ablation compared with $24 540 to $50 509 for rate control and $38 425 to $55 795 for rhythm control. The authors concluded that catheter ablation was unlikely to be cost-effective in patients with a low risk of stroke but that, in patients with a moderate risk of developing stroke, catheter ablation may be cost-effective if the efficacy rate of catheter ablation is sufficiently high.

3. The third study was published in the *Journal of Cardiovascular Electrophysiology* in 2007. The authors were Khaykin *et al.* (2007). The title of the study was 'Cost Comparison of Catheter Ablation and Medical Therapy in Atrial Fibrillation'. The authors evaluated the costs relating to medical therapy, which included rate and rhythm control medications, physician follow-up visits, hospital admissions, the cost of anti-coagulation, all non-invasive testing, and any cost of complications related to this management strategy. On the other hand, costs related to catheter ablation included the cost associated with the ablation procedure (electro-anatomic mapping or intra-cardiac echocardiography-guided pulmonary vein ablation), all the physician costs and hospital costs and, finally, costs related to peri-procedural medical care and complications. To model the efficacy, they did a sensitivity analysis, looking at a range of initial success rates (50-75%), late attrition rates (1-5%), and the prevalence of congestive heart failure (CHF) (20-60%). The discounting was performed at between 3% and 5% per year. Costs were calculated in Canadian dollars. The results of this study showed that the cost of catheter ablation ranged from $16 278 to $21 294, with an annual cost of $1 597 to $2 132, while the annual cost of medical therapy ranged from between $4 176 to $5 060. When estimating the on-going costs of ADT vs. catheter ablation for PAF, the costs equalised at between 3.2-8.4 years of follow-up. The authors concluded that catheter ablation was a "fiscally sensible" alternative to ADT for patients in PAF with costs converging at four years.

4. The fourth study was published in *Heart (BMJ)* in 2009. The authors were McKenna *et al.* (2009). The title of the study was 'Cost-effectiveness of radiofrequency catheter ablation for the treatment of atrial fibrillation in the United Kingdom'. The authors used a probabilistic decision analytical model to evaluate the short-term and long-term costs of treating AF patients with either drugs or catheter ablation. The outcome of the study was freedom from arrhythmia at 12-months and the outcomes were expressed in terms of QALYs. They used the CHADS2 index as the baseline risk for stroke. The study staged their results in two formats. The first was a mean lifetime cost and QALYs for both catheter ablation and ADT comparing cost-

effectiveness by means of incremental cost-effectiveness ratios (ICER). The second reported on the probability that each strategy would be considered the more cost-effective option for a given cost-effectiveness threshold. McKenna *et al.* (2009) found that, when evaluating the lifetime analysis for cost-effectiveness, the ICER for catheter ablation vs. AADs was between £7 763 and £7 910 for each additional QALY across the CHADS2 scores. They also reported that the probability that catheter ablation was cost-effective at both thresholds, £20 000 and £30 000, per QALY was between 0.981 to 0.992 and 0.996 to 1.00. The authors reported on the ICER at the point of the five-year follow-up: When comparing catheter ablation and ADT, the ICER was £20 831 and £27 745 per QALY gained, respectively. At these values, the probability of being cost-effective at the commonly used thresholds in the UK of £20 000 and £30 000 was lower, at 0.091 to 0.418 and 0.577 to 0.881 respectively.

5. The fifth study to be evaluated for cost analysis was published in *Health Technology Assessment* in 2008. The authors, Rodgers *et al.* (2008), had previously published a cost-effectiveness analysis on the subject for submission to NICE. This study was titled 'Curative catheter ablation in atrial fibrillation and typical atrial flutter: systematic review and economic evaluation'. The aim of the study was to determine clinical effectiveness, safety and finally cost-effectiveness of treating patients with AF and flutter with catheter ablation or ADT. The primary outcome was the number of patients who were free of arrhythmia at 12month follow-up. The authors completed a systematic review on relevant literature which suggested that catheter ablation was effective at reaching the primary endpoint of being free of arrhythmia at 12 months in between 28% and 85.3% (mean 76%) of patients with AF. It was also found to be effective in between 85% and 92% (mean 88%) of patients with atrial flutter. They reported findings that were robust over a range of assumptions and resulted in between £7 763 and £7 910 per additional QALY. The authors made the assumption that, if the benefits of catheter ablation were not maintained for more than five years, then the cost-effectiveness in favour of catheter ablation would be dependent on the following factors:

    - The prognostic benefit of being in sinus rhythm
    - The magnitude of differences in quality of life between catheter ablation and ADTs
    - The long-term reduction of risk factors.

   Rodgers *et al.* (2008) reported that catheter ablation was a safe and efficacious procedure for the management of AF and typical atrial flutter and cost-effectiveness ranged from £23 000 and £38 000 when factors a-c above were explored.

6. The next study to be investigated was published in the *Journal of Cardiovascular Electrophysiology* in January 2009. The title was 'Cost comparison of ablation versus antiarrhythmic drugs as first-line therapy for atrial fibrillation: An economic evaluation of the RAAFT pilot

study'. The authors, Khaykin *et al.* (2009), evaluated the data from the Pilot RAAFT study and evaluated the costs related to medical therapy which included, among others, the cost of drugs, costs associated with anti-coagulation, physician follow-up visits, non-invasive testing, hospital admissions, and the costs which were related to managing any complications. Ablation-related costs included costs associated with equipment and disposables used, hospital and physician costs, as well the cost of managing any peri-procedural complications. Costs were based on the Canadian Registry of Atrial Fibrillation (CARAF), government fee schedules, and published data. Included in the analysis was a range of success rates between 50 and 75%, late attrition rates of between 1% and 5% and the prevalence of congestive heart failure (20-60%). A simple decision tree was used and, although the RAAFT pilot study only had data just beyond one year, the authors modelled the data to two years. The upfront costs of ablation were four times higher than ADT and, at two months, the cost of ablation was $10 465 compared with $2 556 for the ADT arm. At one year, the costs in the ablation arm were still significantly higher, at $12 823 compared to ADT costs of $6 053. By the end of the second year, the costs had converged and the costs in the catheter ablation arm were $15 303 vs. $14 392 for the ADT arm. The authors concluded that, in patients with symptomatic AF, the costs were cost neutral at two years.

7. Martin-Doyle and Reynolds (2010) concluded, in the *Journal for Atrial Fibrillation* in 2010, 'after evaluating a number of studies discussed above that catheter ablation is somewhat cost-effective in the short term vs. ADT.'

8. Finally, Khaykin and Shamiss (2011) reported that 70 to 80% of all AF patients are admitted to hospital at some stage of their disease. They stated that catheter ablation appeared most cost-effective in the younger patients, who were at moderate risk of stroke ($28 000/QALY gained). Catheter ablation was still cost-effective, although less so, in older patients at moderate risk of stroke ($51 800/QALY gained). It was least cost-effective in young patients with a low risk of stroke ($98 900/QALY gained) (Khaykin & Shamiss, 2011: 3).

6.6 QUALITY OF LIFE AND ATRIAL FIBRILLATION

When investigating mortality, morbidity and quality of life related to AF, the following was discovered. Pappone *et al.* (2003) examined 1 171 consecutive patients from all over Italy, who all had symptomatic AF. Circumferential pulmonary vein ablation (PVI) was performed on 589, while 582 patients were treated with ADT. Of the ADT group, 33% were treated with Amiodarone, 15% with Flecainide, 13% Sotalol, 9% Quinidine, 6% Disopyramide and 7% were on more than one ADT. Table 6.10 demonstrates the baseline characteristics of patients in both groups. Recurrence of atrial fibrillation was defined as a symptomatic episode lasting more than ten minutes and confirmed by ECG.

Table 6.10: Baselines characteristics of patients receiving PVI or ADT

Characteristic	Ablation group (n=589)	ADT group (n=582)	p value
Age	65 ±9	65 ±10	0.99
Gender (male)	58	59	0.95
Follow-up days	861 (161-1491)	911 (179-1508)	0.22
Duration of AF (years)	5.5 ± 2.8	3.6 ±1.9	<0.001
% patients with PAF	69	71	0.45
No of trials on ADT	3.1 ±2.1	2.3 ±1.5	<0.001
% patients with no cardiac disease	34	35	0.72
% patients with hypertension	46	43	0.29
% patients with diabetes	11	10	0.60
Patients with prior stroke of TIA	16	15	0.12
LVEF on Echo	54 ±12	55 ±14	0.22
LA diameter (long-axis view) (mm)	46 ±9	45 ±8	0.06

Source: Pappone et al., 2003: 188.

In this study, the overall median follow-up was 900 days with 19 (2%) of patients lost to follow-up. The mortality results are tabulated in Table 6.11. At the end of the follow-up period, 6% of the patients in the ablation group had died, compared with 14% in the group treated with ADT. There was a 69% reduction in cardiovascular deaths in the catheter ablation group compared to the ADT group. There were no deaths due to sudden cardiac death in the catheter ablation group, compared with 2.1% of deaths in the ADT group. It is important to note that of the 77 patients who died from cardiovascular deaths, 75% were in AF at the time and that 74% of the deaths from heart failure and 61% from myocardial infarction were in patients who were in AF at the time.

Table 6.11: Adverse events in the catheter ablation and ADT group, measured per 100 of the population

Adverse event	Ablation group (n=589)	ADT group (n=582)	ADT group/ ablation group
CHF	5.43	9.79	1.80
AMI	1.19	1.37	1.15
Peripheral embolism	0.17	0.52	3.06
TIA	1.36	4.64	3.41
Ischaemic stroke	0.68	2.58	3.79
Haemorrhagic stroke	0.34	1.2	3.53
Total	9.17	20.1	2.19
No of patients with events	46	98	144

Source: Adapted from Pappone et al., 2003: 189.

Figures 6.6 and 6.7 illustrate the cause of deaths by percentage in the catheter ablation and ADT groups. In the catheter ablation group, 46 (8%) had adverse events compared with 98 (19%) in the ADT group.

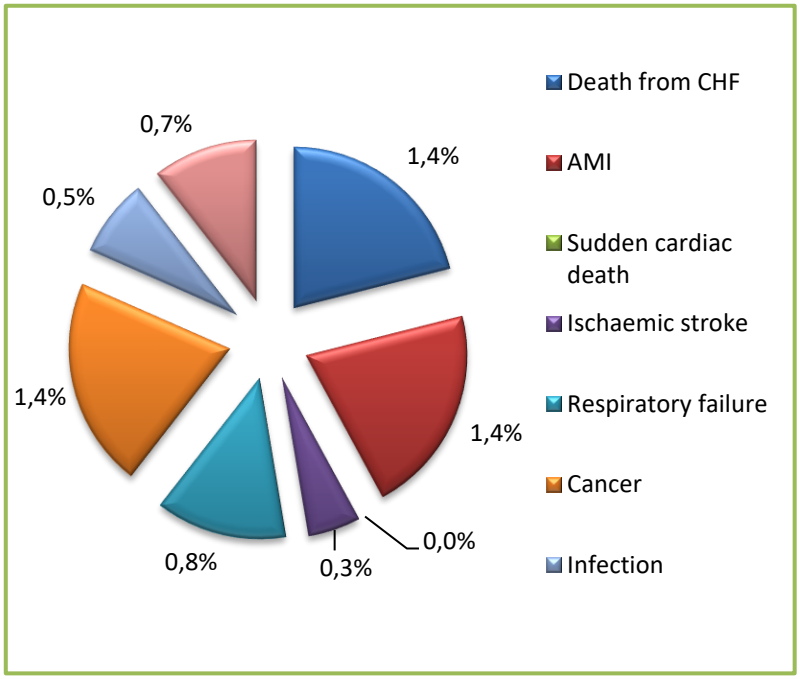


Figure 6.6: Cause of death in the catheter ablation group

Source: Pappone et al., 2003: 189.

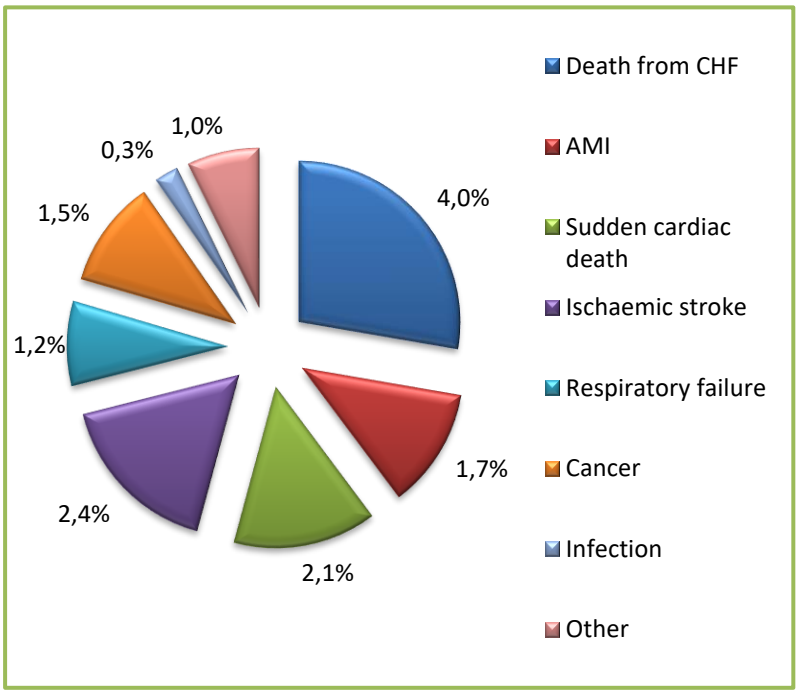


Figure 6.7: Cause of death events in the ADT group

Source: Pappone et al., 2003: 189.

Table 6.12 demonstrates the side effects in both the catheter ablation and ADT groups.

Table 6.12: SF-36 quality of life scores across AF and five control groups

	Patient Groups					
SF-36 Scale	**AF (n=152)**	**PTCA* (n=69)**	**PTCA** (n=78)**	**CHF (n=216)**	**Post MI (n=69)**	**Healthy (n=47)**
General health	54±21	51±23	65±22	47±24	59±19	78±17
Physical function	68±27	60±29	76±25	48±31	70±26	88±19
Role physical	47±42	47±45	71±39	34±40	51±39	89±28
Vitality	47±21	48±26	60±20	44±24	58±19	71±14
Mental health	68±18	74±18	75±16	75±21	76±16	81±11
Role emotional	65±41	64±44	83±35	64±43	73±38	92±25
Social functioning	71±28	74±29	87±21	71±33	85±21	92±14
Bodily pain	69±19	68±17	73±31	63±31	73±25	77±15

*Notes: *Patients 6 months after PTCA from St Michael's Hospital Toronto*
***Patients after PTCA*

Source: Krumholtz et al., 1997.

The total number of serious adverse events per 100 of the population in the ADT group was more than double that of the catheter ablation group. Congestive heart failure contributed to the greatest number of adverse events in both the catheter ablation group and the ADT group. However, there was almost a twofold increase in the number of adverse events from CHF in the drug group compared to the ablation group. TIA, haemorrhagic stroke and ischaemic stroke in the ADT group was almost a fourfold increase from that of the catheter ablation group.

Finally, Pappone *et al.* (2003) stated that circumferential ablation improved not only the mortality and morbidity of patients with AF, but that there was an associated improvement in quality of life, as illustrated by Figures 6.8 and 6.9.

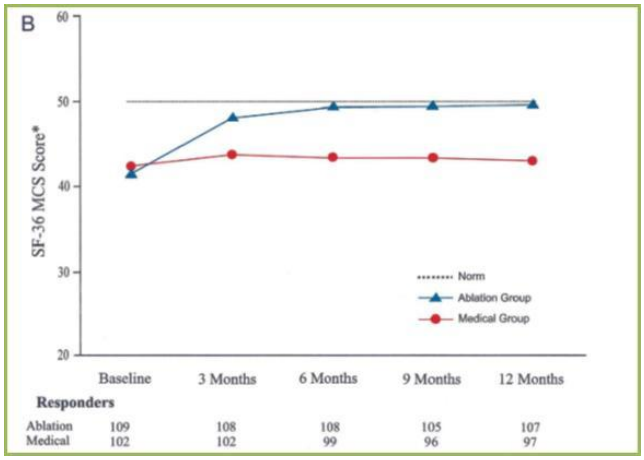


Figure 6.8: Computation aggregates scores for physical component of the SF-36 questionnaire

Source: Pappone et al., 2003: 195.

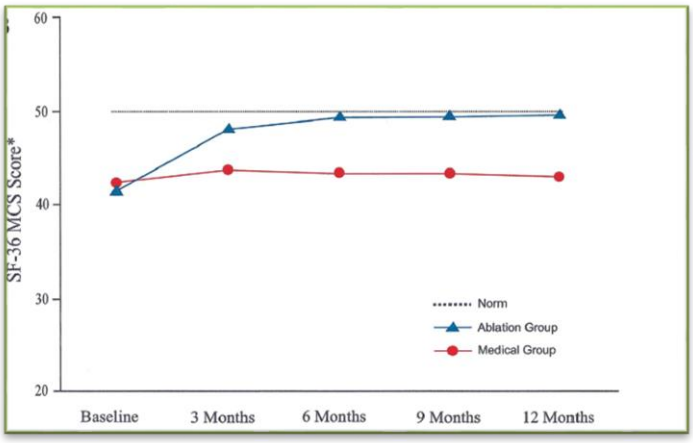


Figure 6.9: Computation aggregates scores for mental component of the SF-36 questionnaire

Source: Pappone et al., 2003: 195.

Dorian *et al.* (2000) investigated the impact that paroxysmal atrial fibrillation had on health-related quality of life. They assessed 194 patients with PAF from outpatient units in four centres where the patients were requested to complete the Medical Outcomes Study Short Form 36 (SF-36), Specific Activity symptoms checklist, Illness intrusiveness and University of Toronto AF severity scales. Five control groups were used. The first group (n=47) were healthy individuals. The other four control groups were comprised of cardiac patients: published data (n=78), a PTCA group (n=69), published heart failure group (n=216) and, finally, a published post myocardial infarction group (n=107).

The patients in the AF group were eligible to enter the study if they were over the age of 18, could read English or German, had no cognitive or sensory limitations and had at least one documented episode of paroxysmal AF. Patients with permanent AF with a continuous duration of more than six months were excluded. Patients where AF was secondary to other causes, e.g. post-op cardiac surgery or hyperthyroidism, were also excluded. Of the 194 consecutive patients with AF who were referred to the four participating centres, 175 met the inclusion criteria and 152 completed all the required forms. The average age of the AF group was 58 (±12 years), and 73% were male. AF was paroxysmal in 60.5% of patients and the other 39.5% of patients had persistent AF. In the entire AF group, 99% were considered NYHA class I or II with respect to exercise capacity at a time when the patients perceived themselves to be in sinus rhythm. This was similar to the NYHA status of the post-PTCA control group. Only a small number of patients had other cardiac arrhythmias- Wolff-Parkinson-White syndrome in 2%, atrioventricular (AV) nodal re-entrant tachycardia in 2%, and other supraventricular tachycardias in 5% and atrial flutter in 16%. A total of 5% had coronary artery disease (CAD) which required prior PTCA, 4% had coronary artery bypass surgery and 4% had heart valve replacement surgery. The mean left ventricular ejection fraction, when available, was 61 (±16%) and the mean LA diameter was 42mm (±6mm). At the time of assessment, 76% of patients were on anti-coagulants, 61% were receiving some antiarrhythmic therapy, and 42% were taking AV nodal blocking drugs. Of all the AF

patients, 51% had undergone at least one cardioversion with a mean number of 1.2 (±1.4). More than half of all patients (51%) had been hospitalised for their AF at least once in the previous year, while 44.6% had visited an emergency room at least once in the previous year. Almost 90% of patients had seen a specialist on at least one occasion, with a median of three visits per year for each patient, and 33% had had five or more visits to a specialist in the previous year.

The outcome measurements incorporated the following: patient demographics, including age, gender, and clinical history, such left ventricular function, anti-arrhythmic medications, history of hypertension, history of heart failure, echocardiographic left atrial diameter and New York Heart Association classification (NYHA). Patients were given questionnaires to evaluate QoL and symptom burden in the arrhythmia clinic and were requested to mail them back within a two-week period in postage-paid envelopes.

The results indicated that, during AF (perceived or documented), the exercise function in the AF group was poorer, with only 38% in NYHA class I. Most patients (90%) had some symptoms during AF, including palpitations (68%), fatigue (62%) and shortness of breath (60%).

The healthy control group was comprised of 47 healthy subjects with a mean age of 54 (±14 years) and 55% were female. There were significantly more men in the AF group compared with the group of healthy subjects (p=0.0025), and the patients in the AF group were also significantly older than the healthy control group (p=0.0329). There was no record of ventricular function in this group, but their exercise tolerance, as measured by the SAS, was excellent (92 ±6 14, range 58 to 100). In the cardiac control group of patients, all who had coronary artery disease with prior angioplasty were significantly older and had worse left ventricular function than patients with AF (p=0.001 and p=0.004 respectively).

The authors found that, when comparing the AF patients with the healthy group among all scales, both for the disease specific as well as generic QoL, the patients with AF were significantly worse than those in the control groups (Table 6.12). The extent of these differences was, in almost all cases, close to a full standard deviation.

When comparing the AF patients with patients from the cardiac control groups for all spheres of the SF-36, the patients in the AF group were either worse than those in the published group or the same as study-created PTCA patients. This was in spite of the fact that the patients in the created PTCA group were older, had worse left ventricular function and required a major procedural intervention.

When compared to the patients in the congestive heart failure group, the physical functioning scores were all worse than in the AF group. The only exception was vitality, which was as impaired in the AF group as in patients with heart failure (47 ±21 *vs*. 44 ±24, p=NS). In contrast, the psychological and social domains were either significantly better (mental health 68 ±18 *vs*. 75 ±21, p<0.01) or the same (role emotional, social) as in congestive heart failure patients when compared with the AF group. In

the same vein, AF patients, despite being younger and having better LVEF, were either significantly more impaired in general health, vitality, mental health, and social function or equivalently impaired with regard to physical function, role physical, role emotional and bodily pain, as the post myocardial function patients.

Finally, the atrial fibrillation patients were the same as the PTCA group with regard to illness intrusiveness and the Specific Activity Scale, but they compared significantly worse than the PTCA group on global life satisfaction (62 ±20 *vs*. 68 ±18. $p<0.05$). Compared to the PTCA group, the AF group was significantly worse on the measures of symptom frequency and severity (22 ±10 *vs*. 16 ±10 and 19 ±8 *vs*. 13 ±9, both $p<0.01$).

The authors concluded that quality of life in patients with paroxysmal AF was significantly more impaired in relation to healthy patients and equal to patients with significant cardiac disease.

There are at least 34 different QoL instruments that have been used in published AF studies. Reynolds *et al.* (2008) believe that this reflects a lack of consensus on a single optimal approach. The most consistently used generic QoL scales in AF studies include, among others, the Medical Outcomes Study Short Form Health Survey (SF-36), the Short Form-12 (SF-12), which is derived from the SF-36, and the EuroQOL/EQ-5D. The SF-36 is a 36-item questionnaire aimed at assessing eight health domains, namely, general health perception, physical functioning, social functioning, role limitations due to physical problems, bodily pain, mental health, role limitations due to emotional problems, and vitality. There are also an additional eight subscales in the SF-36 scale which generate physical (PCS) and mental component summary (MCS) scores. The SF-36 scale has been used successfully in a number of prior AF studies where the greatest changes are typically seen in the scales relating to physical function. The biggest limitation of such generic measures is that, by design, they reflect general health and functioning and, therefore, scores among AF patients are strongly influenced by patient demographics and co-morbid conditions. Cardiac-specific questionnaires have been used in a few studies, but typically these have not been designed for patients with AF. Of these, the most commonly used is the Arrhythmia Symptom Checklist: Frequency and Severity. Developed in the late 1980s, it was used to evaluate the impact of early catheter ablation and pacing technologies on a variety of arrhythmias. This checklist asks respondents to rate the frequency (from 0 to 4) and severity (from 1 to 3) of sixteen symptoms commonly associated with AF. Frequency and severity scores therefore range from 0 to 64 and 0 to 48, respectively.

The authors suggest that, as AF is often entirely asymptomatic, the impact of AF on QoL may be strongly influenced by the segment of the AF population that is studied. The converse of this may also be true, in that some patients with AF are severely symptomatic and thus, evaluating only their QoL scores may reflect scores that do not represent the asymptomatic patients. While this may hold true, it must not be forgotten that when evaluating treatment options for patients with AF, the aim is to establish and maintain sinus rhythm in these patients and, as purported in recent studies, the

maintenance of sinus rhythm is associated with lower mortality and stroke. Therefore, even if a patient is asymptomatic with AF, their risk of stroke or death is not necessarily decreased but may, in fact, be increased as they may go undiagnosed and not be anti-coagulated (Reynolds *et al.,* 2008: 765). It should therefore be remembered that QoL is only one concern with these patients and that prevention of complications such as stroke is vital.

The FRACTUAL registry, which looked at healthcare resource utilisation and costs associated with recurrent episodes of AF, included in their analysis a SF-12 derived physical component summary scales (PCS) and mental component summary scales below age-adjusted population norms, and the AF symptom checklist. The result from the FRACTUAL registry indicated that the results were not as poor as in typical clinical trials as, with treatment, the QoL scores improved to approximate population norms within three to six months, and generally remained stable thereafter. Some of the factors that influence the QoL in patients with AF are the fact that many studies have traditionally relied on these “generic” instruments and it may be expected that results may be influenced by age and co-morbid medical conditions.

This was noted in the FRACTAL, where NYHA class, valvular heart disease, and chronic pulmonary disease had the biggest impact on QoL scores. Other factors existent at baseline, such as the presence of coronary artery disease and diabetes, revealed a worsened QoL over time in the RACE trial. Table 6.13 is a summary of some of the studies in AF which have used QoL in the study.

In conclusion, of the thirteen studies reviewed and summarised in Table 6.13 no less than 12 (92%) used the SF-36 scale, five (38%) used the symptoms checklist and two (15%) used the University of Toronto severity scale. The biggest improvement in QoL scores seem to be among the ablation group, where 100% of the studies cited a statistically significant improvement in QoL in the catheter ablation group. When compared to the studies looking at either rate or rhythm control with ADT, almost all reported modest to no improvement in QoL.

Table 6.13: Selected quality of life studies in atrial fibrillation

Trial name	Population	Study design	Measure of QoL	Results
Anti-arrhythmic drugs				
CTAF	264 patients with recent paroxysmal or persistent AF without prior AAD exposure	Randomized (2:1:1) to Amiodarone, Sotalol, or propafenone	SF-36, Symptom Checklist, Duke Activity Status Index, University of Toronto AF Severity Scale	Modest improvements in SF-36 PCS and MCS scores and ~20% reduction in Symptom Checklist scores. No differences between groups, despite less AF in Amiodarone group
SAFE-T	665 patients (99% men) with persistent AF	Randomized to Amiodarone, Sotalol, or placebo. Those in AF after 4 weeks were electrically cardioverted	SF-36, Symptom Checklist, Specific Activity Scale, University of Toronto AF Severity Scale	By intention to treat, no differences between groups at 1 year except for decreased mental health score in Amiodarone group
Rate *vs*. rhythm control studies				
PIAF	252 patients with AF between 7- and 360-days duration	Randomized to rhythm control (Amiodarone ±cardioversion) *vs*. rate Control. QoL data obtained at baseline and 12 months	SF-36	4/8 subscales improved in rhythm control versus 6/8 in rate control. No significant differences observed between groups
STAF	AF for >4 weeks, excluding those with low and very high risk of recurrence (n=200)	Randomized to rhythm control (cardioversion + AAD) *vs*. rate control (drugs). QoL data obtained at baseline and 12 months	SF-36	At 12 months, 2/8 subscales improved in rhythm control group *vs*. 5/8 in rate control group. No overall between group differences
RACE	352 patients with persistent AF included in the RACE study	Randomized to rate (drugs) or rhythm control (Cardioversion, AADs). QoL data collected at baseline, 1 year, and 24–36 months	SF-36	QoL similar between groups at study end. Rate control group had improvement in 3 subscales versus 0 subscales in rhythm control group
AFFIRM	25% of AFFIRM sites participated in QoL sub-study (n =716)	Patients randomly assigned to rate or rhythm control group. QoL data collected at baseline, 2 months, 12 months, and annually for 4 years	SF-36 Perceived health, Ladder of life, QoL index, Symptom Checklist	Quality of life scores improved modestly and to a similar degree in rate and rhythm control groups

Table 6.13: Selected quality of life studies in atrial fibrillation (continued)

Trial name	Population	Study design	Measure of QoL	Results
Catheter ablation- Non-randomized series				
Erdogan *et al.*	30 patients with paroxysmal AF refractory to multiple AADs	Linear RF ablation in the right atrium only ("catheter Maze"). QoL data obtained pre- and 3, 6, 9, 12, 24, 36 months post ablation	SF-36, symptom specific checklist (locally derived)	Patients without AF recurrence (9/30) had statistically significant improvements in all eight SF-36. Subscales over 2 years. Patients with AF recurrence had little change
Pappone *et al.*	589 ablation patients with drug refractory AF (70% paroxysmal), compared with 582 patients who declined ablation	109 ablated and 102 medically treated patients did QoL surveys every 3 months for 1 year. Patients were treated with circumferential isolation of all PVs using RF	SF-36	PCS and MCS scores significantly rose from ~40 to ~50 within 6 months after ablation, but did not change in reference cohort treated with drugs
Hsu. *et al.*	58 patients with CHF, LVEF <45% and AF (>90% persistent or permanent)	Cohort matched (by age, sex, AF type) to additional 58 patients without CHF. RF ablation: PVI, usually with linear in ablation in LA roof and/or mitral isthmus	SF-36, Symptom Checklist	Significant improvements in Symptom Checklist and SF-36 scores reported for both groups after ablation. PCS/ MCS increased 24/21 points in CHF group, 18/14 points in control group
Chen *et al.*	377 consecutive patients with Symp-tomatic AF refractory to AADs. Study performed on 94 patients with LVEF <40%	Ostial PVI performed with closed internally irrigated RF catheter; 10% also underwent cavo-tricuspid isthmus ablation	SF-36	Significant improvement in on all SF-36 subscales 6 months following PVI irrespective of LV function. Scores more than doubled on most scales
Weerasooriya *et al.*	63 consecutive patients with symptomatic paroxysmal AF refractory to ≥2 AADs	PVI plus linear ablation in mitral isthmus and cavo-tricuspid isthmus using externally irrigated RF catheter. QoL data collected at baseline, 3 and 12 months	SF-36, Symptom Checklist	Significant improvement in 8/8 SF-36 subscales and symptom checklist scores at 3- and 12-months post ablation. Largest changes in role physical (36 points) and bodily pain (31 points) scales
Wazni *et al.*	70 patients with at least monthly symptomatic PAF for at least 3 months and no prior treatment with AADs	Patients randomized to mitral PVI using RF (8 mm tipped catheter) or AAD (Flecainide or Sotalol). QoL data obtained at enrolment and 6 months	SF-36	Improvement in QoL significantly greater (by 6-20 points) in PVI group than AAD group in 5/8 subscales of the SF-36

Table 6.13: Selected quality of life studies in atrial fibrillation (continued)

Trial name	Population	Study design	Measure of QoL	Results
Catheter ablation- Randomised study				
Oral *et al.*	146 patients with chronic" AF	Randomly assigned to 1-2 cardioversion over 3 months or ablation (circum-ferential PVI + linear ablation in LA roof and mitral isthmus with 8 mm RF ca-theter). Both groups received Amiodarone for 3 months	Symptom Severity Questionnaire (locally derived, 5 symptoms)	12 months after ablation, symptom scores fell from17±4 to 6±2 in patients without AF recurrence and from 17±4 to 12 ±4 in patients with AF recurrence. Recurrence less common with ablation. High rate of cross-over to ablation

Notes: AAD = antiarrhythmic drug; PCS = physical component summary score; MCS = mental component summary score. PV = pulmonary vein; PVI = pulmonary vein isolation; CHF = congestive heart failure.

Source: Reynolds et al., 2008: 762-768.

6.7 DATA USED TO UNDERPIN TOTAL HEALTHCARE EXPENDITURE (THE)

Large randomized trials with people in AF who are at risk of stroke have not demonstrated any significant mortality benefit when using rhythm control as opposed to rate control strategies for managing AF. Neither of these drug strategies is efficacious at maintaining sinus rhythm beyond one year. This may be of particular relevance, as post-hoc analyses have indicated that, regardless of the method of treatment, patients who achieved and remained in sinus rhythm suffered fewer strokes and had better mortality than those patients who were in AF (Chan *et al.,* 2006: 2513).

Survival is improved in patients who achieve sinus rhythm and the modest efficacy of AAD in achieving sinus rhythm is well documented. Radiofrequency ablation for substrate modification or electrical isolation of the pulmonary veins (circumferential pulmonary vein ablation) is still a relatively new therapy but offers an alternative approach to achieving sinus rhythm. Final outcomes, such as being free of AF recurrence at one, two years and quality adjusted life years (QALYs) are useful when assessing cost-effectiveness as they provide a standard unit of measure which can be compared across a range of therapeutic areas.

The modelled economic evaluation employed a decision tree and Markov model process to compare the costs and healthcare outcomes of radiofrequency catheter ablation (PVI). The model was based on the outcomes reported in the APAF trial by Pappone *et al.* (2006), a single centre, and randomized trial.

After an extensive literature review, this study was chosen as the model for the following reasons:

- The trial was published in a peer-reviewed journal (*Journal of American College of Cardiology,* 2006).
- Of the three systematic reviews and meta-analysis written, comparing PVI to ADT, the first included only studies up to Jan 2007 but did not include this study published in Dec 2006, while the other two both included this study in their meta-analysis (Calkins *et al.,* 2009: Noheria *et al.,* 2008: Piccini *et al.,* 2009).
- Finally, on reviewing the content of each study, the Pappone trial allowed tracking of each individual patient with relative ease.

6.7.1 The APAF study

This study by Pappone *et al.* (2006) was designed to compare the efficacy of RFA and ADT for the treatment of patients with PAF. All the patients had already failed AADs. In the ADT arm, the patients were randomized to receive one of three commonly used AADs. In the other arm, consecutive patients with PAF, who were referred to the electrophysiology lab at the San Raffaele University Hospital starting from January 2005, were screened for the inclusion and exclusion criteria shown in Table 6.14.

Table 6.14: Inclusion and exclusion criteria

Exclusion criteria	Inclusion criteria
Intra-atrial thrombus, tumour	18 < Age < 70
LA diameter >65mm	Creatinine concentrations <1.5md/dl
Rheumatic mitral valve disease	AF history > 6 months
Prior treatment with Amiodarone, Flecainide or Sotalol	AF burden > 2 episodes/month in last 6 months
CHF symptoms > NHYA functional class II	
LVEF <35%	
Contra-indication to beta-blocking agents	
AF secondary to transient or correctable abnormality	
Unstable angina or AMI in < 6months	
WPW syndrome	
Renal or hepatic failure	
Implanted device either pacemaker or ICD	
Need to ADT for arrhythmia other than AF	
Contra-indication to ADT or Warfarin	
History of CVA	
Prior catheter ablation or surgical ablation for AF	

Source: Pappone et al., 2006: 2341.

6.7.2 The study design

The patients were randomized to either the PVI arm or to the ADT arm. Patients randomized to the ADT arm were again randomized to receive one of the following three drugs: Amiodarone (n=33), Sotalol (n=33) or Flecainide (n=33). The drugs were administered as a single dose, or in combination, and at the maximum tolerable dose. Table 6.15 charts the characteristics of the patients in each group.

Table 6.15: Patient characteristics

Characteristic	PVI (n=99)	ADT (n=99)	*p*-value
Age (years)	55±10	57±10	0.24
Gender % male	70	65	0.54
AF episodes per month	6±4	6±6	0.81
Duration of AF (years)	6±4	6±6	0.81
LA diameter (mm)	40±6	38±6	0.25
Diabetes	5.1%	4%	1.00
Hypercholesterolemia	17%	21%	0.59
Hypertension	56%	57%	1.00
LVEF (%)	60±8	61±6	0.49
CAD	2%	2%	
Valvular heart disease	3%	1%	0.22
Congenital heart disease	2%	1%	
No of previous ADTs	2±1	2±1	0.63

Source: Pappone et al., 2006: 2343.

6.7.2.1 The circumferential pulmonary vein ablation arm

All circumferential pulmonary vein ablations (PVIs) were performed using a navigation system, either CARTO (Biosense Webster Diamond Bar, California) or NavX (Endocardial Solutions Inc. St Paul Minnesota) (see Figure 6.10).

Ablation was performed using one of the following catheters: Navistar 8mm (Biosense Webster), Livewire TC (St Jude Medical, St Paul Minnesota), Cool-Path (St Jude Medical) or Navistar Thermocool 3.5mm (Biosense Webster). All the PVI settings were as follows: 60-100W at 50-65ºC and 25-40W at 35-40ºC.

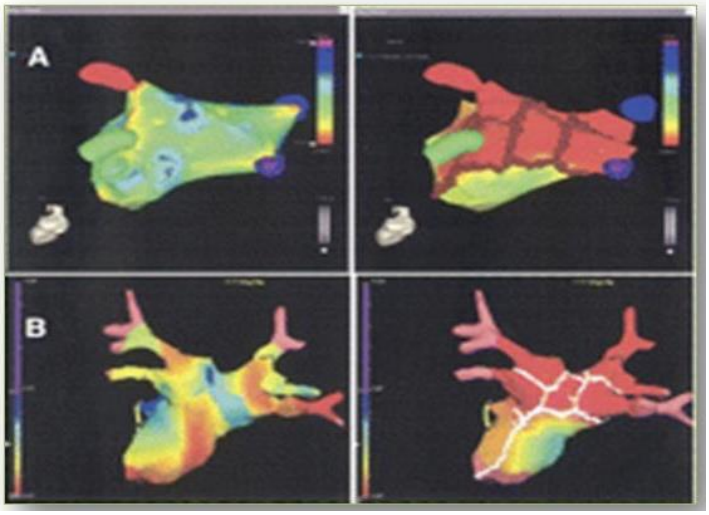


Figure 6.10: Pre- and post-ablation voltage maps of the LA with (a) CARTO and (b) NavX navigation systems

Source: Pappone *et al.,* 2006: 2342.

All the patients underwent an ablation using circumferential pulmonary vein isolation (PVI). The mean radiofrequency energy used was 35W (±12). The average procedure time was 81 minutes (± 31min). Completeness was assessed across the Mitral isthmus and ablation was performed at the cavo-tricuspid isthmus to prevent isthmus dependent atrial flutter. All patients were placed on ADT for a six-week blanking period (not described in detail) after which a 12-month follow-up period started. If there was AF recurrence after the six-week blanking period, a second PVI could be performed if the patient so chose.

6.7.2.2 The anti-arrhythmic drug therapy arm

Flecainide was given orally at an initial dose of 100mg twice daily up to a total of 300mg per day. Oral Sotalol was started at 80mg eight hourly and increased up to a maximum of 320mg per day. Amiodarone was started with a loading dose of 600mg per day for the first week, then decreased to 400mg per day for a week and finally maintained on 200mg per day. If patients presented with adverse events, the drug dose was first reduced and then stopped if the adverse events persisted. If AF persisted but the investigator deemed the clinical response acceptable with regard to frequency and duration of AF, the drug dose could be maintained. This is referred to in the model as “AF controlled”.

In the case of the failure of the first drug, a second drug in single dose could be prescribed, or the patients could be placed on a combination therapy of drugs, either Amiodarone 200mg and Flecainide 200mg, or Sotalol 240mg and Flecainide 200mg. The minimum period that the second drug choice must have been used was three months. Only after two trials of ADT had failed would patients be considered to crossover to PVI.

All the patients were anti-coagulated with Warfarin and monitored to maintain an international normalised ratio (INR) of between 2.0 and 3.0. Anti-coagulation could be stopped if sinus rhythm was achieved for at least six weeks in the absence of concurrent contra-indications.

6.7.3 Follow-up

The patients were seen at the outpatient clinic during the screening period before randomisation and then at three months, six months and 12 months after randomisation. The following diagnostic tests were done at each visit: a 12-lead ECG, 48-hour Holter monitor and a transthoracic echo. At the three-month follow-up, thyroid functions, liver function tests and serum chemical measurements were obtained. Chest X-ray and potential corneal deposits were evaluated in patients receiving long-term Amiodarone. Finally, all the patients were provided with an event monitor and asked to record their heart rhythm between one and three times daily.

6.7.4 Endpoint

The endpoint of the study was freedom of documented recurrent atrial tachycardia during the 12-month follow-up period. This endpoint was considered to have been reached as soon as the patient had a first episode of an atrial tachycardia (AT). Cases where a second ADT was added, or where patients required a further PVI, were considered failures. A recurrence of AT was defined as any AT that lasted more than 30 seconds.

6.7.5 The results

6.7.5.1 The PVI group

After the six-week blanking period, recurrent AF was documented in eleven patients, while three experienced atrial tachycardia (AT). During the follow-up period, a total of 85 patients were free from AT. The three patients with AT underwent a further ablation and remained free from AT. Of the eleven patients with recurrent AF, five were controlled on ADT (four on Flecainide and one on Sotalol) and the other six patients underwent a second PVI, which was successful in five out of the six patients.

The reported complication rate associated with PVI was low. One patient suffered a TIA, which resolved in seconds, and a second patient had a pericardial effusion (not as a result of perforation) and did not require drainage. As mentioned above, three patients developed atrial tachycardia, and these were successfully ablated.

6.7.5.2 The ADT group

Of the patients who were randomized to ADT, only 24 were reported to have their AF suppressed by a single ADT drug. There were twelve from the Amiodarone group, seven from the Flecainide group and five from the Sotalol group. AF recurrence was present in 75 of the original cohort of 99 patients, with 27% being symptomatic. Of these 75 patients, 49 were placed onto a combination of 200mg Flecainide and 200mg Amiodarone, while 26 were placed onto a combination of 200mg Flecainide and 240mg Sotalol.

Eleven of the patients on Amiodarone and Flecainide were free from AF, while the other 64 still had AF. Of these patients, 42 elected to have an ablation after a mean of 5.8 months, while the other 22 were controlled on ADT. At the end of the 12-month follow-up, 36 of the 42 patients (86%) who crossed over to ablation were free of AF.

6.7.5.3 Hospitalisations

The total number of hospitalisations in the follow-up period in each group can be seen in Table 6.16. Nine patients in the catheter ablation group had a total of 24 hospital admissions, which included the admissions for the procedure to be re-done. In the ADT group there were a total of 209 hospital admissions. There were 42 patients who underwent catheter ablation in the follow-up period and a further 167 admissions for other reasons. In total, including all procedures, the PVI group had 123 hospital admissions compared with the 209 in the ADT group.

Table 6.16: Total number of hospital admissions after the six-week blanking period

Reason	Catheter ablation group	ADT group
Ablation	9	42
Other reason	15	167
Total	24	209

Source: Pappone et al., 2006: 2344.

Figure 6.11 illustrates the outcomes in the APAF study, (A) the Kaplan-Meier analysis.86% of patients randomized to receive circumferential pulmonary vein ablation needed only a single procedure and were free from AT after 12 months, compared with 22% of the patients in the ADT group ($p<0.001$) who did not require additional drugs.

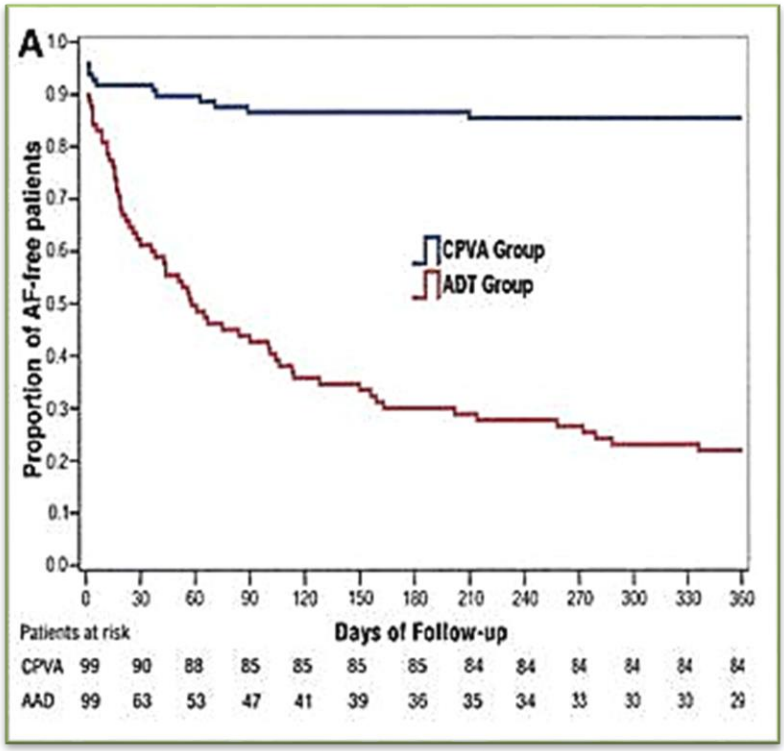


Figure 6.11: Outcomes in the APAF trial

Source: Pappone et al., 2006: 2345.

6.8 THE APAF FOUR-YEAR STUDY

On 15 August 2011, the APAF four-year study results by Pappone *et al.* (2006) were accepted for publication in the American Heart Association's publication, *Circulation: Arrhythmia and Electrophysiology*. This was published online on 23 September 2011, before going to print. This is a continuation of the 2006 study, on which the above cost-effectiveness model has been built. At the time of being published online, the model and this dissertation were complete. This section is meant to determine whether the use of the four-year data as opposed to the two-year data makes any material difference to the conclusion regarding cost-effectiveness.

The study evaluated the efficacy of PVI *vs*. ADTs over a 48-month follow-up period, according to an intention-to-treat analysis. QoL was also analysed at baseline and again at 48 months. Published data have shown that paroxysmal AF has a natural progression towards persistent AF, of approximately 15% to 30% over a period of one to three years.

6.8.1 Data collection and follow-up

Patients were followed-up quarterly, or whenever the patients needed medical attention over the four-year period. At each visit, a 12-lead ECG, 48-hour Holter monitor and transthoracic echocardiography were performed. Patients were provided with TT 12-lead ECG and patients were asked to record their rhythm twice per week and whenever they felt symptomatic. Patients completed SF-

36 QoL questionnaires at baseline, four years after randomisation and before crossover to PVI if applicable. Anti-coagulation was stopped in patients with a $CHADS_2$ score of zero. Crossover from ADT to PVI was only permitted for the following reasons:

- After intolerance of the drug.
- After serious side effects.
- Failure of ADT in different classes or with combination of drugs occurred.
- After sustained recurrences of more than 12 hours.

Figure 6.12 illustrates the cumulative probability of crossover to catheter ablation among patients assigned to ADT.

At follow-up, 99.6% of patients were from the PVI group, compared with 99.5% from the ADT group. The mean number of visits to the clinic was 3.3 (±0.7). Among the PVI patients, two had recurrences of AF and were deemed silent, compared to 33 patients in the ADT group who had episodes of silent AF. The recurrences in patients in the ADT group were often highly symptomatic and lasted longer than 12 hours.

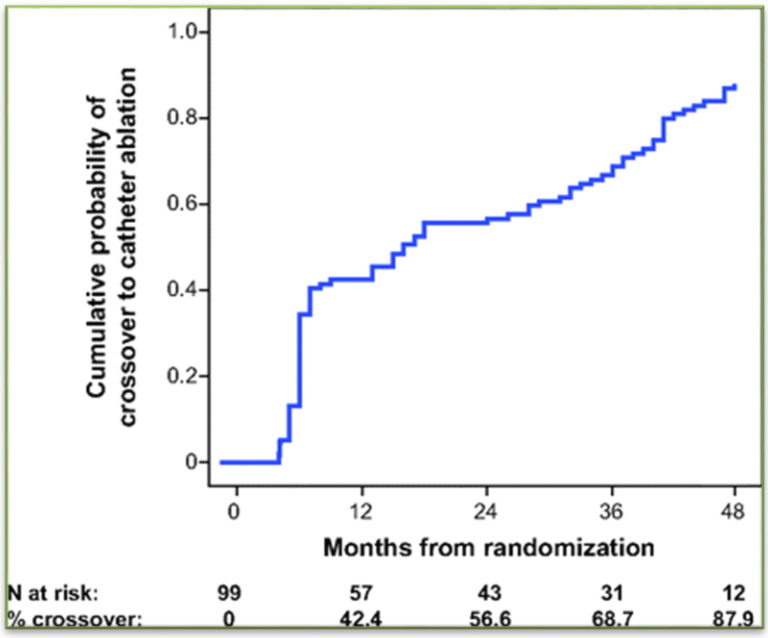


Figure 6.12: The cumulative probability of crossover to catheter ablation among patients assigned to ADT

Source: Pappone et al., 2011: 24.

6.8.2 Results

When analysing the primary endpoint on an intention-to-treat basis, 72 of the initial 99 patients (72.7%) in the PVI group reached the primary endpoint after a single procedure. In the ADT group, only twelve (12.1%) patients met the primary endpoint of no AT.

Among the PVI group, 27 patients underwent a second ablation for recurrence of AF/AT (see Figure 6.13). Of the 99 patients randomized to ADT, only 12 were free from AF at the end of the follow-up period, while the other 87 patients elected to undergo PVI. Of the 87 patients who crossed over to PVI, 68 had paroxysmal AF, while the other 19 had progressed to persistent AF. The mean time to crossover was 10.1 months (±7.2). Of the patients who crossed over to PVI, 71.3% were free from AF at 48 months.

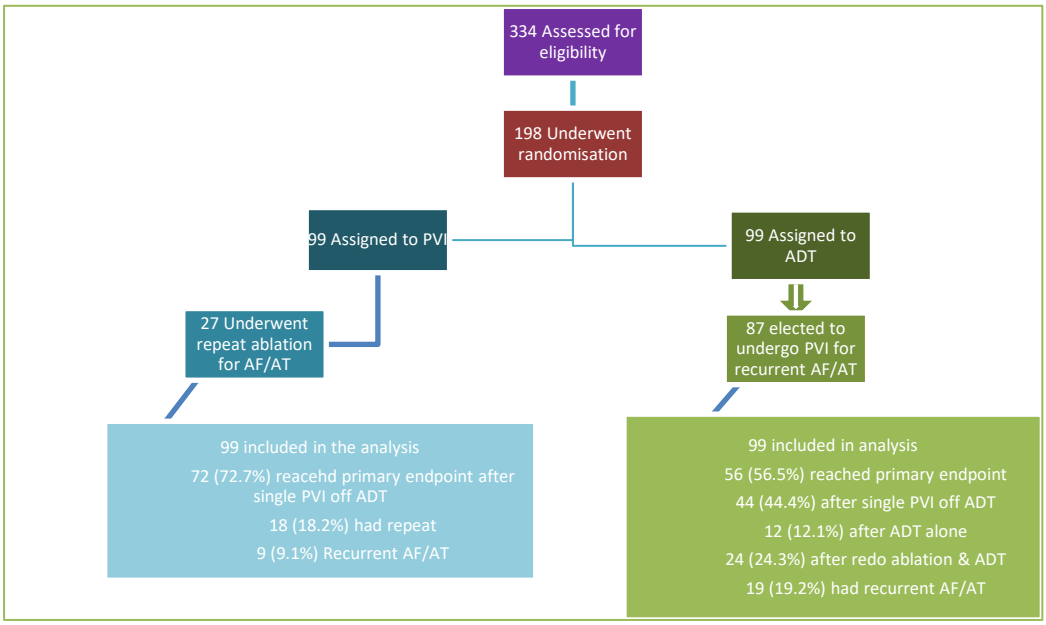


Figure 6.13: Randomisation, results and follow-up of patients in PVI and ADT arm of APAF study at 48 months

Source: Pappone et al., 2011: 22.

The Kaplan-Meier curve in Figure 6.14 demonstrates the freedom from AF/AT in both groups four years after randomisation after a single PVI procedure.

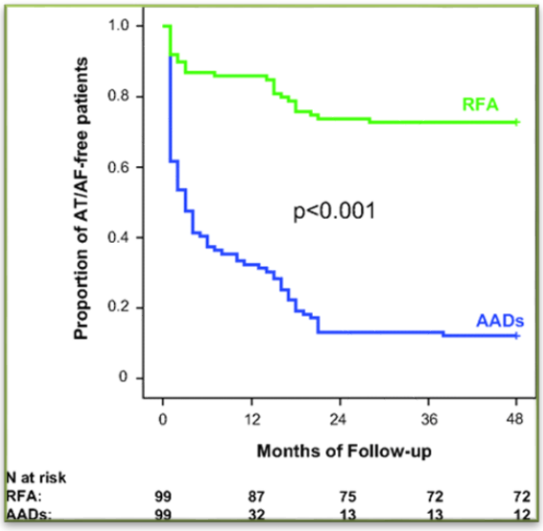


Figure 6.14: Kaplan-Meier curve of patients free of AF/AT for both PVI and ADT

Source: Pappone et al., 2011: 23.

6.8.3 Complications and other events

Among the PVI group there were three femoral hematomas, one transient ischaemic attack (TIA), which resolved within seconds, and one pericardial effusion, not requiring drainage. No procedure-related late complications were observed in the PVI group. In the group assigned to ADT, there were 68 patients who discontinued their medication due to lack of efficacy or adverse events. Adverse events among the patients in the Amiodarone group were transient, but included fifteen patients with symptomatic bradyarrhythmias, subclinical thyrotoxicosis in nineteen patients, and hepatitis in one patient, and visual or dermatological events in two patients.

6.8.4 Hospital admissions

The total number of hospitalisations in the ADT group was more than double the number in the PVI group, with a total of 126 admissions at 48 months in the PVI group for catheter ablation, and 130 admissions in the ADT group for catheter ablation. The PVI group only had 34 admissions at the end of 48 months for other causes, compared with 195 admissions in the ADT group for other causes. The total number of hospital admissions in the PVI group over the 48-month period was 160 compared with 325 in the ADT group (see Table 6.17).

Table 6.17: Hospitalisations at 12 months and 48 months for PVI group and ADT group

Reason	PVI		ADT	
	12 months	48 months	12 months	48 months
Ablation/redo ablation/AT	108	126	42	130
Other causes	15	34	167	195
Total	123	160	209	325

Sources: Pappone et al., 2006: 2344; Pappone et al., 2011: 12.

6.8.5 Quality of life (QoL)

The QoL scores shown in Table 6.18 illustrate that patients who underwent PVI showed a significant long-term improvement in QoL scores. Analysis of the QoL scores of both groups on an intention-to-treat basis shows little difference between the PVI and ADT groups. However, it is noted that 90% of patients initially randomized to ADT before crossing over to PVI showed significantly poorer QoL.

Table 6.18 demonstrates QoL scores at baseline, prior to crossover, and at 48 months. The quoted p-values refer to the change from the baseline value to that at 48 months and not between the crossover and 48 months.

Table 6.18: Comparisons of QoL scores for PVI and ADT at baseline, before crossover and at 48 months

	PVI (n=99)			ADT's (n=99)			
	Baseline	**48 months**	**p-value**	**Baseline**	**Prior to crossover**	**48 months**	**p-value**
Physical functioning	69±18	85±12	<0.0001	68±21	***67±16*	82±15	<0.0001
Role physical	63±19	82±14	<0.0001	61±17	61±14	80±15	<0.0001
Bodily pain	68±19	80±17	<0.0001	66±24	***63±19*	77±21	<0.0001
General health	65±17	79±15	<0.0001	67±17	***63±17*	77±16	<0.0001
Vitality	56±22	71±23	<0.0001	55±18	***53±16*	68±21	<0.0001
Social functioning	68±22	87±14	<0.0001	66±20	***64±17*	86±14	<0.0001
Role emotional	70±24	86±18	<0.0001	70±22	***66±19*	84±19	<0.0001
Mental health	66±21	81±17	<0.0001	67±19	***62±15*	78±17	<0.0001
PCS	44.4±9	52.3±9	<0.0001	45.7±9	***44.1±7*	52.6±8	<0.0001
MCS	43.7±11	52.9±9	<0.0001	44.4±10	***42.5±10*	51.9±9	<0.0001

*Notes: Those in italics** indicate a deterioration from baseline.*

Source: Pappone et al., 2011: 20 & 21.

Based on the results of the 48-month follow-up study, it would appear reasonable to expect that the cost-effectiveness results, where PVI dominates ADT in all areas, would not change. This is based on the fact that the costs for PVI and ADT break even at approximately 1.5 years. Moreover, given that large economic burden studies have shown that 50% of costs are attributed to hospitalisation, the likelihood that cost-effectiveness would be in favour of ADT is small. Therefore, the model used to test the cost-effectiveness of catheter ablation versus ADT in the South African context will be based on the original Pappone *et al.* (2006) study published in the *Journal of the American College of Cardiology*.

6.9 CONCLUSION

There is sufficient evidence from published meta-analysis and controlled randomized trials to build a cost-effectiveness model for radiofrequency ablation compared to ADT with a particular focus on efficacy. There are also a significant number of trials evaluating the impact on quality of life that AF has for patients and also the improvement in quality of life after radiofrequency catheter ablation. The focus of Chapter 7 is the model, which is built and used to establish whether the use of radiofrequency ablation is more cost-effective than commonly used anti-arrhythmic drugs in South Africa.

CHAPTER 7: APPLYING THE MODEL TO EXPLORE THE COST-EFFECTIVENESS OF CATHETER ABLATION IN SOUTH AFRICA

7.1 INTRODUCTION

Five percent of the South African population is over the age of 65, compared with more than 15% of the population in Europe and the USA. This means that there are, as a percentage of the total population, fewer South African patients per million of the population who are affected by non-rheumatic atrial fibrillation than in European and American countries. It is, however, not an insignificant disease in South Africa, as it is associated with a high morbidity and mortality rate. Increasingly, patients search for answers on the internet and other media, and present to electrophysiologists for the ablation of their atrial fibrillation. This has increased the awareness of the cost implications of treating atrial fibrillation by means of ablation.

To address the issue of cost and effectiveness, a systematic literature review - discussed in Chapter 6 - was conducted. The first step in developing a model to explore the cost-effectiveness of catheter ablation in South Africa was to establish the relevance of this treatment in clinical practice. This was verified by means of interviews and a questionnaire presented to electrophysiologists in South Africa. It was important to establish whether the studies performed overseas were aligned with how the South African electrophysiologists treat patients with AF in South Africa. It was also critical to determine whether the same choice of drugs is available to South African patients.

The next step in the process was to collect the data relating to cost. These included the costs of physician’s visits, diagnostic tests, blood tests and medication, as well as the procedural costs and the costs associated with hospitalisation. A decision analytical model was then developed, using TreeAge software. Both a decision tree and Markov model were included in the model to input data with regard to probabilities, outcomes, costs and transition states. Discounting was calculated at 3.5% per year.

The results confirmed the various costs associated with the treatment of AF. A cost-effectiveness analysis was run using TreeAge Pro software and, finally, sensitivity analyses were run for all the parameters tested.

Chapter 7 incorporates the following:

- Establishing the relevance of the chosen studies within the South African context.
- Designing the model to run a cost-effectiveness model.
- Data collection for the costs associated with both RFA and ADT.
- Running the model and getting results.
- Interpreting the results.
- Reporting on the results.

7.2 ESTABLISHING RELEVANCE IN CLINICAL PRACTICE IN SOUTH AFRICA

There is a paucity research relating to AF ablation in South Africa. Contributions to research in the field of electrophysiology by South African electrophysiologists has typically been conducted in Europe or as contribution world-wide registries. No local studies have been performed in South Africa comparing catheter-based ablation with drug therapy in the South African population. It was for this reason that it was decided to mirror data from a peer reviewed research paper by Pappone *et al.* (2006) and to develop a model for the evaluation of cost-effectiveness in the South African scenario. The authors of the APAF study (Pappone *et al*., 2006), describe their management protocol of patients included that were included in the trial. Failing to establish if the manner a correlation in which patients with AF were treated in the Pappone *et al.* (2006) trial and South Africa would render our study meaningless. It is for this reason that a questionnaire was developed which would establish if the management of South African patients with AF, were similar to the protocols used in the Pappone *et al.* (2006) study.

At the time there were only ten physicians trained and accredited by the Cardiac Arrhythmia Society of Southern African who regularly performed electrophysiology studies in South Africa. (The names of the physicians interviewed can be found in Appendix H). Each electrophysiologist was approached by means of an email in which the purpose of the interview was explained and permission for an interview was requested. Interviews were conducted either telephonically or, where possible, in person. At the outset of the interview, the setting was explained, identifying the patient population being studied as well as the purpose of the study.

7.2.1 The questionnaire design

The questionnaire was divided into a number of sections:

1. Number of years in practice, number of PVI procedures performed each year.
2. Type of procedure, use of CARTO, NavX, Cryoablation or PVAC techniques.
3. First patient consultation, type of diagnostic tests performed e.g. ECG and Echo.
4. A list of anti-arrhythmic drugs was cited, and the physician was asked to identify drugs that he would typically prescribe. Included in the list were all the drugs listed in the Pappone *et al*. (2006) study, but in no specific order.
5. Practice with regard to cardioversion. Although there is no detail in the Pappone *et al.* (2006) study of cardioversion, this was required to establish costs. The same information was explored in Section Seven.

6. Specific protocols when performing circumferential pulmonary vein ablation (PVI). Here it was also established how many times the electrophysiologist would recommend PVI if the first procedure was not successful.
7. What would be expected at a typical follow-up at an outpatient visit. This included any diagnostic tests that would be performed as well as the frequency of follow-up visits.
8. Each physician was asked for their specific recommendations with regard to frequency of INR blood tests for their patients on anti-coagulants. This was to establish the average number of INR blood tests required in a 12-month period.
9. Finally, the physician was asked to comment about any aspects with regard to treating a patient with PAF that had not been considered, either from a clinical or cost perspective. (Sample questionnaire can be found in Appendix G)

7.2.2 The findings from the South African questionnaire

A total of 8/10 (80%) electrophysiologists were interviewed. Interviews were conducted in person with five (63%) and telephonically with three (37%) electrophysiologists. The mean number of years in EP practice was 14.6 (range 1-35). The average number of PVIs performed each year was 24 (range 7-75). All but one performed catheter ablation for atrial fibrillation (88%). Seven (88%) used either a 3D mapping system, such as CARTO (Biosense Webster, Diamond Bar, California), or NavX (Endocardial Solutions Inc. St Paul Minnesota). Five (63%) also used cryoablation for their PVI procedures and one (13%) used cryoablation exclusively for PVI, but also used 3D mapping if the patient developed an atrial tachycardia and required extra ablation. At the time of the interview, only one person was known to perform PVI without cryoablation or a 3D mapping system and there was only limited use of PVAC after the release of data in 2011 relating to increases in micro-emboli in patients who underwent PVAC.

These interviews confirmed that all of the electrophysiologists performed an ECG and an Echo, including 2D, MMode and, in most cases, colour Doppler at the first consultation. Holter monitoring varied from some physicians not doing any Holter monitor recordings to some doing Holter monitors on 30-50% of patients. There was a large degree of similarity regarding the type of blood tests which would be requested, with all the electrophysiologists selecting U&E, FBC, TSH, T_4, and INR. Two respondents (25%) request ProBNP, while one routinely requests LFT.

Table 7.1 illustrates the drugs cited by the South African electrophysiologists as drugs they usually prescribe. Not all these drugs would be used in PAF, as some would be used in rate control strategies for patients who had persistent or permanent AF. The reason they were included was to establish similarity between practice in South Africa and Italy, where the Pappone *et al.* (2006) study was conducted.

Table 7.1: Drugs typically prescribed for patients with AF by South African electrophysiologists

Drug	Number	%
Warfarin	8/8	100
Sotalol	6/8	75
Amiodarone	8/8	100
Flecainide	7/8	88
Propafenone	0/8	0
Digoxin	6/8	75
Diltizem	5/8	63
Verapamil	6/8	75
β blockade	7/8	88

Source: Results of interviews with electrophysiologists (see Appendix I).

The loading doses of Amiodarone varied quite significantly among the various practitioners: One prescribes 800mg initially, then 600mg and 400mg for four days each, before maintaining at 200mg daily; one prescribes 600mg for a month, then maintaining on 200mg daily; and two prescribe 1 200mg for two weeks, 800mg for two weeks, 400mg for two weeks, and then 200mg daily. Seven respondents request INR testing weekly for between one and six weeks and one suggests INR testing twice a month. All respondents suggested testing the INR once a month if the INR was stable. The mean number of INR tests in a 12-month period was 16.2.

When performing a PVI on a patient, all respondents admitted the patient to either a high care unit (HCU) or a coronary care ICU (CCU). The average length of stay reported by the doctors was 1.4 days. Only 3/7 (43%) routinely did a CT scan and one doctor reported that they would only do so on the first admission. Follow-up procedures would not require a CT scan. Most cited that the procedure took between 240 and 300 minutes while two said it took between 120 and 180 minutes. General anaesthesia was used in 4/7 (57%), while the others made use of conscious sedation. Almost all did a TEE at the time of the procedure, while one respondent routinely used intra-cardiac echocardiography (ICE).

The average number of follow-up visits in the first 12 months was 3.4 (range 2-4) after which the patient would be seen annually or sent back to the referring doctor if they were stable. In response to the question of diagnostic tests requested at follow-up visits, the respondents named the following:

- ECG was requested by ten physicians (100%).
- Echo was requested for an average of 64% of patients.
- Most stated that they would request Holter monitoring in between 40% and 100% of visits, with each patient having Holter monitoring at least once in a 12-month period.

7.3 METHOD

A decision analytical model and Markov model were developed using TreeAge Pro Software from TreeAge Software Inc. The first stage of the model is a decision tree, where patients are randomized to receive either catheter ablation (PVI) or anti-arrhythmic drugs (ADT). This is followed in each arm by a Markov process, where patients go through four health states. These were “No AF”, “AF controlled”, “PAF” and “Dead,” in six-month cycles over a period of two years. The probability of passing through each health state is different for both the ADT arm and the PVI arm and these data are derived from clinical data by Pappone *et al.* (2006) and McKenna *et al.* (2009). To calculate cost-effectiveness using the TreeAge Markov process, three data sets were required: cost, outcome and transition probability.

7.3.1 Measuring costs

All costs were calculated using Discovery Health rates. This rate was selected as Discovery Health administers 41.3% of all schemes and thus represents a good sample size of actual costs (Council for Medical Schemes (CMS), 2010: 110). A discount rate of 3.5% per annum was applied to both costs and outcome. This is consistent with the lower range of the inflation target set for South Africa and in line with the discount rate adopted by agencies such as NICE.

Resources used are expressed in terms of events associated with each treatment strategy and are illustrated in Table 7.2. These include the following four categories: outpatient costs, hospital costs for PVI, hospital costs for recurrence of AF and medical therapy (including monitoring of INR). These costs were confirmed as the typical costs that would be incurred by a patient who presented with PAF to an electrophysiologist in South Africa. Interviews were also held with a sample of anaesthesiologists, radiographers and cardiac technologists. The sample of the questionnaires can be found in Appendices E-G. Total treatment costs were allocated by multiplying the mean medical resource used for each treatment group by the appropriate unit price.

Outpatient costs were calculated for office visits with electrophysiologists and for major outpatient cardiac testing and procedures, including transthoracic echocardiography, ECG, stress ECG, and ambulatory Holter monitoring.

Table 7.2: Costs associated with treating AF in South Africa

Outpatient costs	Hospitalisation for PVI	Hospitalisation for recurrence of AF	Medical therapy
Consultation in rooms	Procedure costs	Hospital stay	Warfarin
ECG	Hospital stay	Electrophysiologist fee	Sotalol
ECHO	Anaesthesiologist fee	Anaesthesiologist fee	Flecainide
Holter Monitoring	Radiographer fee	Cardioversion	Amiodarone
Bloods	Technologist fee		INR testing
	Electrophysiologists fee		

Sources: Adapted from Reynolds *et al.,* 2007: 629; Pappone *et al.,* 2006.

For the hospital costs, data were used from actual patient accounts at Netcare hospitals where more than 80% of all PVI procedures with either Carto or NavX mapping systems are performed. All patients were assumed to have their PVI procedure using Carto as the 3D mapping system, and the costs of all EP catheters were based on Biosense Webster products at 2011 net acquisition price for single use. A sample of 51 consecutive patient accounts were used from Sunninghill Hospital after the procedure was completed. The author was blinded to the identity of the patient and the data were supplied by Netcare head office. A sample size of 51 represents about 19% of all the AF procedures done in South Africa in a single year and 23% of all AF procedures performed at Netcare hospitals in a single year.

Hospital costs for the recurrence of AF included the cost of hospitalisation, the in-hospital visits by the electrophysiologists, and cost of cardioversion. These costs were based on an average of 5.2 days, as determined in two major studies where resources were calculated for episodes of AF (Reynolds *et al.,* 2007: 630; Stewart *et al.,* 2004: 288).

The single exit price of drugs was taken from the Department of Health website and was used to calculate the average cost of AF-related outpatient prescription medication as required (rate controlling agents, anti-arrhythmic agents and Warfarin). All costs were at 2011 prices in ZAR. The prescribed dispensing fee was included in the cost of the medication. INR testing was calculated at one test per week for the first month, one test every second week for the second month and thereafter one test per month for the rest of the year if the patient's INR was stable. This indicates that a minimum of sixteen INR tests were done per patient per year. Hospital re-admissions were calculated for emergency admissions for the recurrence of AF and heart failure and were based on actual patient data.

Costs that were not included in the study were any admission to hospital that related to a change in the dosing of ADT. While this is common practice in the USA and some European countries for dosing of drugs like Flecainide, which is known to be arrhythmogenic, it is not practiced in South Africa because of the cost implications. Also not included in the costs were any out-of-pocket medical expenses, including time spent on travel. Loss of productivity was also not included in the costs. The

cost of managing stroke and its complications were not included because of the limited access to patient data. However, by including the cost of stroke one would expect the cost of treatment in the ADT group in particular to increase.

7.3.2 Measuring outcomes

Health outcomes were measured as time free of AF and QALYs gained. The latter was taken from published data. Utility values are the numerical representation weighted to represent differences in the quality of life and can range from 0 (death) to one (perfect health). Patients who were restored to sinus rhythm or the "No AF" state were assumed to return to having the same QoL as the general population. Decrements as stated in McKenna *et al.* (2008: 546) were used for other states i.e. AF controlled and PAF after failed PVI or ADT. Table 7.3 defines the QoL parameters.

Table 7.3: Quality of health parameters

QoL parameters				
General population	AF given ADT	AF given PVI	No AF given ADT	No AF given PVI
0,835	0,7425	0,8316	0,8151	0,835

7.3.3 The model

The model used both a decision tree analysis and a Markov model to capture and simulate costs and outcomes over a two-year period. There are four health states, namely "No AF", "AF controlled", "PAF" and "death". Each cycle is over a six-month period, with a total of four cycles. In the PVI arm, it is assumed that, for patients who require a second PVI, the procedure is done within the first six months, while in the ADT arm, the patients were only allowed crossover to PVI at six months if they had failed at least two trials of ADT. The study stipulates that crossover was at a mean of 5.8 months. (Pappone *et al.,* 2006: 2344). The study states that, at the end of follow-up, all but three of the patients in the PVI group who were free of AF (n=82) were on oral anti-coagulants (OAT). It was assumed that all patients who had PVI and were successful, were on OAT for six months after PVI. This assumption is based on standard South African practice and may add some bias in favour of the ADT arm, although minimal. The model design (see Appendix M) shows that all patients entered into the study with paroxysmal AF (PAF) (n=198). They were then immediately randomized to either the ADT arm (n=98) or the PVI arm (n=98). After randomisation the Markov process started. Patients in the ADT group were again randomised to receive one of three drugs, namely Amiodarone (n=33), Sotalol (n=33) or Flecainide (n=33).

7.3.4 Transition probabilities

Figure 7.1 is a schematic representation of the health states and transition probabilities used in the model. The model uses a simple decision analysis at the start of the model and thereafter uses a Markov model.

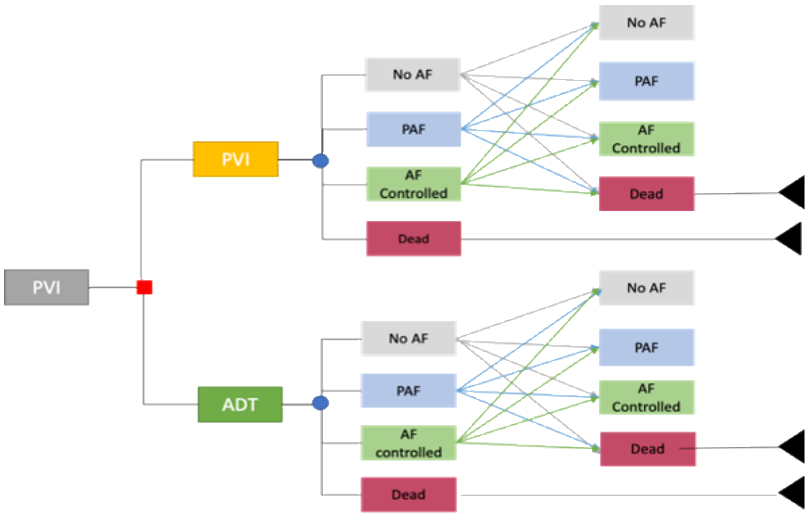


Figure 7.1: Possible transitions between health states in the Markov process

Source: Adapted from Pappone et al., 2006.

Table 7.4 describes all the possible health states, namely “AF”, “PAF”, “AF controlled” and “Dead”, found in the decision tree analysis and the Markov model, together with the source, if applicable. It also describes the various treatment options that were available, for example, ADT and PVI.

Table 7.4: Description of health states in the Markov model

Health state/ treatment option	Brief description
AF	All patients enter the decisions tree analysis with AF, having failed at least one ADT (Pappone *et al.*, 2006: 2343).
PVI	Patients randomised to circumferential pulmonary vein ablation (PVI).
ADT	Anti-arrhythmic drug therapy.
No AF	This includes patients who are converted to sinus rhythm or who are still in AF but with episodes of less than 30 seconds.
PAF	This group includes patients with paroxysmal episodes of AF lasting longer than 30 seconds.
AF controlled	This included patients with persistent AF where the investigator (and patient) determined that there was an acceptable clinical response with regard to duration and frequency of arrhythmia recurrences.
Dead	Patients entered this state based on all-cause mortality as per Calkins *et al.*, (2001) and then progression through the model is terminated.

Source: Adapted from Pappone et al., 2006.

Table 7.5 tabulates the transition probabilities for both the radiofrequency ablation arm and the ADT arm used in the Markov model as well as the source of each.

Table 7.5: Transition probabilities applied to the Markov process for the ADT arm

The probability of:	Probability	Source
Receiving Amiodarone	0.33	Pappone *et al.*, 2006
Receiving Flecainide	0.33	
Receiving Sotalol	0.33	
Amiodarone suppressing AF	0.36	
Flecainide suppressing AF	0.21	
Sotalol suppressing AF	0.15	
Receiving Amiodarone and Flecainide	0.65	
Receiving Sotalol and Flecainide	0.35	
Crossover from drug to PVI	0.56	
AF Free on Amiodarone and Flecainide	0.22	
AF controlled on Amiodarone and Flecainide	0.33	
AF controlled on Sotalol and Flecainide	0.23	
AF recurring after one year	0.29	McKenna *et al.*, 2009
Adverse events (ADT)	0.30	Calkins *et al.*, 2009
Death (ADT)	0.03	Calkins *et al.*, 2009
AF free (PVI)	0.86	Pappone *et al.*, 2006
Having AF (PVI)	0.03	
Being AF controlled (PVI)	0.05	
Require second PVI	0.06	
AF free after second PVI	0.83	
AF recurring after one year (PVI)	0.0335	McKenna *et al.*, 2009
Adverse events (PVI)	0.049	Calkins *et al.*, 2009
Death (PVI)	0.007	Calkins *et al.*, 2009

Sources: Calkins et al., 2009; McKenna et al., 2009; Pappone et al., 2006.

Transition probabilities estimated from nine clinical studies and shown in Table 7.5 are summarised below:

- Pappone *et al.* (2006) describe PVI *vs*. ADT in patients with PAF, n=198.
- McKenna *et al.* (2009) report on the probability of AF recurring after one year in both PVI and ADT group. The study also describes decrements in utilities in health states.
- Calkins *et al.* (2009) describe both the death rate in both the PVI arm and ADT arm, these are specific to death related to PVI and ADT from a meta-analysis of both treatment options and did not include the death rates described in chapter 4.8.
- Chan *et al.* (2006) report on stroke rate and death rate from stroke.
- Stewart *et al.* (2000) report on hospitalisations and length of stay.
- Reynolds *et al.* (2007) report on hospitalisations and length of stay.
- Bunch *et al.* (2010) report on one, three- and five-year mortality.
- Stewart *et al.* (2002) describe cardiovascular hospitalisations, stroke and cardiovascular death.
- Pappone *et al.* (2003) report on stroke, number of hospital visits and number of deaths.

7.4 THE RESULTS

7.4.1 The costs associated with treating atrial fibrillation (AF)

7.4.1.1 The outpatient costs

Outpatient costs were calculated based on the number of visits reported in the Pappone *et al.* (2006) study and the type of diagnostic tests performed with each visit. This was confirmed in the survey of the South African electrophysiologists and the only discrepancy was with regard to the number of 24-hour Holter monitoring performed.

The Pappone *et al.* (2006) study included Holter monitoring at each visit, while the South African physicians only do Holter monitoring in 40% of the patients. The reason for the discrepancy is twofold:

1. In a clinical study that is evaluating the efficacy of a treatment it is important to be able to track that efficacy. In this case, Holter monitoring is a safe, non-invasive and reasonably reliable method for tracking the absence or presence of an arrhythmia.

2. South African electrophysiologists recognise the value of doing Holter monitoring, but all stated in their interviews that it added extra cost to the patient and, as such, they did not perform a Holter with every follow-up visit.

Table 7.6 illustrates the cost per patient per follow-up visit. This cost applies to both the ADT arm as well as the PVI arm. The mean cost was R2 495.40, the median was R2 363.30 and the range was from R2 363.30 to R2 891.70.

Table 7.6: Cost and codes for outpatient visits

Outpatient visit	Billing code	Cost	1st visit	3 months	6 months	12 months
Rooms visit	0191	R389.30	Yes	Yes	Yes	Yes
ECG/stress	1231	R88.10	Yes	Yes	Yes	Yes
	1233	R114.50	Yes	Yes	Yes	Yes
	1235	R528.40	Yes	No	No	No
Echo	3260	R419.70	Yes	Yes	Yes	Yes
	3621	R209.90	Yes	Yes	Yes	Yes
	3622	R419.70	Yes	Yes	Yes	Yes
24-hour Holter	1238	R484.30	Yes	Yes	Yes	Yes
	1239	R237.80	Yes	Yes	Yes	Yes
Total cost per visit			R2891.70	R2363.30	R2363.30	R2363.30

Source: Cost calculations adapted from Discovery, 2011.

7.4.1.2 The costs associated with blood taken at pathologist for management of AF

Table 7.7 is a summary of the most common blood tests performed on patients under the care of a physician for AF. The data were taken from the interviews performed and a conservative estimate was used for blood tests. This assumption is based on the fact that patients who revert to sinus rhythm are essentially treated as healthy patients and only those on Warfarin require regular and careful monitoring of their INR. Based on this, calculations for blood tests were done for U&E, FBC and TSH twice yearly and INR sixteen times per year. This is for patients in both the PVI and ADT groups, who were considered to be in the “controlled AF” or “No AF” health states.

Table 7.7: Cost and codes for blood tests at pathologist laboratory

Blood Test	Billing code	Cost	Total tests per year	Total cost per year
U & E	4171	R161.31	2	R322.62
Creatinine	4032	R36.90	2	R73.80
FBC	3755/3797	R129.73	2	R259.46
TSH	4507	R199.57	2	R399.14
Amylase	4006	R52.75	2	R105.50
ALP	4001	R52.75	2	R105.50
AST	4130	R55.02	2	R110.04
ALT	4131	R55.02	2	R110.04
INR		R61.13	16	R978.08
INR dosing		R61.13	16	R978.08
Total pathology costs per year				R3 442.26

Source: Cost calculations adapted from Discovery, 2011.

7.4.1.3 The costs associated with drugs used for ADT in patients with AF

In the Pappone *et al.* (2006) study the following four drugs are used in both the ADT and the PVI arms, namely Warfarin, Sotalol, Amiodarone, and Flecainide. The study defines the dosage and period of time each drug was used. Based on this data, a search was conducted on the Department of Health website to find the cost, dosage and supplier of each of these drugs. Table 7.8 tabulates the specific drugs chosen for the model. The specific item was selected to get the most cost-effective combination of drugs, based on dose and pack size. The cost also included the dispensing fee.

Table 7.8: Cost of drugs and pack size as per South Africa

Active Ingredients	Strength	Unit	Pack Size	Dosage Form	Manufacturer Price	Logistics Fee	VAT	SEP	Unit Price	Dispensing Fee	SEP + Disp Fee	Unit Price incl Disp Fee	Effective Date
Warfarin Sodium	5	mg	100	TAB	116.24	15.02	18.38	149.63	1.50	38.90	188.53	1.89	29 November 2010
Sotalol	80	mg	100	TAB	321.73	45.22	51.37	418.32	4.18	59.00	477.32	4.77	03 March 2009
Flecainide	100	mg	60	TAB	347.37	34.74	53.50	435.61	7.26	59.00	494.61	8.24	22 May 2010
Amiodarone	200	mg	30	TAB	430.01	13.30	62.06	505.37	16.85	59.00	564.37	18.81	26 May 2010

Source: Department of Health (DoH), 2011.

Once the specific drugs and prices had been identified, a calculation was performed to measure the cost per day and per month for each individual drug. This was then entered into the model at the applicable place. Table 7.9 illustrates the cost by drug per day.

Table 7.9: Cost per dosage and cost per day

DRUG	STRENGTH	COST PER DOSE	TOTAL DOSE	COST PER DAY	PACK SIZE
Warfarin	5mg	R1.50	5mg	R1.50	100
Sotalol	80mg	R4.18	320mg	R16.72	100
Flecainide	100mg	R7.26	300mg	R21.78	60
Amiodarone	200mg	R16.85	600mg	R50.55	30
			400mg	R33.70	30
			200mg	R16.85	n/a
Combination1	Flecainide & Amiodarone		200mg & 200mg	R31.37	n/a
Combination 2	Flecainide & Sotalol		200mg & 400mg	R21.06	n/a

Sources: Adapted from DoH, 2011; Pappone et al., 2006.

Table 7.10: Cost of drugs per month and per year

Cost of drugs	Cost per month	Cost per year
Sotalol	R508.29	R6 099.46
Flecainide	R662.12	R7 945.45
Warfarin	R45.49	R545.85
Amiodarone**	R541.73	R6 500.73
Amiodarone 1st month	R866.09	
Amiodarone months 2-12	R512.24	

*Notes: **Cost per month is calculated as the average over 12 months.*

Sources: Adapted from DoH, 2011; Pappone et al., 2006.

For the ADT group, Pappone *et al.* (2006) described the following: Oral Flecainide was given at an initial dose of 100 mg twice daily with a maximum tolerable dose of 300mg per day. Oral Sotalol was started at an initial dose of 80mg three times daily and increased to a maximum tolerable dose of 320mg per day, while oral Amiodarone was started at an initial loading of 600mg/day for the first week, 400mg/day for the next week, after which a daily maintenance dose of 200mg was given daily. All of these were based on the clinical response and/or the occurrence of side effects. Doses of each drug were reduced if intolerable adverse reactions occurred, and treatment was stopped if they persisted. If the first assigned drug failed at the maximum tolerable dosage, the choice of a

second drug was at the discretion of the primary physician, who could choose from the other two anti-arrhythmic agents or use a combination of two of the three agents used in this study. The patient had to remain on the next drug combination for a minimum period of three months before the drug trial could be considered unsuccessful. Only after two failed trials of ADT could patients be considered for crossover to PVI. Based on this, the monthly cost for each drug was calculated as shown in Table 7.10.

7.4.1.4 The costs associated with catheter ablation for AF

The costs associated with treating a patient with PVI for AF is made up of the following components: hospital costs, the professional fee of the Anaesthetist, the professional fee of the cardiac technologist, the professional fee of the radiographer and the professional fee of the electrophysiologist.

The fee for the electrophysiologist includes consultation at admission, a fee for performing the procedure, including EP study, transseptal puncture, TEE and ablation. The fee also includes all post-operative visits in the ward or CCU for the duration of each hospital stay. The hospital costs can be broken down into the following:

- Hospital stay, including the CCU/ward fees, monitors, oxygen and medication.

- Theatre fees, including a fee for the use of specialised equipment, for example, bi-plane X-ray, 3D mapping system and ablation generator. This fee also includes any drugs used in theatre, as well as any disposables used and, in particular, EP and ablation catheters. For the purpose of the study, the cost of all EP and ablation catheters were subtracted from the actual cost and replaced with equivalent Biosense Webster Carto catheters and diagnostic catheters at the 2011 net acquisition price. All catheter prices were calculated at single-use, as recommended by the manufacturer. The ablation catheter of choice was the Navistar RMT Thermocool as single-use.

A sample of 51 consecutive patient accounts was used to calculate the costs of PVI. The questionnaire responses by the South African electrophysiologists revealed that the average amount of time each patient spent in hospital when undergoing a procedure was 1.4 days, while the actual number of days calculated from the 51 patients was 2.2 days, with a median of 1.8 days and a range between 1.5 days and 5.5 days. The total average cost of the PVI was R134 411 with a median of R134 641. Table 7.11 tabulates the costs associated with PVI for AF.

Table 7.11: Costs associated with PVI for AF

Description	Costs of PVI	
	Sub-category	Value
Average days		2
Average hospital costs		R103 327
	Procedure costs	R37 877
	EP catheters	R54 101
	Hospital stay	R11 350
Average fee for Anaesthetist		R9 965
Average fee for radiographer		R1 617
Average fee for technologist		R2 919
Average fee for electrophysiologist		R16 582
Average total cost of hospitalisation for PVI		R134 411

Sources: Patient accounts, 2011; Discovery price file, 2011; Data from interviews, 2011; Biosense Webster Price list, 2011.

7.4.1.5 The costs associated with hospitalisation for AF

According to the study by Pappone *et al.* (2006: 2344) the total number of hospital admissions after the six-week blanking period was as follows: a total of 24 admissions in the catheter ablation group, nine of which were for a repeat ablation. In the ADT group there were a total of 209 hospital admissions, 42 of which were for catheter ablation and the other 167 for recurrence of AF and heart failure. When allocating costs for these hospitalisations all hospital admissions related to a repeat ablation or a first ablation for those on the ADT arm, costs were allocated as described in Section 7.3.4. For the admissions related to heart failure or the recurrence of atrial fibrillation a sample group of six patient hospital admissions were used. The measures of interest were number of days in hospital per admission and the total cost. Included in the total cost were hospital costs, pathologist's costs, cost of cardioversion, daily CCU or ward consultation with electrophysiologist, and one follow-up visit after discharge.

From the data collected the mean number of days was 5.1. This is 2% lower than the value of 5.2 days used in the model, which is based on an average from the Stewart *et al.* (2004: 288) and Reynolds *et al.* (2007: 631). The median number of days in hospital was 5.5 days with a range from 2 days to 9 days.

The average cost per day was R7 787.93 with the median cost per day of R8 096.42 and a range between R5 819.48 and R9 419.96. Based on this a value was assigned to hospitalisation per admission of R40 497.26. Table 7.12 tabulates the cost for hospital admission.

Table 7.12: Costs associated with hospital admission for recurrence of AF or heart failure

	Average	Median	Std Dev	Lower range	Upper range
Number of days	5.1	5.5	2.4	2	9
Hospital costs	R27 455.97	R21 847.95	R12 630.17	R14 388.40	R46 529.80
Electrophysiologist	R2 348.27	R2 641.80	R1102.22	R880.60	R3 962.70
Pathology costs	R1 616.50	R1 572.63	R782.73	R740.00	R2 812.00
Cost of cardioversion	R572.40	R572.40	R0.00	R572.40	R572.40
Total Cost	R37 791.63	R32801.66	R16 719.74	R18 373.86	R63 576.46
Cost per day	R7 787.93	R8 096.42	R1 651.56	R5 819.48	R9 419.96

Sources: Patient accounts, 2011; Discovery price file, 2011; Data from interviews, 2011.

7.4.2 The cost-effectiveness analysis

7.4.2.1 The analytical methods

Based on the calculations above, a Monte Carlo simulation model was run using TreeAge Pro software (Williamson, Massachusetts) with a simulation sample size of 1 000. As South Africa does not have a specific threshold at which a therapy is considered cost-effective, it was difficult to measure a cost per QALY threshold, but a sensitivity analysis was performed to assess the impact of other variables on cost-effectiveness using TreeAge Pro and, when measuring the total monetary benefits, a “willingness to pay” (WTP) threshold of R120 000 was used.

On questioning the Council for Medical Schemes with regard to a “willingness to pay” threshold for South Africa (CMS, 2010), they were unwilling to reveal such a threshold, rather stating that the threshold differs with each disease state. Currently, drug therapy is the “gold standard” for treating atrial fibrillation and drug therapy, either alone or with cardiac resynchronisation therapy (CRT), is the “gold standard” for treating congestive heart failure, one of the major complications of atrial fibrillation.

Congestive heart failure is one of the prescribed minimum benefits (PMBs) established by the Council for Medical Schemes. In the absence of an official WTP threshold for South Africa, the cost of treating heart failure patients with drugs and/or CRT is therefore an unofficial threshold. Treatment for congestive heart failure with CRT can be with either low power or high-power CRT devices, as determined by large, randomized clinical trials. In order to establish the average cost of CRT the costs were established for a low power device or Bi-ventricular pacemaker with three endocardial pacing leads as well as the cost of a high-power device or CDT-D with three endocardial pacing leads.

The cost was established from two major pacemaker companies (St Jude Medical and Medtronic). The average cost for a low power CRT device was quoted as R70 000.00, while the average cost of a high-power CRT device was quoted as R150 000.00. In order to establish a WTP threshold, an average of the two devices was calculated and 10% was added to cover the cost of implantation. The calculation is seen in Table 7.13.

Table 7.13: Calculation of WTP threshold based on cost of CRT devices in South Africa

Description	Value
CRT	R70 000
CRT-D	R150 000
Total	R 220 000
Average	R110 000
10%	R11 000
Total threshold	R121 000

Source: Adapted from data from Medtronic and St Jude South Africa, 2012.

This estimate of R120 000 as a "willingness to pay" threshold using CRT devices in South Africa is only based on the cost of the device. This is assuming that 50% of all CRT devices are low power while the other 50% are high power. An additional 10% has been added to the cost for "other" medical expenses. The other medical expenses, which have not been included in detail, are the cost of the procedure, hospitalisation costs, cost of the Anaesthetist, radiographer, cardiac technologist and electrophysiologist. Other costs not included in this cost are follow-up visits and cost of reprogramming the device. All of these costs, if added to the cost of the CRT device, would increase the limit of the threshold to over R121 000.

7.4.2.2 Cost-effectiveness analysis

A simulation model for cost-effectiveness (C-E) was run using TreeAge Pro software. The input data were established from the literature reviews performed. The model simulated 1000 patients who were randomised to receive either PVI or ADT. The statistics of the C-E analysis are tabulated in Table 7.14 and refer to cost and effectiveness.

Table 7.14: Summary of cost-effectiveness analysis statistics: Variables cost and efficacy

Variable	PVI-mean	ADT-mean
Cost per patient	R168 996	R206 520
Efficacy per patient	1.64	1.52

Figure 7.2 illustrates, in graphical form, the cost-effectiveness analysis of PVI *vs*. ADT. The χ-axis refers to cost, where the cost increases from left to right on the axis. The *y*-axis shows effectiveness increasing as the axis moves upwards. The PVI group is indicated by a small red square located in the top left-hand quadrant. The cost is R168 000 with an efficacy of 1.64 QALYs per patient. In this analysis, when compared with the cost of ADT, PVI has high effectiveness at low cost. The ADT treatment group is represented by a small blue triangle in the far-right corner of the bottom right quadrant. The cost of the ADT group is R187 000 per patient with an effectiveness of 1.52 QALY. This indicates that the ADT group has high cost but low effectiveness. The blue triangle of ADT is encircled by a small yellow dot demonstrating domination of ADT by PVI as more cost-effective.

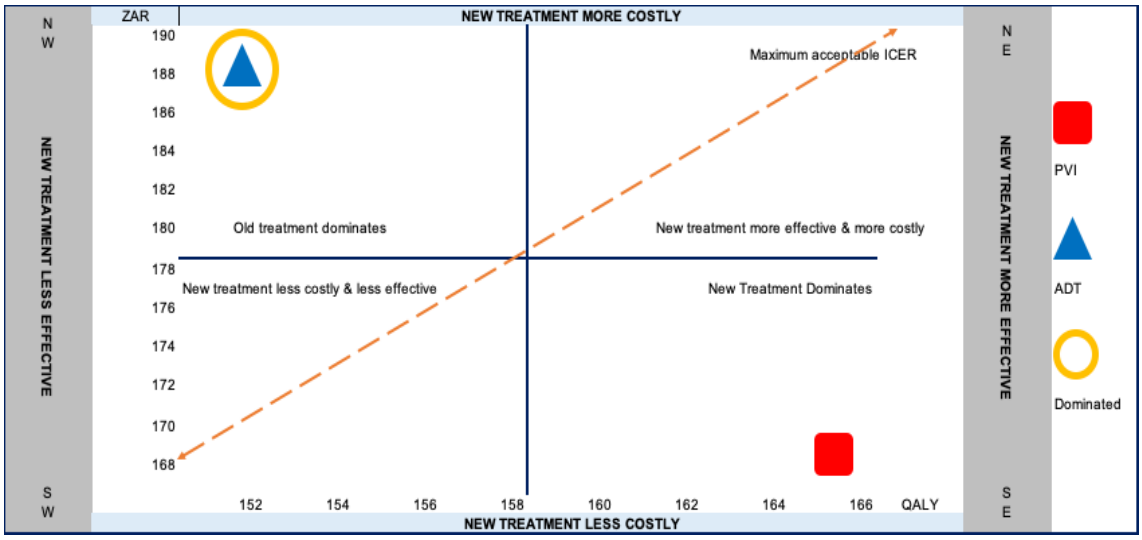


Figure 7.2: Cost-effectiveness analysis of PVI *vs* ADT for AF showing the ADT is dominated

Source: Markov model dated 27 February 2012.

7.4.2.3 Sensitivity analysis

When performing a cost-effectiveness analysis, it is prudent to also perform a sensitivity analysis. The sensitivity analysis determines the impact on the model's output or results if the variables or inputs are changed. In this study the variables of particular interest for the sensitivity analysis were cost, QALY, duration of hospital stay, the duration of the treatment, and the relative risk of death. These are discussed below:

- The change in cost is referred to as the discounted cost and is denoted by *dCosts*. Cost was measured as the actual cost which formed the baseline value and the sensitivity analysis was performed at a discounted rate of 3.5%.
- The baseline value of the QALY was determined in the study from the literature review. The variable was denoted as *dQALY* and was measured at a discounted rate of 3.5%.

- The duration donated as *tDuration.* The original study by Pappone *et al.* (2006) was performed over a period of two years. This became the baseline measure and a sensitivity analysis was also performed at one year, three years and four years.
- The average length of stay in hospital for re-admissions for AF or heart failure was denoted as *kAveLoS.* The baseline was measured at 5.2 days as per the literature review. The sensitivity analysis was performed using an increase and decrease of 20%.
- The relative risk of dying (rrADT) is the relative risk of dying when treated with ADT compared with PVI. The literature review indicated that the relative risk of death was 2.2 and was used as the baseline. The sensitivity analysis was performed with an increase and decrease of 20%.

Discounted costs (dCost)

For all measurements of cost-effectiveness, the period of two years was used as a baseline. The first variable to be tested was cost, where actual cost over the two-year period was used and then, in order to perform the sensitivity analysis, a discount rate of 3.5% was applied.

Table 7.15 refers to this sensitivity analysis where the variable of cost was changed. The total cost for PVI at two years was R168 790 compared with the cost of R190 728 per patient for ADT. PVI dominated ADT as more being cost-effective at both baseline and again at the discount rate of 3.5%.

Table 7.15: Sensitivity analysis of discounted cost (*dCost*) per patient

Strategy	Variable	Cost/patient	Eff	CE	IC	IE	ICER	Dominated
PVI	0	R168 790	1.64	102882	0	0	0	
ADT	0	R190 728	1.53	125030	R21937	-0.12	-190 494	(Dominated)
PVI	0.035	R168 437	1.64	102667	0	0	0	
ADT	0.035	R187 357	1.53	122821	R18920	-0.12	-164 295	(Dominated)

Source: Markov model dated 27 February 2012.

In Figure 7.3 the χ-axis refers to the cost, where cost increases from left to right and the y-axis refers to effectiveness which increases from the bottom to top. ADT is represented by a blue triangle and is found in the bottom right quadrant while PVI (the red square), is in the top left quadrant, indicating that ADT, even when discounted, costs more and is less effective than PVI and PVI dominates ADT, represented in Figure 7.3 by the yellow dot around the ADT icon.

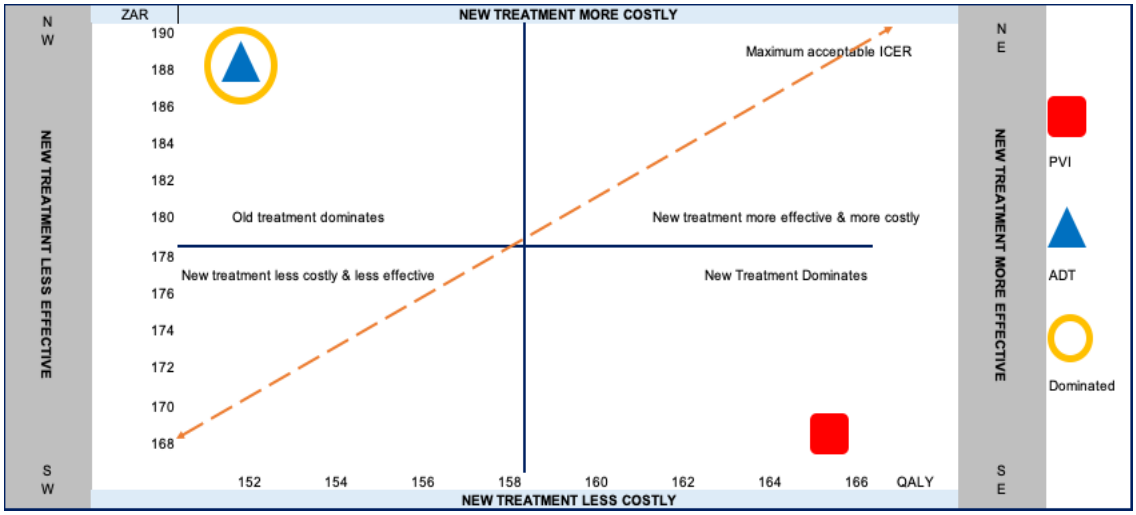


Figure 7.3: Cost-effectiveness of PVI *vs*. ADT with reference to change in cost

Source: Markov model dated 27 February 2012.

When a sensitivity analysis was performed on the variable of cost and a discount rate of 3.5% was applied, the following were noted:

1. The average cost (Figure 7.4) shows that when discounting cost by 3.5% the impact is greatest for ADT, but that ADT, as a treatment, remains costlier than PVI. The average cost for PVI is lower than ADT and remains reasonably constant for the period of two years.

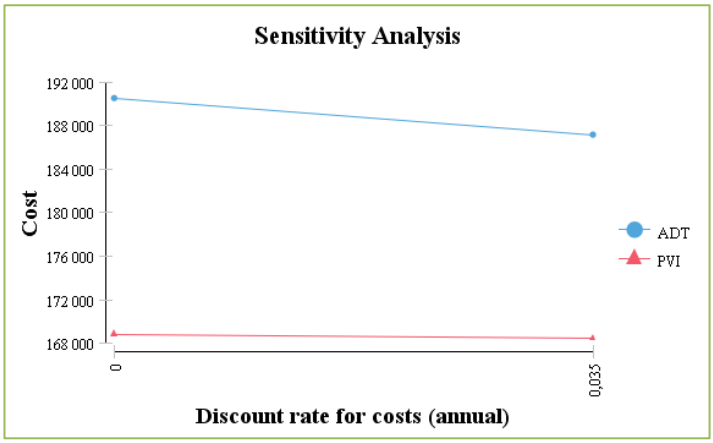


Figure: 7.4: Sensitivity analysis when a discount rate of 3.5% was applied to costs

Source: Markov model dated 27 February 2012.

2. Incremental cost (Figure 7.5) shows the impact of discounting cost on the incremental cost-effectiveness. Here, although the costs start to converge, PVI still dominates over ADT.

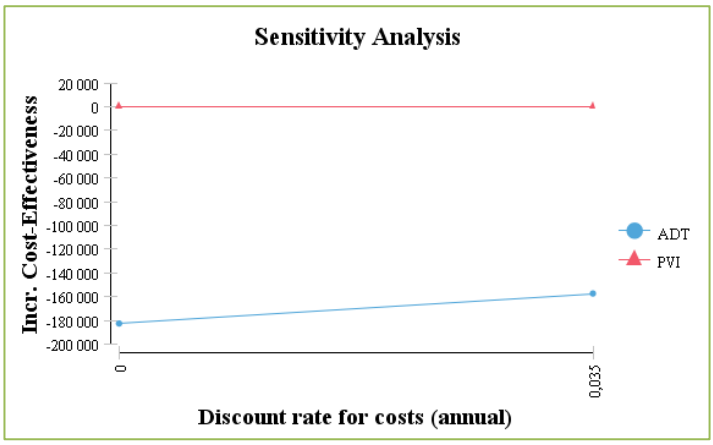


Figure 7.5: Sensitivity analysis of the incremental cost-effectiveness when a discount rate of 3.5% was applied to costs

Source: Markov model dated 27 February 2012.

Discounted QALY (dQALY)

The second step in the sensitivity analysis was to establish what impact there would be on the variable QALY if discounting methodology was applied. The same discount rate of 3.5% was applied for QALYs. Table 7.16 demonstrates that PVI dominated over ADT when testing the variable QALY at both baseline and a discount rate of 3.5%.

Table 7.16: Sensitivity analysis of discounted QALY (*dQALY*)

Strategy	Variable	Cost	Eff	CE	IC	IE	ICER	Dominated
PVI	0	R168 437	1.67	100950	0	0	0	
ADT	0	R187 357	1.55	120852	R18 920	-0.1182	-160 057	(Dominated)
PVI	0.035	R168 437	1.64	102667		0	0	
ADT	0.035	R187 357	1.53	122821	R18 920	-0.1152	-164 295	(Dominated)

Source: Markov model dated 27 February 2012.

In Figure 7.6 the χ-axis refers to the cost, which increases from left to right and the y-axis refers to effectiveness and increases from the bottom to top. ADT is represented by a blue triangle and is found in the bottom right quadrant while PVI (the red square), is found in the top left quadrant. In the previous sensitivity analysis where a discount rate of 3.5% was applied it was noted that the blue triangle (ADT) was at the intersection of R190 000 on the χ-axis and 1.53 on the y-axis. The red square (PVI) was at the intersection of R170 000 on the χ-axis and 1.65 on the y-axis. Discounting was applied to QALY and the blue triangle (ADT) was found between R185 000 and R190 000 on the χ-axis and 1.54 QALYs on the y-axis, showing an improvement in cost-effectiveness. The red square (PVI) was found at the intersection of between R165 000 and R170 000 on the χ-axis and between 1.65 and 1.70 QALYs on the y-axis, which also indicates an improvement in cost-effectiveness. When a discount rate of 3.5% was applied to QALY, PVI dominated over ADT.

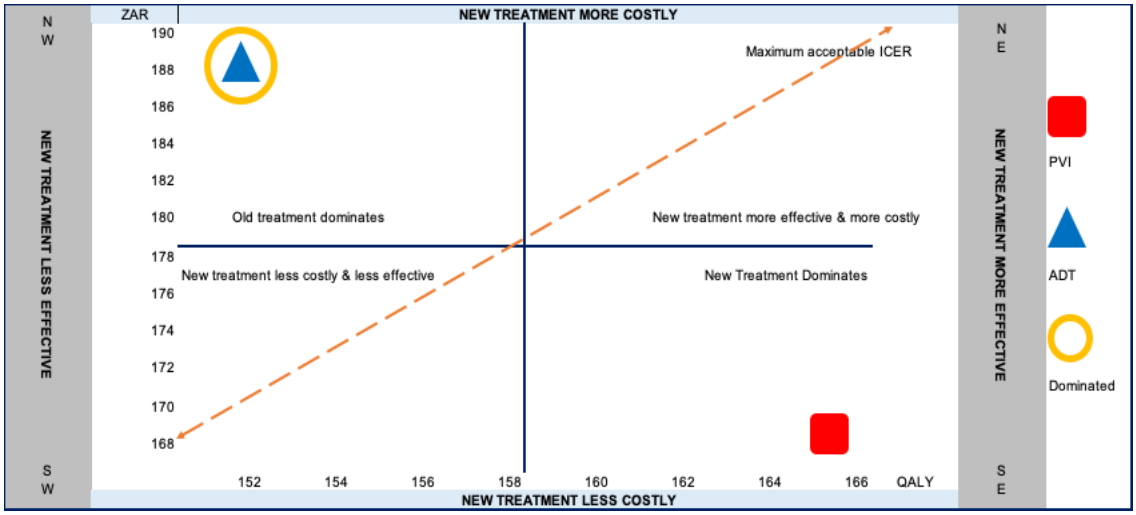


Figure 7.6: Cost-effectiveness of PVI *vs.* ADT when measuring impact of change on QALY

Source: Markov model dated 27 February 2012.

When a sensitivity analysis was performed on the variable of QALY and a discount rate of 3.5% was applied, the following were noted:

1. The average cost showed no change when a discount rate of 3.5% was applied to QALY. The average cost of PVI remained lower than ADT (Figure 7.7).

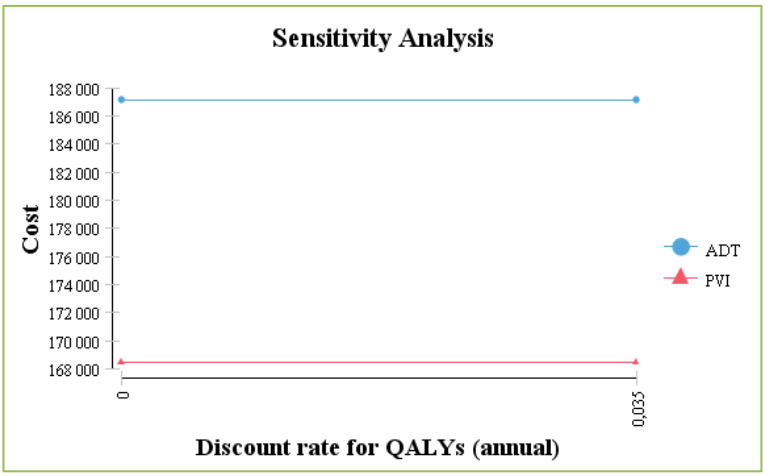


Figure 7.7: Measure of average cost when a discount rate of 3.5% is applied to QALY

Source: Markov model dated 27 February 2012.

2. The incremental cost for ADT remained around R18 000, while the incremental cost for PVI remained at 0 (Figure 7.8).

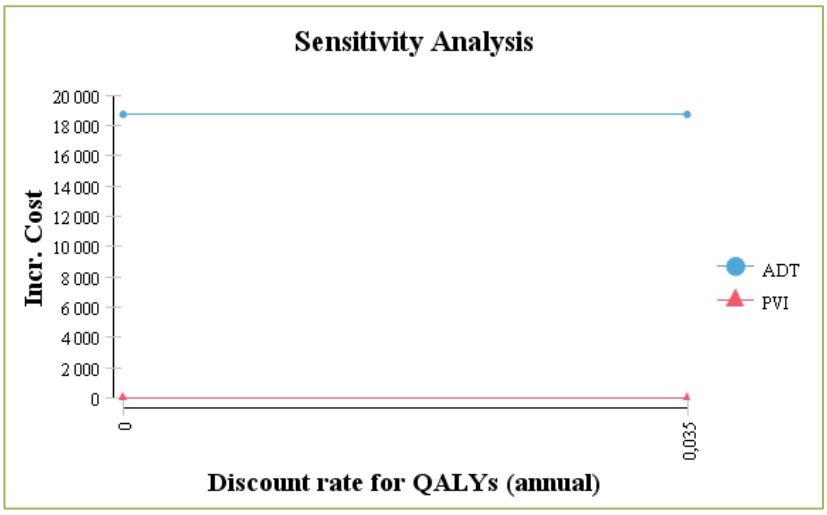


Figure 7.8: Measure of incremental cost when a discount rate of 3.5% is applied to QALY

Source: Markov model dated 27 February 2012.

3. The average effectiveness showed a decrease in effectiveness of less than 2% in both the ADT group and the PVI group (Figure 7.9).

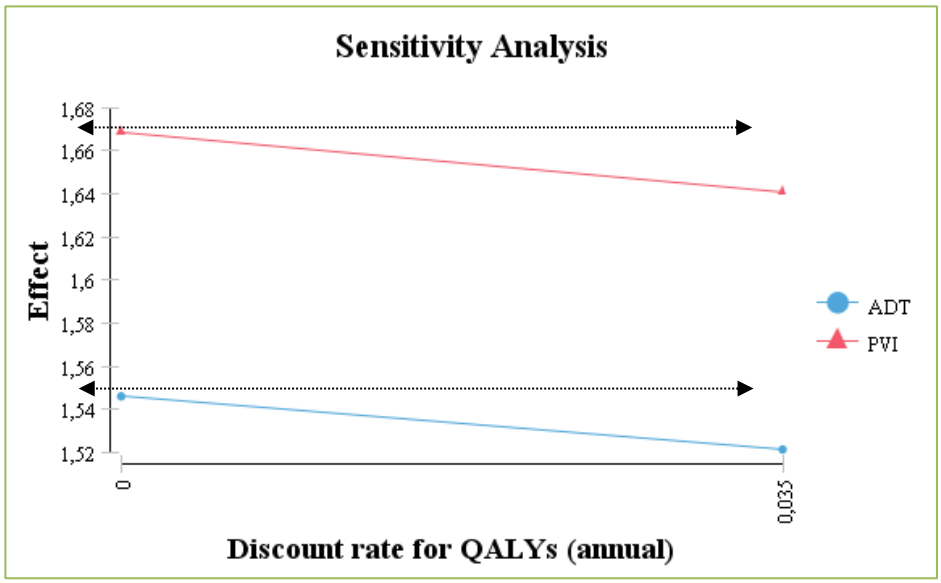


Figure 7.9: Measure of the average effectiveness when a discount rate of 3.5% is applied to QALY

Source: Markov model dated 27 February 2012.

4. The incremental effectiveness showed no change in the incremental effectiveness in the PVI group and a minimal improvement in the effectiveness for the ADT group (Figure 7.10).

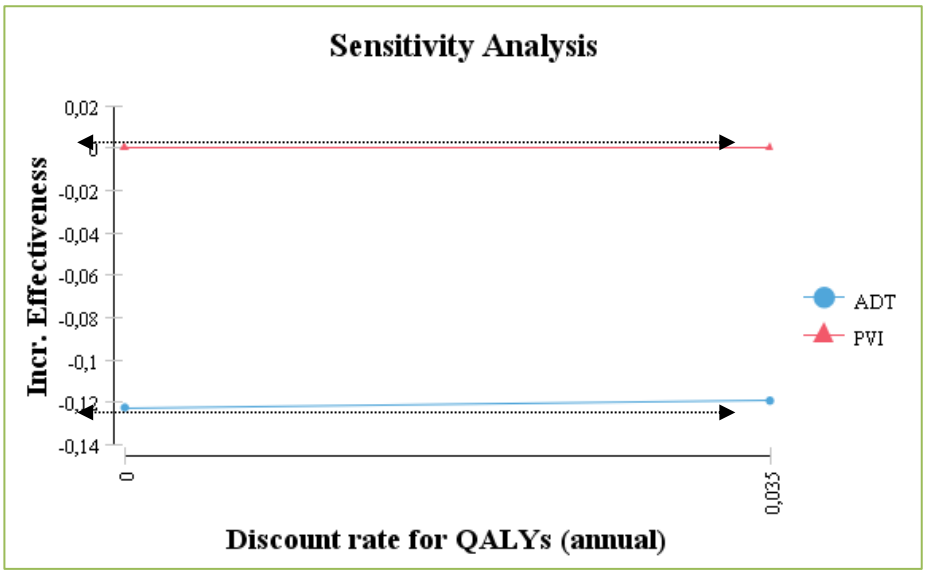


Figure 7.10: Measure of the incremental effectiveness when a discount rate of 3.5% is applied to QALY

Source: Markov model dated 27 February 2012.

5. The incremental cost-effectiveness is demonstrated in Figure 7.11 and illustrates that, in spite of the fact that PVI did not change and there was a small change in the ADT group, PVI still dominated over ADT.

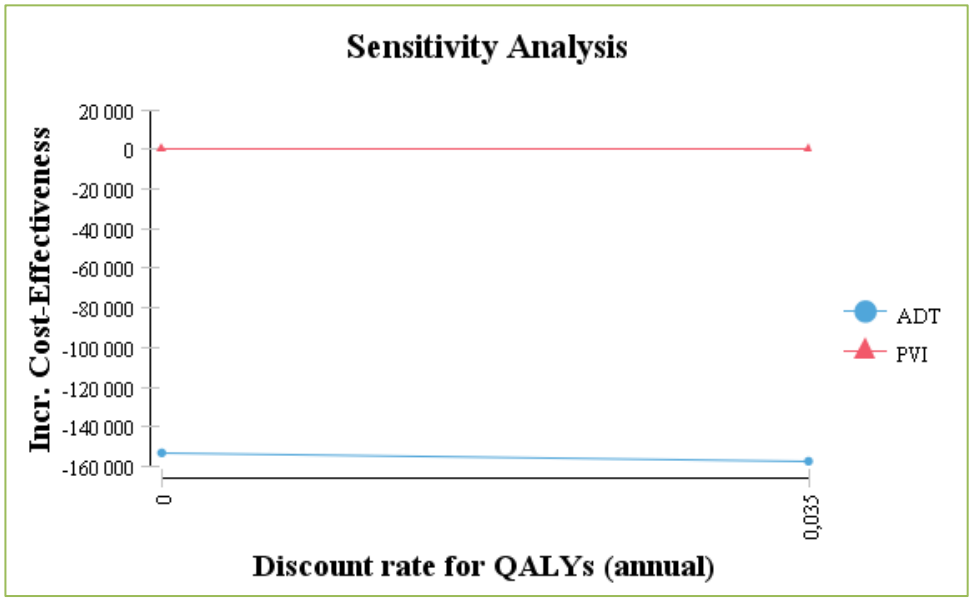


Figure 7.11: Measure of the incremental cost-effectiveness when a discount rate of 3.5% is applied to QALY

Source: Markov model dated 27 February 2012.

6. The net monetary benefit at a willingness-to-pay value of R120 000 shows that, for the PVI group, the benefit drops from about R32 000 to about R29 000, while the net monetary benefits for ADT start at below zero and drop further to about -R2 500 (Figure 7.12).

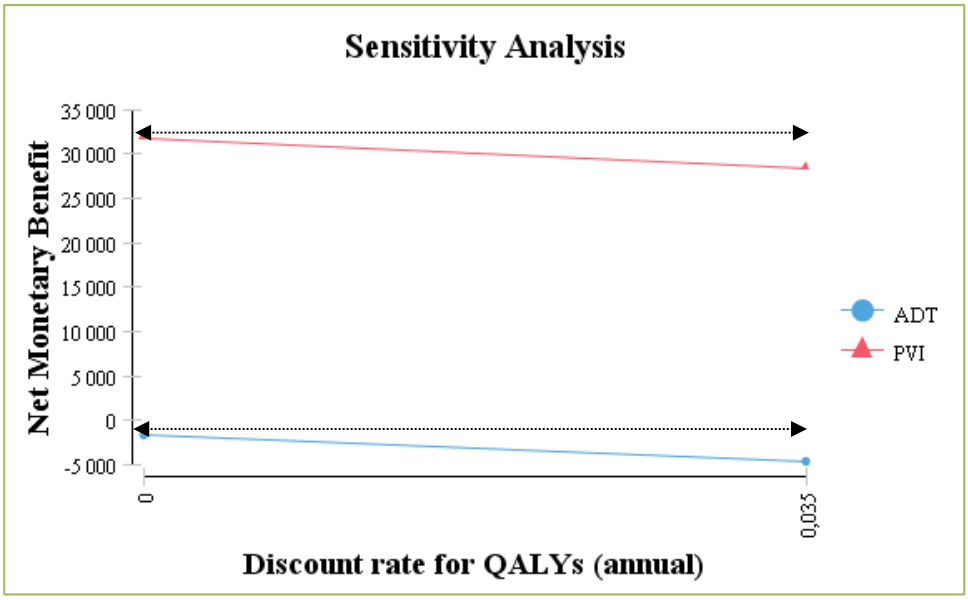


Figure 7.12: The net monetary benefits when a discount rate of 3.5% is applied to QALYs at a WTP 120 000

Source: Markov model dated 27 February 2012.

Duration of the study (tDuration)

The baseline for the measurement of duration of the study was two years. This was based on the fact that the original APAF study performed by Pappone *et al.* (2006) was over a two-year period. Other reasons for using two years as the duration of the study were as follows:

2. Most of the data found in literature reviews for ablation *vs*. ADT do not extend beyond a two-year period.

3. There is a perception that South African medical aids tend to base their decisions on a short-term rather than long-term view, taking into consideration the number of patients who change from one medical aid scheme to another. If this is indeed the case, then two years may be too long.

The χ-axis refers to the cost, where cost increases from right to left and the y-axis refers to effectiveness and increases from the bottom to top. Figure 7.13 represents a period of one year. Again, the ADT group is represented by a blue triangle and is found in the bottom left quadrant. The red square (PVI) is also found in the bottom left quadrant. This indicates that, while PVI is marginally more cost-effective at one year, it does not dominate ADT, and this is confirmed in Table 7.17.

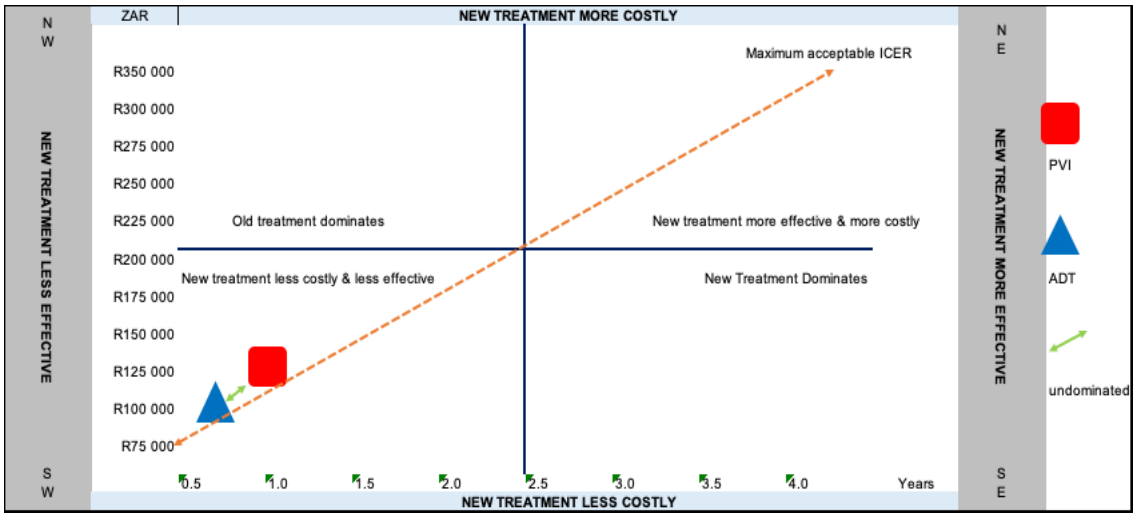


Figure 7.13: Cost-effectiveness of PVI *vs*. ADT with reference to change in duration of the study

Source: Markov model dated 27 February 2012.

However, at a period of two, three and four years, PVI dominates ADT as being more cost-effective. This is shown is Table 7.17. Assuming that the same efficacy is found at three years and four years, then PVI would continue to dominate ADT.

Table 7.17: Sensitivity analysis of duration (*tDuration*)

Strategy	Variable	Cost	Eff	CE	IC	IE	ICER	Dominated
PVI	1 year	R132 275	0.77	171 247	0	0	0	
ADT	1 year	R158 866	0.82	193 600	R26 591	0.048	552059	
PVI	2 years	R168 437	1.64	102 667	0	0	0	
ADT	2 years	R187 357	1.53	122 821	R18 920	-0.12	-164295	(Dominated)
PVI	3 years	R180 471	2.43	74 250	0	0	0	
ADT	3 years	R259 999	2.20	118 208	R79 527	-0.23	-344163	(Dominated)
PVI	4 years	R194 621	3.19	60 990	0	0	0	
ADT	4 years	R340 376	2.81	121 305	R145 755	-0.39	-378547	(Dominated)

Source: Markov model dated 27 February 2012.

When a sensitivity analysis was performed on the variable for the duration of the study, with two years as the baseline and with the variable changed to one year, three years and four years, the following emerged:

1. The average cost showed that up to 1.587 years, the cost of PVI is more than that of the ADT group; thereafter, the cost of PVI flattens out, while the cost of ADT continues to grow exponentially (Figure 7.14). At one year, the cost of the ADT group is about R130 000, compared to R160 000 for the PVI group. After four years, the cost of the ADT group is about R340 000 while the cost of PVI has increased to about R190 000. This represents an increase in cost of 19% for the PVI group and 162% for the ADT group.

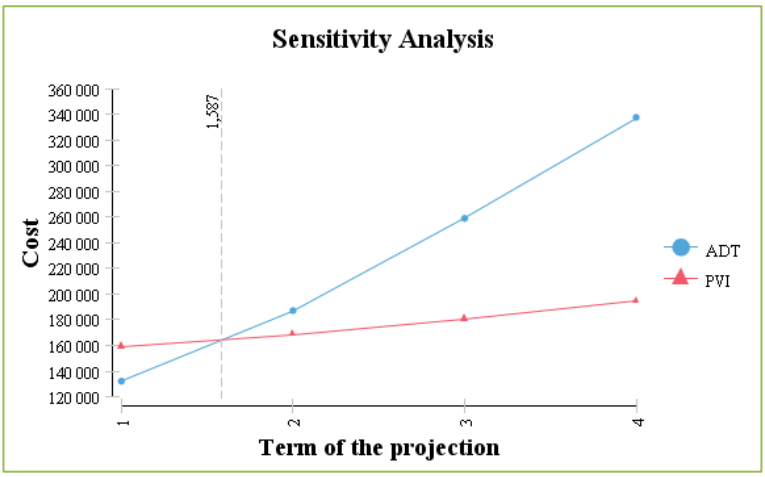


Figure 7.14: Measure of average cost when the duration of the study was measured at one year, two, three and four years

Source: Markov model dated 27 February 2012.

2. Up until 1.587 years, the incremental costs for PVI were greater than the incremental costs for ADT. From the start of the study, the incremental costs for PVI decreased and flattened out at two years, at well below R5 000. This can be accounted for by the fact that the main costs associated with PVI are incurred at the time of ablation. The converse is true for the ADT group, where the costs started at less than R5 000 and, over the four- year period, increased to close to R140 000 (Figure 7.15).

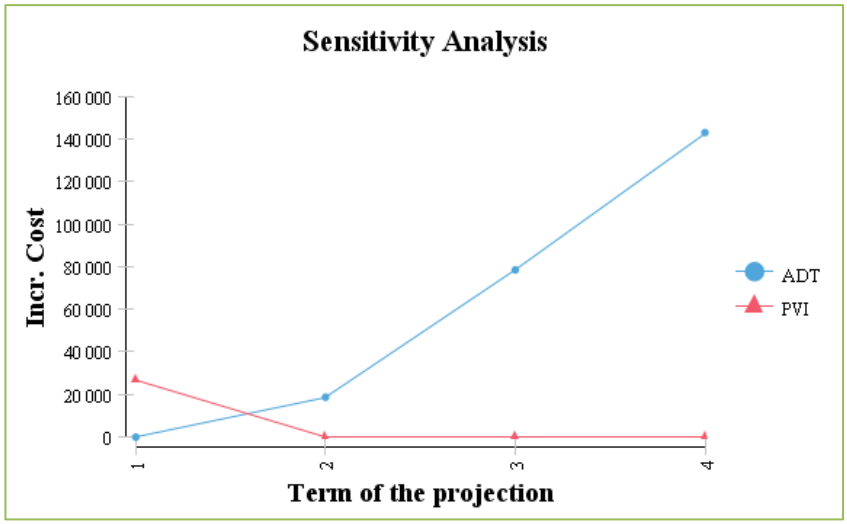


Figure 7.15: Measure of the incremental costs when the duration of the study was measured at one year, two, three and four years

Source: Markov model dated 27 February 2012.

3. Figure 7.16 is a measure of the incremental effectiveness when the duration of the study was measured at one year, two, three and four years. The incremental effectiveness decreased in both the ADT and the PVI group, but the decline in effectiveness in the ADT group was greater than that of the PVI group. The effectiveness plot lines diverged from the start of the study and

continued beyond two years. After two years, the graph in the PVI group appeared to remain unchanged. The decline in the ADT group was greater than the decline in the PVI group. From the results of the four-year APAF study, we know that the effectiveness declines further in both groups but that the decline is greater in the ADT group than in the PVI group.

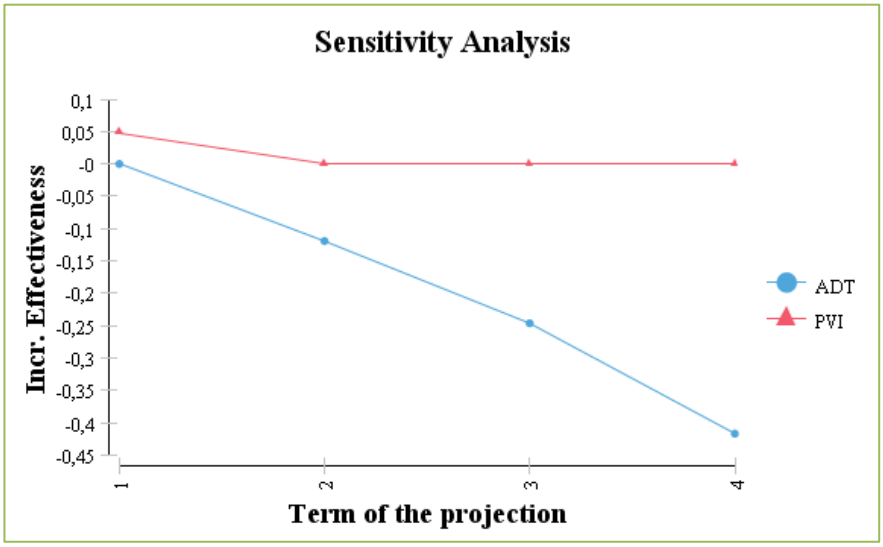


Figure 7.16: Measure of the incremental effectiveness when the duration of the study was measured at one year, two, three and four years

Source: Markov model dated 27 February 2012.

4. Figure 7.17 demonstrates the average cost-effectiveness at one, two, three and four years. Up until 1.587 years, ADT is, on average, more cost-effective than PVI. However, at 1.587 years, the costs break-even and, thereafter, PVI dominates ADT as being more cost-effective.

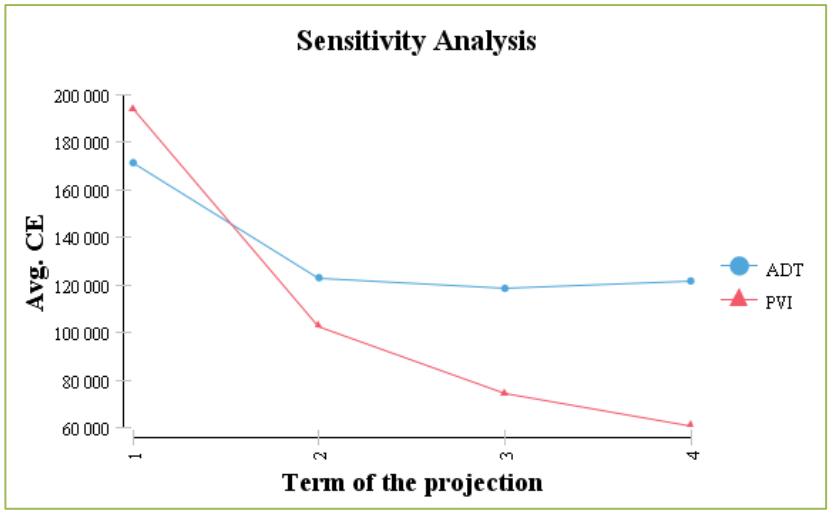


Figure 7.17: Measure of the average cost-effectiveness when the duration of the study was measured at one year, two, three and four years

Source: Markov model dated 27 February 2012.

5. The net monetary benefits (NMB) at a "willingness to pay" threshold of R120 000 shows that the ADT group starts at about -R40 000, compared to the PVI group, which starts at about -R60 000. At year three, the NMB for the ADT group has reached a value of zero but declines again at year four to about -R20 000. The PVI group changes from -R60 000 at the start of the study to about R190 000 by year four, with the break-even point at 1.387 years. (Figure 7.18).

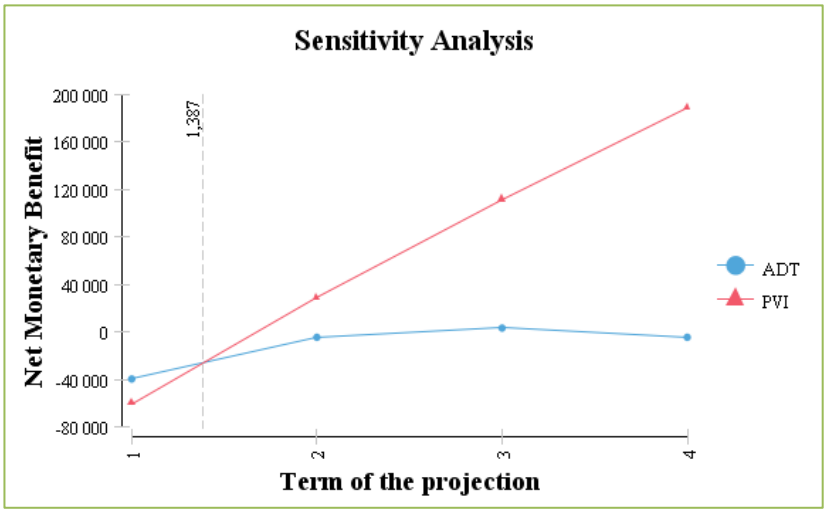


Figure 7.18: Measure of the net monetary benefits when the duration of the study was measured at one year, two, three and four years

Source: Markov model dated 27 February 2012.

Average length of stay in hospital (kAveLoS)

Based on two large published studies by Stewart *et al.* (2002) and Reynolds *et al.* (2007) it was established that the average length of stay in hospital for admission, where AF was the primary or secondary diagnosis, was 5.2 days. With this in mind, the author built the model with 5.2 days as the baseline value and a sensitivity analysis was performed at values of 20% below and 20% above the baseline. The findings are seen in Table 7.18 where, at the baseline of 5.2 days, PVI dominated ADT. If the length of stay was reduced by one day (-20%), it produced an ICER of R11 770. 80 indicating that PVI was more cost-effective, with a cost of R11 770 per QALY gained. When the length of hospital stay was extended by one day to 6.2 days (+20%), it was found that PVI completely dominated ADT.

Table 7.18: Sensitivity analysis of the average length of stay per hospital admission (kAveLoS)

Strategy	Variable	Cost	Eff	CE	IC	IE	ICER	Dominated
ADT	4.2 days	R164 544	1.53	107 866	0	0	0	
PVI	4.2 days	R165 900	1.64	101 120	R1 355	0.12	11770	
PVI	5.2 days	R168 437	1.64	102 667	0	0	0	
ADT	5.2 days	R187 357	1.53	122 821	R18 920	-0.12	-164295	(Dominated)
PVI	6.2 days	R170 973	1.64	104 213	0	0	0	
ADT	6.2 days	R210 170	1.53	137 775	R39196	-0.12	-340361	(Dominated)

Source: Markov model dated 27 February 2012.

In Figure 7.19 the χ-axis refers to the cost, where cost increases from left to right and the y-axis refers to effectiveness and increases from the bottom to top. ADT is represented by the blue triangle and is found in the bottom left quadrant and PVI, represented by the red square, is found in the top left quadrant. At 4.2 days, the cost of ADT was R164 544 or 0.8% lower than PVI at R165 900. However, the effectiveness at 4.2 days for ADT was 1.52 *vs*. 1.64 for PVI, or 7% lower for ADT.

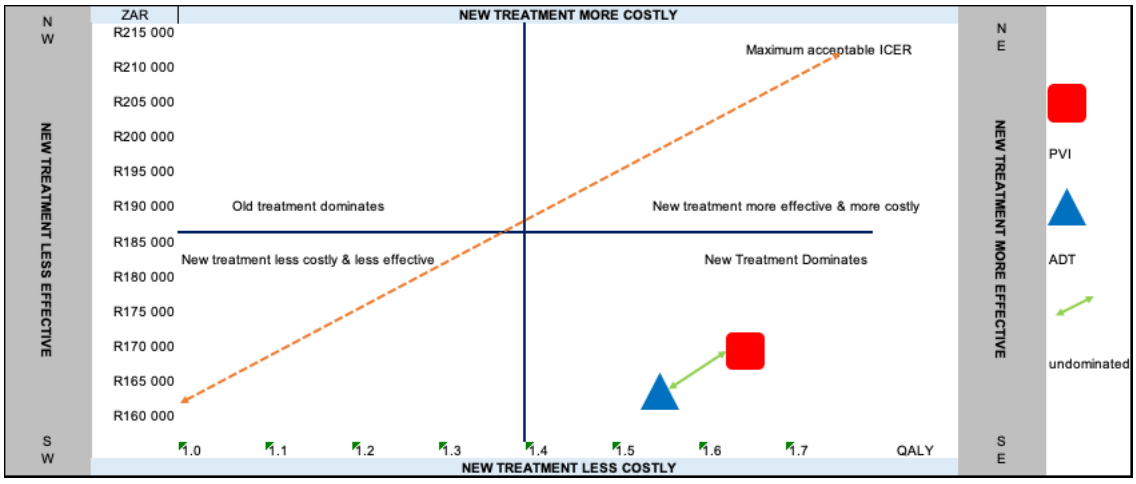


Figure 7.19: Cost-effectiveness of PVI *vs*. ADT with reference to the length of stay in hospital for AF episodes (measured at 4.2 days)

Source: Markov model dated 27 February 2012.

At the baseline value of 5.2 days, the ADT cost was 11% higher than that of PVI, but 7% less effective and, at 6.2 days, the cost of ADT was 22% higher than PVI but still 7% less effective. Therefore, PVI dominated ADT at both 5.2 days and 6.2 days and, at 4.2 days, had an ICER of R11 770. This finding is not unexpected, as we have seen from the large economic burden studies that almost 50% of the total cost of treating AF was allocated to hospitalisation.

When a sensitivity analysis was performed on the variable of the average length of stay in hospital, with two years as the baseline and with the variable decreased by 20% to 4.2 days or increased by 20% to 6.2 days, the following was found:

1. At 4.2 days the average cost for ADT was R164 544 and R165 900 for PVI. At 6.2 days the cost for ADT was R210 170 compared with R170 973 for PVI, indicating an average increase in cost of 28% for ADT compared with an average increase of only 3% for the PVI group. The break-even point was at 4.275 days (Figure 7.20).

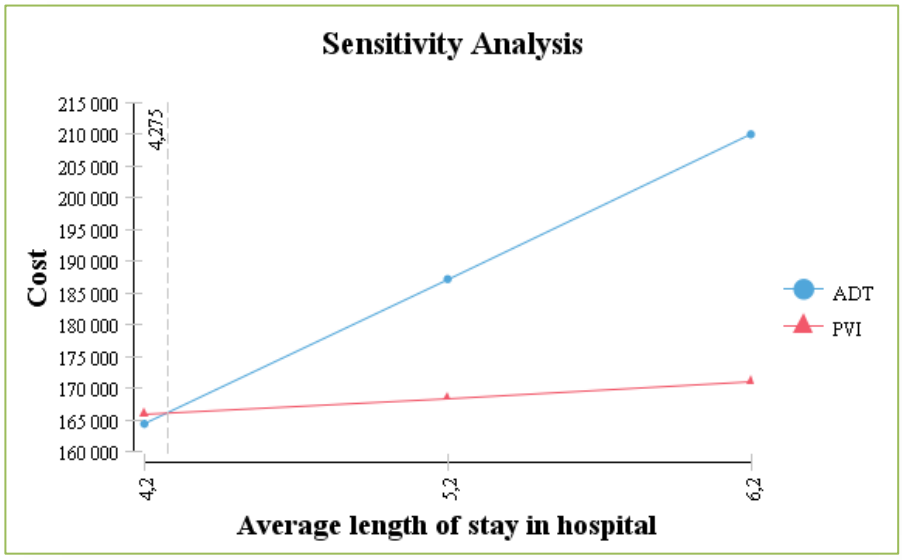


Figure 7.20: Measure of the cost-effectiveness based on the average length of stay in hospital for the treatment of the complications of AF

Source: Markov model dated 27 February 2012.

2. The incremental cost for PVI decreases as the number of hospital days increases from 4.2 days to 6.2 days, while the incremental costs for the ADT changes from less than R2 000 to R39 000 from 4.2 days to 6.2 days (Figure 7.21).

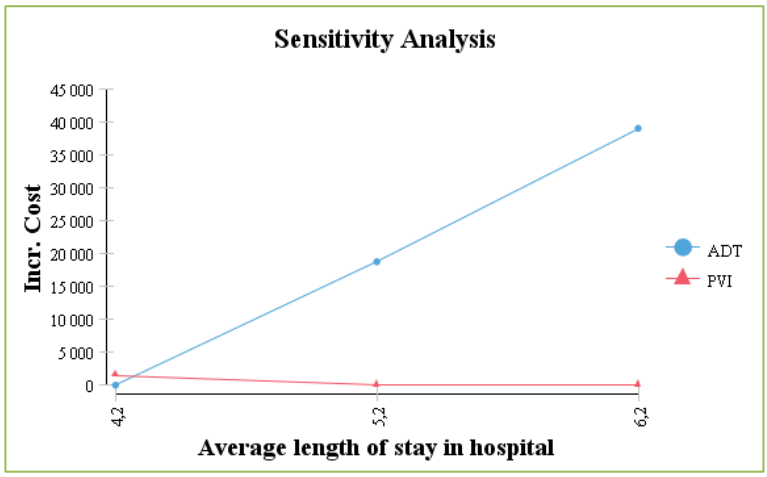


Figure 7.21: Measure of the incremental cost, based on the average length of stay in hospital for the treatment of the complications of AF

Source: Markov model dated 27 February 2012. Figure 7.22 demonstrates that changing the variable of average length of stay in hospital has no impact on the average effectiveness for either PVI or ADT.

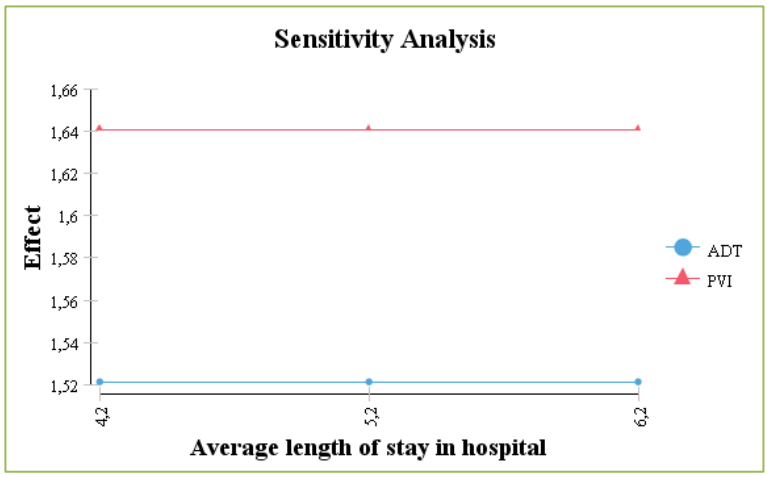


Figure 7.22: Average effectiveness of PVI and ADT when the variable average length of stay is changed by +20% and -20%

Source: Markov model dated 27 February 2012.

3. Figure 7.23 shows that, for both ADT and PVI, the incremental effectiveness decreases from 4.2 days to 5.2 days and remains unchanged from 5.2 days to 6.2 days. In both cases, PVI is more effective.

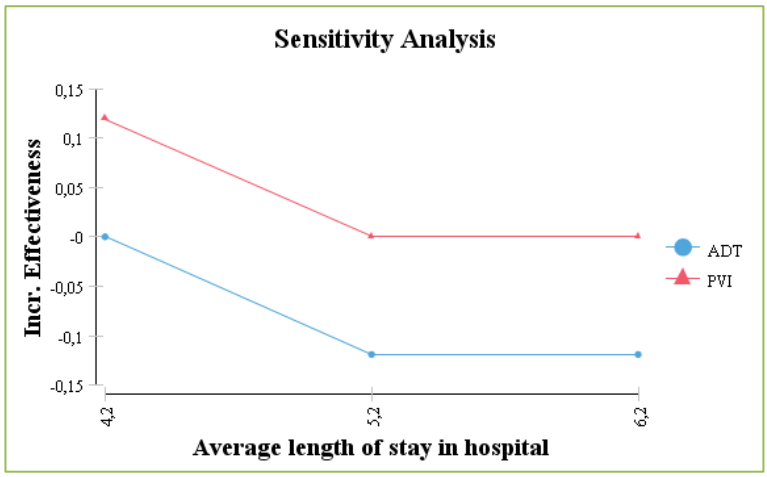


Figure 7.23: Measure of the incremental effectiveness based on the average length of stay in hospital for the treatment of the complications of AF

Source: Markov model dated 27 February 2012.

4. The incremental cost-effectiveness, as seen in Figure 7.24, indicates that, for PVI, there is little change in cost-effectiveness whether the length of stay is 4.2, 5.2, or 6.2 days. This is due to the fact that there are significantly fewer episodes of hospitalisation in the PVI group. The converse is true for the ADT group, where the incremental cost-effectiveness decreases as the length of stay increases from 4.2 days to 5.2 and finally 6.2 days.

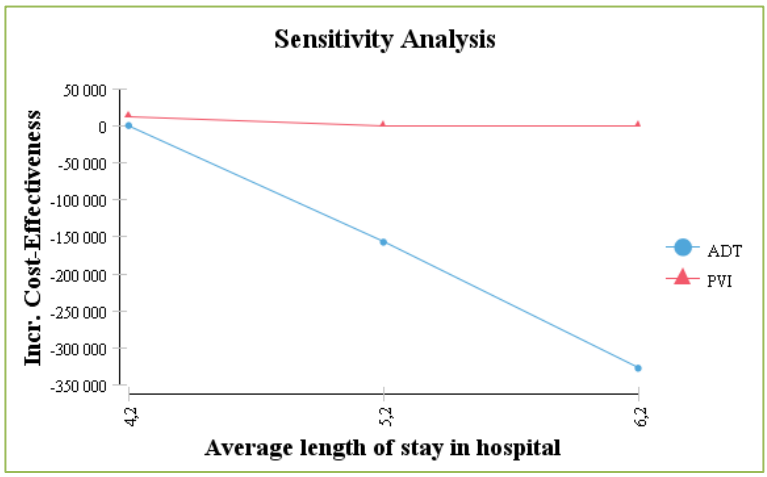


Figure 7.24: Measure of the incremental cost-effectiveness based on the average length of stay in hospital for the treatment of the complications of AF

Source: Markov model dated 27 February 2012.

5. The net monetary benefits (NMB) at a willingness to pay threshold of R120 000 shows that the PVI group started at 4.2 days at approximately R31 000 and declined by 19% to R25 000 at 6.2 days. At the baseline of 5.2 days, the NMB for PVI were approximately R29 000 (-6%). For the ADT group, the NMB at 4.2 days was R20000 and declined to -R27500 by 6.2 days, representing a decline of 238% (Figure 7.25).

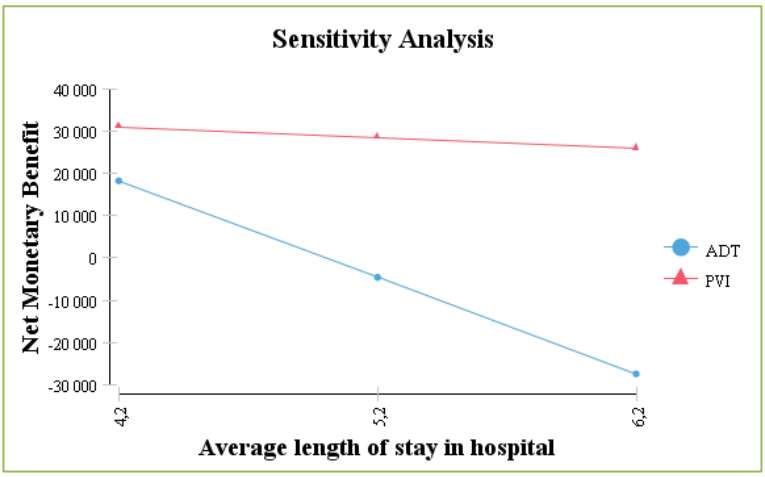


Figure 7.25: Measure of the net monetary benefits based on the average length of stay in hospital for the treatment of the complications of AF

Source: Markov model dated 27 February 2012.

Relative risk of dying on ADT vs. PVI for AF (rrADT)

The final sensitivity analysis that was performed was the relative risk of dying from ADT as tabulated in Table 7.19.

Table 7.19: Sensitivity analysis of the relative risk of death from ADT (rrADT)

Strategy	Variable	Cost	Eff	CE	IC	IE	ICER	Dominated
PVI	1.8	R168 437	1.64	102 667	0	0	0	
ADT	1.8	R187 560	1.53	122 641	R19 123	-0.11	-171858	(Dominated)
PVI	2.2	R168 437	1.64	102 667	0	0	0	
ADT	2.2	R187 357	1.53	122 821	R18 920	-0.12	-164295	(Dominated)
PVI	2.6	R168 437	1.64	102 667	0	0	0	
ADT	2.6	R187 155	1.52	123 002	R18 718	-0.12	-157226	(Dominated)

Source: Markov model, dated 27 February 2012.

The literature by Calkins *et al.* (2009) indicates that the treatment of AF with ADT has a 2.2 relative risk of death over PVI. Using relative risk of ADT of 2.2 as the baseline, a sensitivity analysis was run by changing the variable rrADT by +20% and -20%. For all three scenarios, ADT was dominated by PVI, which was therefore more cost-effective.

In Figure 7.26 the χ-axis refers to the cost, increasing from left to right, and the y-axis refers to effectiveness and increases from the bottom to top. ADT is represented by the blue triangle in the bottom right quadrant. The red square, representing PVI, is found in the top left quadrant. ADT has a cost of between R185 000 and R190 000 per patient, with an effectiveness of approximately 1.53 QALY. PVI has a cost of between R165 000 and R170 000 per patient, with an effectiveness of 1.65 QALYs. ADT is encircled by a yellow dot and is therefore dominated by PVI for the variable of rrADT.

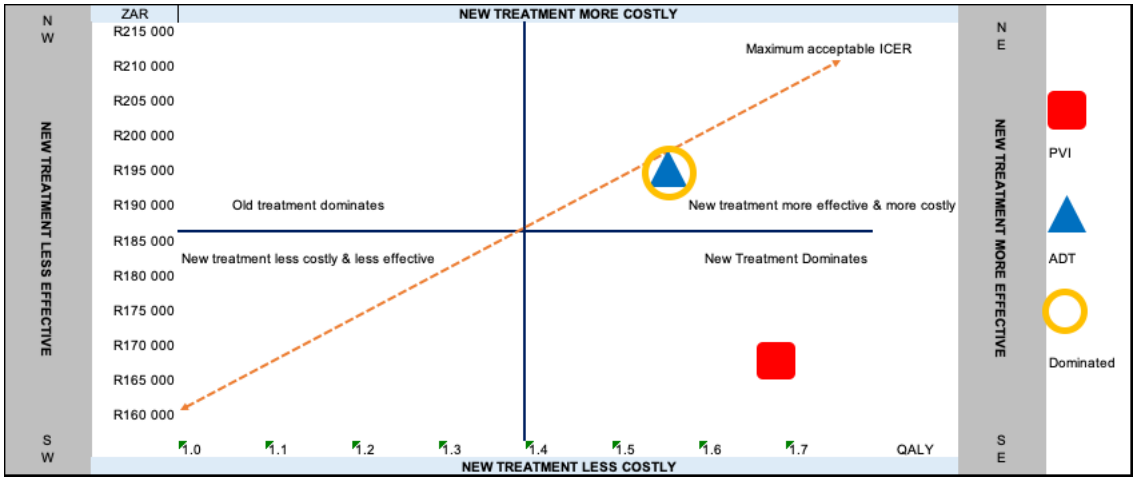


Figure 7.26: Cost-effectiveness of PVI *vs*. ADT with reference to the relative risk of dying from ADT (rrADT)

Source: Markov model, dated 27 February 2012.

For all the variables tested in the sensitivity analysis for rrADT the cost of ADT was 11% higher than PVI and 7% less effective. The full sensitivity analysis is discussed below with reference to Figures 7.29 to 7.34.

The average cost for ADT was R188 000, compared with PVI at R168 000. ADT shows a small decline in cost between the baseline of 2.2 and 2.6, as indicated in Figure 7.27. The same is noted in Figure 7.28 when testing for incremental cost.

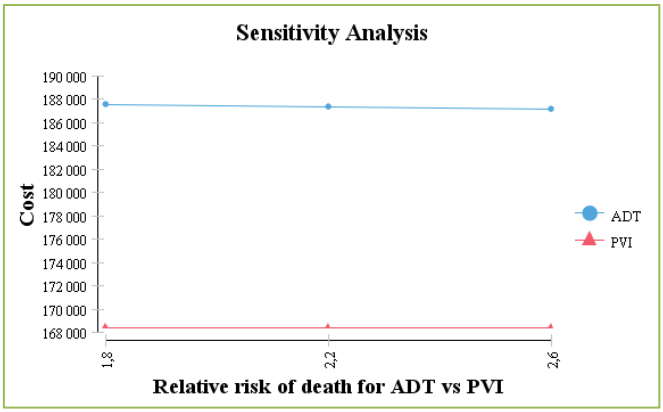


Figure 7.27: The average cost for ADT and PVI when testing for the relative risk of death between ADT and PVI

Source: Markov model, dated 27 February 2012.

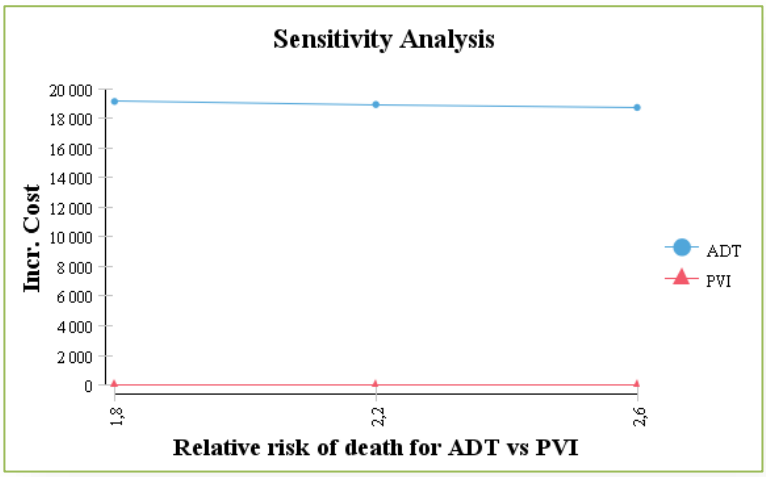


Figure 7.28: The incremental cost for ADT and PVI when testing for the relative risk of death between ADT and PVI

Source: Markov model, dated 27 February 2012.

Figure 7.29 explores the impact that the rrADT had on the effectiveness of both ADT and PVI. There was no change in effectiveness for the PVI group and a -1% change for the ADT group.

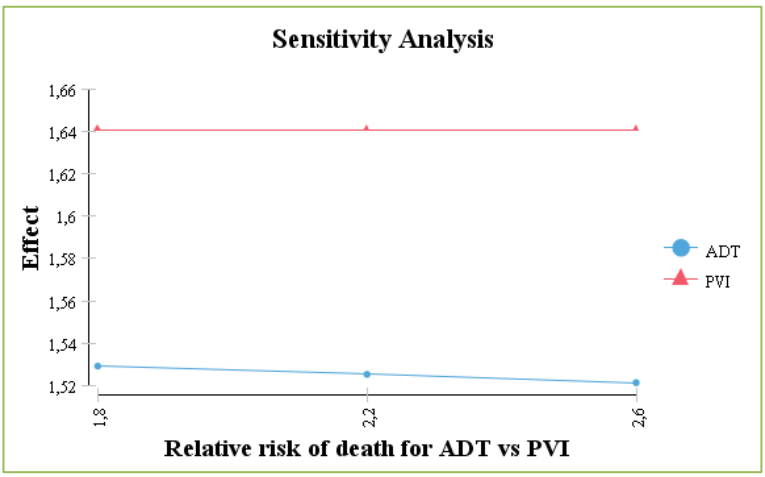


Figure 7.29: Measuring the effectiveness for ADT and PVI when testing for the relative risk of death between ADT and PVI

Source: Markov model, dated 27 February 2012.

The incremental effectiveness was unchanged in the PVI group as the rrADT changed, while the incremental effectiveness declined by 7% in the ADT group (Figure 7.30).

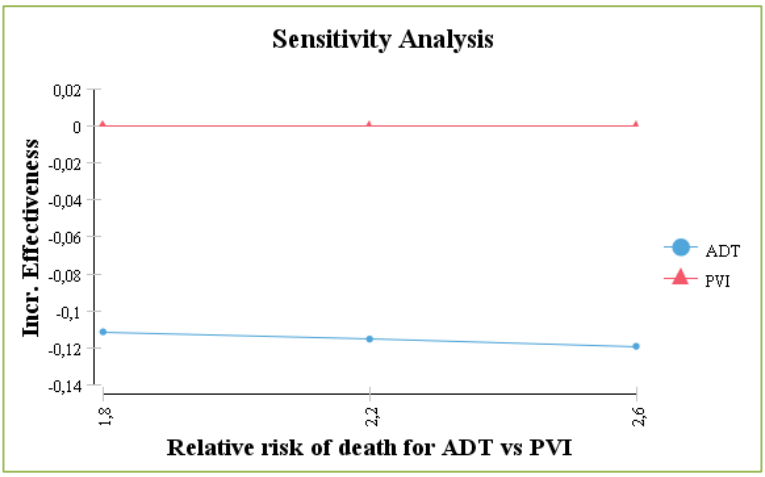


Figure 7.30: Measuring the incremental effectiveness for ADT and PVI when testing for the relative risk of death between ADT and PVI

Source: Markov model, dated 27 February 2012.

The incremental cost-effectiveness (ICER) was unchanged in the PVI group. The ICER for the ADT group improved by 9% when the relative risk of dying increased from 1.8 to 2.6. This indicates that, for the ADT group, the more people on ADT who die, the more cost-effective the treatment option becomes (Figure 7.31).

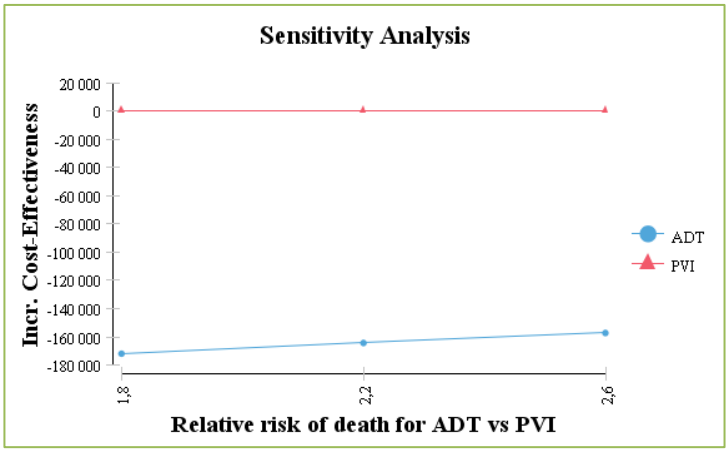


Figure 7.31: Measuring the incremental cost-effectiveness for ADT and PVI when testing for the relative risk of death between ADT and PVI

Source: Markov model, dated 27 February 2012.

Figure 7.32 demonstrates that for the PVI group, the net monetary benefits (NMB) remained at R28 000 in spite of the changes in the rrADT from 1.8 to 2.2 and, finally, to 2.6. The NMB for the ADT group declined from a negative R4 000 to a negative R4 500 from a relative risk of 1.8 to 2.2 and 2.6. Again, this is a small change in the NMB for the ADT group, as money is saved with each patient who dies.

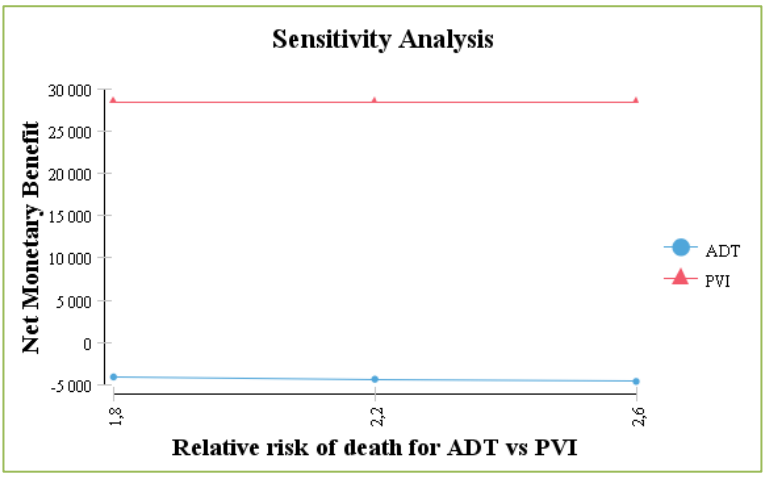


Figure 7.32: Measuring the net monetary benefits (NMB) for ADT and PVI when testing for the relative risk of death between ADT and PVI

Source: Markov model, dated 27 February 2012.

Finally, a series of one-way sensitivity analysis was conducted on key parameters within the model to test for variation in results associated with parameter change. These results are graphically represented as a Tornado diagram in Fig 7.33 where ranges of results associated with particular parameters are staked according to descending variation. The one-way sensitivity analysis showed that the model was reasonably robust to the cost estimations of medicines and quality of life valuations for atrial fibrillation.

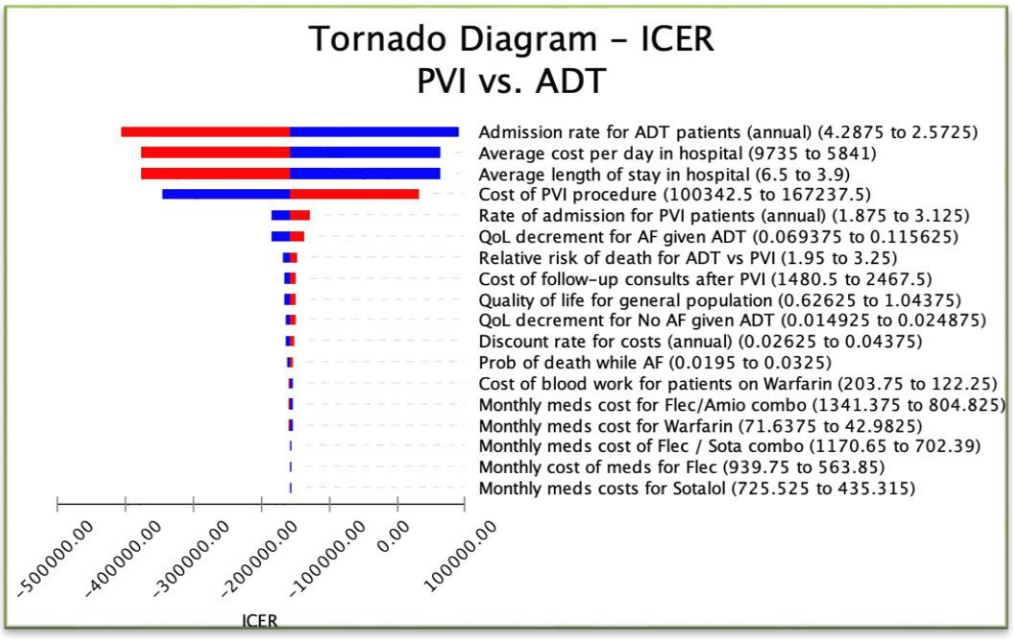


Figure 7.33: Tornado Diagram-ICER PVI vs. ADT

Source: Model 25th August 2019

The model was most sensitive to variations in annual admission rate for ADT patients, length and cost of stay in hospital for an AF-related event and the cost of the PVI procedure. However, at the

extreme of the sensitivity analysis the predicted ICER did not exceed R100,000/QALY for PVI vs ADT, providing reasonable confidence in the results of the analysis. A one-way sensitivity analysis is limited in that it assumes parameter variation ceteris paribus when in practice certain parameters are likely to vary in correlation i.e. if medicine costs are greater, cost of hospital stay is also likely to be greater. A gold standard sensitivity analysis would have included sensitivity analysis where all parameters are varied across a given distribution, however, given the availability of data and resources available for the analysis the authors have provided a one-way analysis to provide indicative understanding of the implications of parameter variation

7.5 CONCLUSION

The 2010 ACC/AHA/European guidelines for AF, which were published in the *European Heart Journal* (2010: 2369-2429), recommend anti-arrhythmic drug therapy before catheter ablation for symptomatic paroxysmal and persistent AF in patients with relevant organic heart disease. The guidelines cite the fact that successful ablation is more difficult to achieve and that patients may require more than one procedure. Results of meta-analysis and randomised trials, comparing ablation with anti-arrhythmic drugs, have found that, although medical therapy remains the foundation of the treatment of AF, catheter ablation is assuming an increasingly greater role. Currently, the guidelines are as follows:

> Catheter ablation for paroxysmal AF should be considered in symptomatic patients who have previously failed a trial of anti-arrhythmic medication. This is based on IIa evidence and level A evidence. Class II is determined by the fact that there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure, and Class IIa suggests that there is a weight of evidence/opinion in favour of usefulness/efficacy. Level A evidence refers to the fact that there is data derived from multiple randomised clinical trials or meta-analyses, which is favourable over single centre studies, or non-randomised studies.
>
> Ablation of persistent symptomatic AF that is refractory to anti-arrhythmic drug therapy should be considered as a treatment option (Class IIa) with level of evidence B, where the level of evidence B refers to data derived from a single randomised clinical trial or large non-randomised studies.

Recent reports of meta-analyses cited in the 2010 ACC/AHA guidelines showed that PV isolation for paroxysmal or persistent AF was associated with markedly increased odds ratio of freedom from AF at one year.

The body of evidence is increasing in favour of PVI for the treatment of paroxysmal AF. The results from this study, which reviewed a number of clinical studies and meta-analysis for both ADT therapy and PVI for treating paroxysmal AF, has shown that PVI is more effective in the following categories:

1. Effectiveness of therapy: At the end of two years there were more patients who were initially randomised to PVI free from AF compared with the patients who were initially randomised to ADT.
2. There were fewer hospitalisations among the patients who were randomised to PVI compared with the ADT group.
3. Although there were adverse advents in both treatment arms, the adverse events in the PVI group were of a more serious nature than in the ADT group. However, the total adverse events in the PVI group were less than 5%, while the adverse events in the ADT group were close to 30%.
4. Treating patients with ADT had a 2.2 relative risk of death over two years compared with treating patients with PVI.
5. In all the categories tested, i.e. cost, effectiveness, QALY, duration of hospital stay, average length of stay in hospital and relative risk of death and net monetary benefit, PVI was more cost-effective compared to ADT. PVI dominated ADT in all but two categories.

Based on these results, there are several issues which should be addressed in South Africa. The 2010 ACC/AHA/European guidelines for AF suggest that successful ablation is more difficult to achieve and that patients may require more than one procedure. There are a limited number of electrophysiologists in South Africa who perform this procedure and it should be ensured that these physicians receive adequate training to overcome the concerns cited by the ACC/AHA/European guidelines. A second issue to address is to educate the patients and referring physicians about the benefits of each therapy option available. Finally, the funders need to be made aware of the significant cost and effectiveness benefit available to their patients if they receive the correct treatment, performed in the hands of a skilled operator. This could not only save a lot of money but also have a positive impact on many patients' lives.

Chapter 8 will summarise this study, recognise the limitations of the study and make recommendations for further research in this field.

A summary of this chapter, carrying the title 'Cost-effectiveness of Radiofrequency Ablation vs Anti-arrhythmic Drugs for PAF', has been prepared for submission as a journal article. This is attached to this dissertation as Annexure B.

CHAPTER 8: CONCLUSION

8.1 OBJECTIVES

The primary objective of this study was to measure the cost-effectiveness of radiofrequency catheter ablation compared with anti-arrhythmic drugs for the treatment of paroxysmal atrial fibrillation in the South African population. The secondary objectives of this study were to explore the various aspects of healthcare expenditure in South Africa and to understand how health technology is defined. Together with this the review of available literature indicated the need to analyse the rising costs in South African healthcare expenditure and, in particular, costs related to treatment of various cardiac and cardiovascular diseases.

These objectives were met in this study, as the principles of health economics were introduced, and the healthcare sector in South Africa was explored and compared with other developed and developing nations. The study determined a value of "willingness to pay" within the context of one of the complications of AF, namely congestive heart failure. All the current therapy options were scrutinised for efficacy, practicality, complication rate and side effects, and RFA ablation was determined to be an appropriate alternative to ADT. Finally, real patient cost data were collected and used in the cost-effectiveness model.

8.2 SUMMARY

Atrial fibrillation is a debilitating disease with increased mortality and is a major cause of stroke and worsened heart failure which adversely influence the quality of life of patients who suffer from the disease. The "gold standard" of treatment in patients with symptomatic AF remains anti-arrhythmic drugs and anti-coagulation. However, some drug therapies – either as single agents or in combination - are at best ineffective, with efficacy reported at two to four years of between 12% and 24%. At worst, they are associated with a high incidence of adverse events and a relative risk of death compared to catheter ablation of 2.2.

Pulmonary vein isolation by means of radiofrequency ablation is associated with less AF recurrence, improved quality of life, and a lower hospitalisation rate during 48 months' follow-up. In addition, the benefits of restoring sinus rhythm may be greater in younger patients as doing so may prevent progressive atrial re-modelling that leads to chronic AF (Wazni *et al.,* 2005: 2637). Furthermore, Wazni *et al.* (2005) cite Corley *et al.* (2004). In an analysis examining the predictors of mortality, they found that sinus rhythm was associated with a 47% reduction in the risk of death, whereas the use of anti-arrhythmic drug therapy was associated with a 49% increase in mortality. Based on this, one may pose the question as to whether applying a treatment regime which restores sinus rhythm while simultaneously avoiding the deleterious effects of anti-arrhythmic drugs would improve survival. In this case, PVI may be such a treatment regimen. Pappone *et al.* (2011) found that AF progression from

paroxysmal to persistent and permanent AF was higher in the ADT group than the PVI group, and suggest that the early use of PVI may be of benefit to avoid and limit arrhythmia recurrence and progression.

At present PVI is reserved for patients who have failed medical therapy. Reasons for this are, firstly, the concern about the complications associated with the catheter ablation procedure and, secondly, the costs associated with the procedure. Cappato *et al.* (2010) published their data from a worldwide survey of more than 8 700 AF ablation procedures. They reported an overall major complication rate of 4% (Cappato *et al.*, 2010). The most serious complications resulting in permanent disability were uncommon. These included death (0.05%) and stroke (0.28%). These data were updated in 2010 and a total of 16 309 procedures done between 2003 and 2006 were reported on. What was important to note was that, in the 2005 survey, the typical patient age was between 18 and 82 years of age, while the 2010 survey included patients between 15 and 90 years of age. Also, important to note was the fact that, in the 2005 survey, the average number of procedures per patient was 1.5, while, in 2010, the average number of procedures was 1.3, a decrease of 13%. The overall success rate in 2005 was listed at 75.5% and this had increased to 80% by 2010, an improvement of 6%. The greatest success rate was found in the patients with paroxysmal AF where the success rate was recorded as 84%. The complication rate in the 2010 survey was a total of 4.5% with death accounting for 0.15%, tamponade 1.31%, stroke 0.23% and TIA, 0.71%.

The conclusions from the worldwide survey in 2010 indicate that not only is catheter ablation being increasingly offered to patients with AF, but it is also being offered to sicker and older patients with AF. Radiofrequency remains the dominant energy form used for catheter ablation, with 90% of the procedures reported on in the worldwide survey having used RF ablation. While the success rate of the procedure seems to increase with experience, this increase in experience does not appear to translate to a decrease in the complication rate.

Based on these data and the fact that other meta-analyses indicate that catheter ablation had more than a twofold greater efficacy at twelve months for maintaining sinus rhythm than ADT, that patients treated with catheter ablation had a two-thirds reduction in hospitalisation for cardiovascular causes, and finally that catheter ablation had a procedural complication rate at least equal to the major complications rate associated with high-risk percutaneous coronary interventions, the author feels that catheter ablation for atrial fibrillation should be considered as first-line therapy for patients with symptomatic paroxysmal atrial fibrillation as it is not only more efficacious but also more cost-effective in the South African situation.

8.3 STUDY LIMITATIONS

This study has several limitations in spite of the fact that it has examined many different sources of literature, including randomised controlled trials, meta-analysis, internet sites, interviews and personal experience. As with any research, it is subject to several potential biases. These will be described below.

Firstly, the model is based on a randomised, controlled trial from a single centre. Although randomised, controlled studies are the benchmark for the determination of experimental effect, they may not fully represent patients in everyday practice in the real-world environment. The centre where the study was performed is a high volume centre and a centre of excellence and one would require the same technical skill in everyday practice to achieve the same results for what may be considered very complex catheter ablation techniques. However, it should be noted that the results from the 2005 and 2010 worldwide surveys on catheter ablation, which represent the “real-world” practice, do not yield results that are significantly different from the randomised control trials used in this study.

Secondly, the data collected and used in the model were from the private sector only. As discussed earlier, only 15% of the South African population have access private healthcare and, because we do not have specific costs for hospitalisation *etc.* in the public sector, it would be difficult to calculate the costs in the public sector. While this is a limitation of the study, the positive results of the study indicate that the public sector should investigate the option of treating their AF patients with catheter ablation to drive and improve efficiency and efficacy of treatment for the public sector patients.

Thirdly, the model is based on AF in the ageing population. In spite of the fact that there are as many as 387 000 South Africans who are possibly affected by AF as part of the ageing process, this study does not address patients with AF as result of rheumatic heart disease. There are no studies that examine the outcome of treating patients with rheumatic atrial fibrillation with catheter ablation in spite of the fact that these patients generally develop AF at a much younger age and have the same or greater risk of stroke and heart failure.

One of the most severe and debilitating complications of AF is undoubtedly stroke. Many researchers confirm that stroke in patients with AF is associated with a higher mortality and morbidity rates (Wazni *et al.*, 2005: 2635). One of the limitations of this study was that it did not identify stroke as an independent health state. This was largely due to the fact that it was difficult to find patient-specific details for patients who suffered stroke as result of AF. While the cardiologist and electrophysiologists are the obvious persons to manage patients with heart failure and recurrence of AF, patients presenting with stroke may be referred to a general physician or neurologist and, in fact, the patient or family may not even associate the stroke with AF.

In spite of this limitation, the author believes that adding stroke to the model as a separate health state would have added extra cost to the ADT arm, where more strokes are likely to occur. Thus, it would not have changed the cost-effectiveness model in favour of the ADT arm.

8.4 CONSIDERATIONS FOR THE SOUTH AFRICAN SOCIETY

One of the major considerations to be made when considering South African society as a whole is the fact that training electrophysiologists is both a timely and expensive process. A cardiologist, who then further specialises in electrophysiology, has undergone the following training: six years of general university education plus an additional five years in internal medicine, three extra years in cardiology, and finally an additional two years in electrophysiology. This is a total of eighteen years of education. When compared with the training of general practitioners (six years plus two years community service), training electrophysiologists requires an additional ten years of training. All of the training up to the level of cardiologist occurs in the public sector. South Africa has only trained one electrophysiologist in the country in the past decade; this was done at the University of Cape Town and Groote Schuur Hospital. This was made possible by an education grant offered by Life Healthcare and extra funding through the assistance of companies like Biosense Webster and Medtronic. A number of other South African physicians have been trained in electrophysiology, but it had required them to move to Europe, Canada or the USA to be trained. Funding for this has been a combination of self-funding and/or educational grants offered by industry, for example Biosense Webster, Boston Scientific, Biotronik, Medtronic and St Jude medical.

As a result of this research and work done within the EP community, Biosense Webster has committed more than R2 million towards the training of electrophysiologists in South Africa in the past four years and is currently working with the academic institutions to set up education funds for the next few years.

Besides the input from the industry, the Discovery Foundation was set up in 2006 as an independent trust and is investing over R100 million in grants towards developing South Africa’s scarce specialist healthcare resources. Over the past six years, the Discovery Foundation has already committed over R80 million in grants supporting over 150 specialists in training, and eleven high-achieving healthcare institutions in South Africa.

The Discovery Foundation Awards include scholarships, bursaries and research fellowships, as well as support for teaching and research institutions. It is expected to support the training of new medical specialists for the public sector over a ten-year period, thereby increasing the number of sub-specialists in the country (Discovery, 2014).

The Life Healthcare Foundation in partnership with the College of Medicine SA, has awarded a more than thirteen bursaries to doctors to sub-specialize. As mentioned above, one of these bursaries was awarded to a cardiologist to specialize in electrophysiology. Life Healthcare has committed to

spending R13 million over six years (a total of R78 million), which will cover the training of 32 doctor sub-specialists (The Life Healthcare Foundation, 2014).

8.5 RECOMMENDATIONS

A number of recommendations arise from this study, not only from the perspective of further research, but also pertaining to “real world” policies. These recommendations are as follows:

1. Data needs to modelled out to five years to show the long-term efficacy of the two treatment options. This data will also help clarify if indeed the Pappone *et al.* (2011) study, which showed less progression in AF patients, treated with ablation, from paroxysmal to persistent and permanent.

2. A further recommendation is to include the cost of stroke in the model. To this end, it might be worthwhile forming a collaborative group of interested parties to facilitate the capture of actual patient data with regard to cost and complication rates.

3. While hundreds of thousands of patients are at risk of developing non-rheumatic AF, less than 750 patients are treated with ablation each year. This should be highlighted to referring physicians and the medical aids, who are not offering their patients the best alternatives.

4. Finally, the author would like to encourage participation of the local electrophysiology community, together with the Department of Health and the medical industry to initiate and complete a pilot study looking at the indigent population in South Africa who have rheumatic heart disease and AF. A number of issues should be studied:

    - The burden of AF in the South African population as result of rheumatic heart disease.
    - The efficacy of catheter ablation in these patients at one year, two years and long-term for maintaining sinus rhythm.
    - The cost-effectiveness of catheter ablation in this patient population.

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APPENDICES

APPENDIX A:

WHO regions

A.1 African Region

AFR D				
Algeria	Angola	Benin	Burkina Faso	Cameroon
Cape Verde	Chad	Equatorial Guinea	Gabon	Gambia
Ghana	Guinea	Guinea-Bissau	Liberia	Madagascar
Mali	Mauritania	Mauritius	Niger	Nigeria
Sao Tome and Principe	Senegal	Seychelles	Sierra Leone	Togo

AFR E				
Botswana	Burundi	Swaziland	Congo	Côte d'Ivoire
Uganda	Eritrea	Ethiopia	Kenya	Lesotho
Malawi	Mozambique	Namibia	Rwanda	South Africa
Central African Republic	Democratic Republic of Congo	United Republic of Tanzania	Zambia	Zimbabwe

A.2 Eastern Mediterranean Region

EMR B				
Bahrain	Cyprus	Tunisia	Jordan	Kuwait
Lebanon	Saudi Arabia	Oman	Qatar	
Syrian Arab Republic	Libyan Arab Jamahiriya	United Arab Emirates	Iran, Islamic Republic of	

EMR D				
Afghanistan	Djibouti	Egypt	Iraq	Morocco
Pakistan	Somalia	Sudan	Yemen	

A.3 European Region

EUR A				
Andorra	Austria	Belgium	Croatia	Switzerland
Denmark	Finland	France	Germany	Greece
Iceland	Ireland	Israel	Italy	Luxembourg
Malta	Monaco	Netherlands	Norway	Portugal
San Marino	Slovenia	Spain	Sweden	
United Kingdom	Czech Republic			

EUR B				
Albania	Armenia	Azerbaijan	Bosnia and Herzegovina	Bulgaria
Georgia	Kyrgyzstan	Poland	Romania	Slovakia
Tajikistan	Turkey	Turkmenistan	Uzbekistan	Yugoslavia
The former Yugoslav Republic of Macedonia				

EUR C				
Belarus	Estonia	Hungary	Kazakhstan	Latvia
Lithuania	Republic of Moldova	Russian Federation	Ukraine	

A.4 Region of the Americas

AMR A		
Canada	Cuba	United States of America

AMR B				
Antigua and Barbuda	Argentina	Bahamas	Barbados	Belize
Brazil	Chile	Colombia	Costa Rica	Dominica
Jamaica	El Salvador	Grenada	Guyana	Honduras
Suriname	Mexico	Panama	Paraguay	Saint Lucia
Uruguay				
Dominican Republic	Venezuela, Bolivarian Republic of	Saint Kitts and Nevis	Saint Vincent and the Grenadines	Trinidad and Tobago

AMR D				
Bolivia	Ecuador	Guatemala	Haiti	Nicaragua
Peru				

A.5 South-East Asian Region

SEAR B				
Indonesia	Sri Lanka	Thailand	Timor-Leste	

SEAR D				
Bangladesh	Bhutan	India	Maldives	Myanmar
Nepal	Democratic People's Republic of Korea			

A.6 Western Pacific Region

WPR A				
Australia	Brunei Darussalam	Japan	New Zealand	Singapore

WPR B				
Cambodia	China	Cook Islands	Fiji	Kiribati
Lao People's Democratic Republic	Malaysia	Marshall Islands	Micronesia, Federated States of	Mongolia
Nauru	Niue	Palau	Papua New Guinea	Philippines
Republic of Korea	Samoa	Solomon Islands	Tonga	Tuvalu
Vanuatu	Viet Nam			

APPENDIX B:

List of electrophysiologists interviewed

Name	Hospital	Date of interview	Personal/ Telephonic	Number of years in practice	Number of PVI per year
Dr. D. Milne	Vincent Pallotti Cape Town	8/9/2011	Telephonic	17	0
Dr. R Gopal	Panorama Cape Town	18/10/2011	In person	5	75
Dr. H. Janse Van Rensburg	ZAH Pretoria	No response	NR	NR	NR
Dr. F. Lorgat	CBMH Cape Town	No response	NR	NR	NR
Dr. P. Obel	Milpark Johannesburg	18/8/2011	In person	35	30
(The late) Prof. A. Okreglicki	GSH Cape Town	18/8/2011	Telephonic	16	10
Dr. A Stanley	Sunninghill Johannesburg	15/8/2011	In person	22	30 to 50
Dr. A. Thornton	Sunninghill Johannesburg	16/8/2011	In person	16	30 to 40
Dr. B. Vezi	Ethekwini Durban	18/8/2011	Telephonic	1	7
Dr. M Alison	Sunninghill Johannesburg	17/8/2011	In person	5+	10

APPENDIX C:

Sample questionnaire: South African Electrophysiology Practice

PVI for treatment of AF for patients with PAF or persistent AF

Name of Physician	
Hospital	
Date of Interview	
Type of interview	
Practicing as EP in years	
Approximate PVI per year	

1.Type of Procedure		
	Yes	**No**
3 D mapping		
Conventional		
Cryoablation		
PVAC		

2. First Consultation		
	Yes	**No**
ECG/Stress ECG		
Echo		
24 hour Holter		
Other		
Possible codes used		
1231/1233/1235		
3620/3621/3622		
1238/1239		

3. Bloods		
	Yes	**No**
U& E		
FBC		
TSH		
Pro BNP		
INR		
Other		
LFT		

4. Which AAD, ADT do you typically use?		
	Yes	**No**
Warfarin		
Sotalol		
Amiodarone		
Flecainide		
Propafenone		
Digoxin		
Diltizem		
Other		
Verapamil		
B Blocker		
Amiodarone	**Dose**	**Number of weeks**
	800mg	
	600mg	
	400mg	
	200mg	

5. Cardioversion		
	Yes	**No**
TEE		
Admit CCU		
Admit Ward		
Outpatient/casualty/non-invasive room		
Anaesthetic/test		
Awake Sedation		
Bloods INR		
U&E		
Other Clexane		

6. PVI (between 1-4 times)		
	CCU/HC	**Ward**
Admission		
Days average stay		
CT Scan		
Average Theatre time		
Anaesthetist		
Awake Sedation		
TEE		
Bloods U&E		
FBC		
INR		
Other tests		
TSH, free T4		
Codes for charging	**Code**	**Number of times charged**
Admission charge	0173	
TEE	3636	
TEE	3637	
EP study	1257	
Transseptal	1251	
PVI mapping	1261	
PVI ablation	1262	
Other		

7. Recurrent AF for Cardioversion		
	Yes	**No**
TEE		
Admit CCU		
Admit Ward		
Outpatient/casualty/Invasive room		
Anesthetic/tist		
Awake Sedation		
Bloods U&E		
INR		
TSH free T4		
Other tests		

8. Recurrent PVI (if different to initial PVI)		
	CCU/HC	**Ward**
Admission		
Days average stay		
CT Scan		
Average Theatre time		
Anaesthetist		
Awake Sedation		
TEE		
Bloods U&E		
INR		
TSH and free T4		
Other tests		
Codes for charging	**Code**	**Number of times**
Admission charge	0173	
TEE	3636	
TEE	3637	
EP study	1257	
Transseptal	1251	
PVI mapping	1261	
PVI ablation	1262	

9. Follow-up after PVI		
	Yes	**No**
1 week/2 weeks /3 weeks		
1 month		
3 months		
6 months		
9 months		
12 months		
18 months		
24 months		
Annually		

10. At Follow-up after PVI		
	Yes	**No**
Consultation		
Echo		
ECG		
Holter		
Bloods	U&E and INR	
Other	LFT & TSH if on Amiodarone	

11. Recommended INR testing		
	X weeks/months	
1x week		
1x every two weeks		
1x month		
Other		
Other		
Total INR tests per year =		

APPENDIX D:

Results of interviews with South African electrophysiologists

PVI for treatment of AF for patients with PAF or persistent AF

Demographics				
Type of Interview	P	60%	T	40%
Mean Years in Practice	17.8	Range	1-35	
Average Number of PVI's	24	Range	7-50	

Type of procedure										
3D mapping		X	X	X	X		X	X	NR	NR
Conventional no 3D mapping									NR	NR
Cryoablation	X	X	X		X		X	X	NR	NR
PVAC					X				NR	NR

First Consultation										
ECG/Stress ECG 1231/1233/1235	XXX	XXX	X	XXX	X	XXX	XXX	XXX	NR	NR
Echo 3620/3621/3622	XX	XXX	XX	XXX	XXX	XXX	XXX	XXX	NR	NR
24 hour Holter 1238/1239	XX	XX		50%	30%	50%	50%	XX	NR	NR
Other:									NR	NR

Bloods at first consultation										
U& E	X	X	X	X	X	X	X	X	NR	NR
FBC	X	X	X	X	X		X	X	NR	NR
TSH	X	X	X	X	X	X	X	X	NR	NR
Pro BNP	X	X					50%		NR	NR
INR	X	X	X	X	X	X	X	X	NR	NR
Other							XX	X	NR	NR
LFT				X				X	NR	NR

Cardioversion										
TEE	OE	X	OE	OE	OE		X	OE	NR	NR
Admit CCU	X	X		X	X	X	X	X	NR	NR
Admit Ward			X						NR	NR
Outpatient/casualty/non-invasive room	X	X		X			X	X	NR	NR
Anaesthetic/tist		X		X			50%		NR	NR
Awake Sedation	X		X		X		50%	X	NR	NR
Bloods INR	X	X	X	X	X	X	X	X	NR	NR
U&E	X	X	X	X	X		X	X	NR	NR
Other bloods								X	NR	NR
Other: Clexane		OE					OE		NR	NR
Note: OE – only in an emergency										

Drugs used										
Warfarin	X	X	X	X	X	X	X	X	NR	NR
Sotalol	X	X		X	X		X	X	NR	NR
Amiodarone	X	X	X	X	X	X	X		NR	NR
Flecainide	X	X	X	X	X	X	X		NR	NR
Propafenone		X							NR	NR
Digoxin		X		X	X		X	X	NR	NR
Diltizem	X	X		X	X		X		NR	NR
Other									NR	NR
Verapamil	X			X	X	X	X	X	NR	NR
B Blocker	X		X	X	X	X	X	X	NR	NR
Amiodarone 1200mg weeks			2w		2w				NR	NR
800mg weeks		4 days	2w		2w				NR	NR
600mg weeks	4 w	4 days		1w				1 w	NR	NR
400mg weeks		4 days	2 w	1 w	Daily		10 days	1w	NR	NR
200mg	Daily	Daily	Daily	Daily			Daily	Daily	NR	NR

PVI										
Admission	CCU	CCU	HC	CCU	CCU	NA	CCU	CCU	NR	NR
Days average stay	1	2	1	2	1	NA	1	1-2	NR	NR
CT Scan	X			X		NA		X	NR	NR
Average theatre time (hours)	2-3	4-5	4-5	4	4-5	NA	4-5	4	NR	NR
Anaesthetist		x	50%	X		NA	X	X	NR	NR
Awake Sedation	X		50%		X	NA			NR	NR
TEE	x	x	x	X	X	NA	X	X	NR	NR
Bloods U&E		x	x	X	X	NA		X	NR	NR
FBC		X		X	X	NA		X	NR	NR
INR	x	x	x	X	X	NA	X	X	NR	NR
Other tests ICE	X					NA			NR	NR
TSH, free T4				X		NA			NR	NR
Codes for charging						NA			NR	NR
Admission charge 0173	x	x	x	X	X	NA	X	X	NR	NR
TEE 3636/3637	xx	xx	xx	Xx	Xx	NA	X	X	NR	NR
EP study 1257	x	x	x	X	X	NA	X	X	NR	NR
Transseptal 1251	xx	xx	xx	Xx	Xx	NA	XX	XX	NR	NR
PVI mapping 1261	x	x	xxxx	X	Xx	NA	X	XX	NR	NR
PVI ablation 1262	x	x	xxxx	X	Xx	NA	X	XX	NR	NR
Other rotational CT	x					NA			NR	NR
Number of times redo	2	2-5	2	1-4	2	NA	2	2	NR	NR

Follow-up										
1 week/2 weeks/3 weeks	X	X				NA			NR	NR
1 month				X	X	NA			NR	NR
3 months	X	X	X	X	X	NA	X	X	NR	NR
6 months	X	X	X	X		NA		X	NR	NR
9 months					X	NA	X	X	NR	NR
12 months	X	X		X		NA		X	NR	NR
18 months	X	X	X			NA			NR	NR
24 months	X	X		X		NA			NR	NR
Annually		X		X	X	NA	X		NR	NR
Send back to referring Dr.			X	X		NA			NR	NR
Mean visits in 12 months	4	4	2	4	3	NA			NR	NR

At follow-up										
Consultation	X	X	X	X	X	NA	X	X	NR	NR
Echo	XXX	XXX	X	20%		NA	50%	XXX	NR	NR
ECG	XX	XX		X	X	NA	X	X	NR	NR
Holter	1/yr.	50%		40%	X	NA	30%	X	NR	NR
Bloods U&E				X	X	NA			NR	NR
INR	X	X	X	X		NA	X	X	NR	NR
LFT				X		NA			NR	NR
TSH				X		NA			NR	NR
Stop Warfarin	6mt					NA			NR	NR

INR testing										
									NR	NR
1x week	X3	X4	1-3	X6	X3	X5	X1	X4	NR	NR
1x every two weeks		X2					X1		NR	NR
1x month	If stable	If stable	If stable	If stable	If stable	If stable	If stable	If stable	NR	NR
Other									NR	NR
Average per year	15	16	12-15	15-16	15	15-16	14	15	NR	NR

APPENDIX E:

Sample questionnaire: Anaesthetist

PVI for treatment of AF for patients with PAF or persistent AF

Name of Physician	
Hospital	
Date of Interview	
Type	

Anaesthetics for PVI		
Average time		
Codes		
EPS	1257	
Ablation	1261	
BP control inotropic	0039	
ICU admission	1204	

Other
Modifier ASA 3 or Age 0043 For study ASA3 used.

Anaesthetic for Cardioversion		
Average time		
Codes		
Cardioversion code		

Other
ASA 3

APPENDIX F:

Sample questionnaire: Radiographers

PVI for treatment of AF for patients with PAF or persistent AF

Name	
Hospital	
Date of Interview	
Type	

Radiography for PVI		
Average time		
Codes		
ONCE OFF	39191	
EPS PER 30 MIN	39207	
FLURO	39167	
Attendance per 30 min	39179	
Once-off Attendance	39187	
Total		

Other
References: Calkins Circ Arrhythmia Electro. 2009. **2**: 340-361. 1. Procedure time; 159 min (135 to 183 min) with mapping *vs*. 202 min (171 to 233 min) with no mapping. 2. Fluro time 33 min (26 to 50 min) with mapping *vs*. 59 min (44 to 74 min) not mapping.

APPENDIX G:

Sample questionnaire: Technologists

PVI for treatment of AF for patients with PAF or persistent AF

Name of Technologist	
Hospital	
Date of Interview	
Type	

Technologist for PVI		
Average time		
Codes		
Prep and operation of monitoring	75015	
EPS	75067	
RFA	75014	
Total		

Other

Technologist for Holter		
Average time	NA	
Codes		
Holter code for 24 to 48-hour monitor, set-up, hire, interpret and report to Dr.	75077	

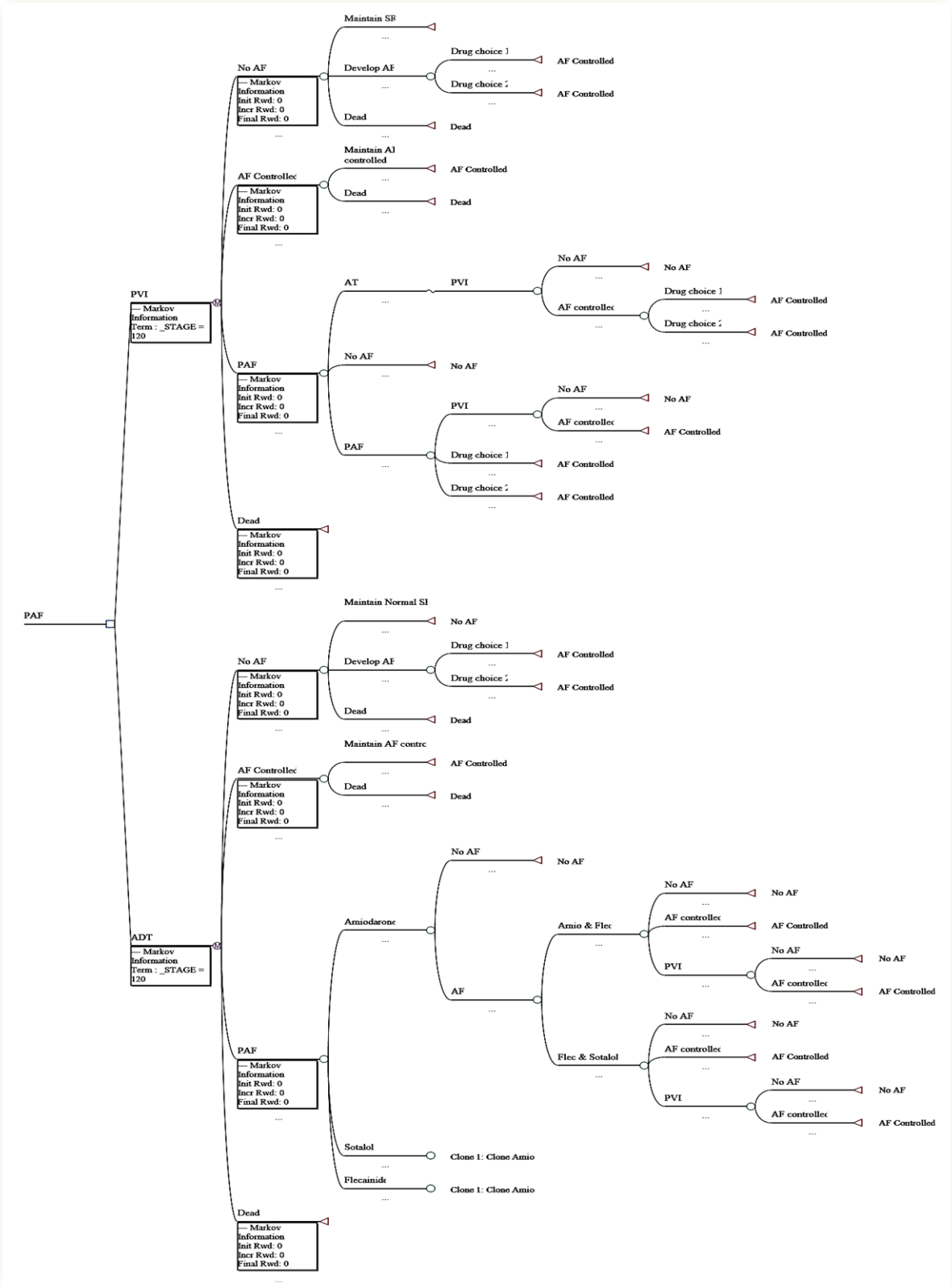
Other

Technologist for Cardioversion		
Average time		
Codes		
	No Tech code for cardioversion	

Other

APPENDIX M:

Model design



APPENDIX H:

Estimated age standardized incidence rates of Atrial Fibrillation with 95% uncertainty interval for men and women in North America, Western Europe, Central Europe and Sub Saharan Africa for 1990 and 2010. (Per 100000 person years)

Estimated age- standardised incidence rates for men and women 1990 (per 100 000 person years) 95% Uncertainty Intervals

	North America		Western Europe		Central Europe		South Sub Saharan Africa	
	Men	Women	Men	Women	Men	Women	Men	Women
<5 years	6.5	4.0	3.2	2.1	3.9	2.3	3.2	2.2
5-9 years	11.9	7.3	5.8	3.8	7.0	4.2	5.9	4.0
10-14 years	3.9	2.5	2.0	1.4	2.4	1.5	2.2	1.5
15-19 years	2.2	1.4	1.0	0.7	1.3	0.8	1.2	0.8
20-24 years	3.9	2.5	1.5	1.0	1.9	1.0	1.6	1.3
25- 29 years	10.5	6.8	4.2	2.7	5.3	2.9	4.3	3.4
30-34 years	17.2	11.1	6.9	4.5	8.6	4.7	7.0	5.5
35- 39 years	37.1	23.2	15.7	10.2	19.3	10.8	16.0	12.3
40-44 years	77.5	47.3	33.5	21.6	41.3	23.4	35.4	26.6
45-49 years	118.9	71.5	53.0	33.6	62.3	35.4	54.5	40.9
50-54 years	185.4	111.0	85.0	54.0	99.7	56.5	86.4	65.5
55-59 years	295.3	174.3	132.9	86.4	162.8	91.4	139.0	106.6
60-64 years	440.9	269.0	202.1	132.2	242.8	135.0	203.1	159.6
65-69 years	639.1	409.6	301.3	197.4	349.7	190.2	286.1	232.7
70-74 years	883.6	623.1	409.7	312.4	472.4	253.8	373.0	320.5
75-79 years	1,201.5	951.4	547.9	514.1	603.1	323.5	472.3	435.1
>80 years	1,952.0	1,618.2	727.6	741.5	837.0	448.9	642.9	625.6

Comprison of South Aub Saharan Africa with North America and Western and Central Europe

	SS Africa vs NA		SS Africa vsWE		SS Africa vs CE	
	Men	Women	Men	Women	Men	Women
<5 years	49%	55%	100%	105%	82%	96%
5-9 years	50%	55%	102%	105%	84%	95%
10-14 years	56%	60%	110%	107%	92%	100%
15-19 years	55%	57%	120%	114%	92%	100%
20-24 years	41%	52%	107%	130%	84%	130%
25- 29 years	41%	50%	102%	126%	81%	117%
30-34 years	41%	50%	101%	122%	81%	117%
35- 39 years	43%	53%	102%	121%	83%	114%
40-44 years	46%	56%	106%	123%	86%	114%
45-49 years	46%	57%	103%	122%	87%	116%
50-54 years	47%	59%	102%	121%	87%	116%
55-59 years	47%	61%	105%	123%	85%	117%
60-64 years	46%	59%	100%	121%	84%	118%
65-69 years	45%	57%	95%	118%	82%	122%
70-74 years	42%	51%	91%	103%	79%	126%
75-79 years	39%	46%	86%	85%	78%	134%
>80 years	33%	39%	88%	84%	77%	139%

Estimated age- standardised incidence rates for men and women 2010 (per 100 000 person years) 95% Uncertainty Intervals

	North America		Western Europe		Central Europe		South Sub Saharan Africa	
	Men	Women	Men	Women	Men	Women	Men	Women
<5 years	7.1	4.3	3.2	2.1	4.1	2.6	3.6	2.3
5-9 years	12.8	8.2	5.8	4.0	7.4	4.7	6.7	4.2
10-14 years	4.3	3.0	2.1	1.5	2.7	1.6	2.4	1.6
15-19 years	2.6	1.7	1.1	0.8	1.5	0.9	1.3	0.9
20-24 years	5.1	3.2	1.7	1.2	2.4	1.4	2.0	1.4
25- 29 years	13.7	9.0	4.7	3.4	6.1	3.6	5.3	3.8
30-34 years	22.3	14.7	7.7	5.6	9.8	5.7	8.7	6.2
35- 39 years	46.6	30.7	17.4	12.4	21.6	12.8	19.4	13.7
40-44 years	94.2	62.0	37.9	26.8	45.9	27.4	41.8	29.2
45-49 years	141.1	92.8	58.5	41.2	73.2	43.7	64.4	44.6
50-54 years	237.5	155.8	103.2	71.5	117.3	69.9	103.5	72.5
55-59 years	409.2	267.4	185.7	126.6	188.6	112.6	168.0	119.5
60-64 years	688.2	455.2	294.4	210.6	283.6	170.2	250.1	182.7
65-69 years	1,138.4	763.8	462.2	356.9	411.8	249.0	356.6	270.9
70-74 years	1,766.1	1,280.4	70.9	634.0	559.1	339.1	475.8	398.8
75-79 years	2,675.3	2,125.7	1,023.8	1,041.6	756.0	463.6	623.4	576.9
>80 years	4,570.2	3,897.3	1,528.7	1,748.2	1,102.6	672.6	864.2	863.5

Comprison of South Aub Saharan Africa with North America and Western and Central Europe

	SS Africa vs NA		SS Africa vsWE		SS Africa vs CE	
	Men	Women	Men	Women	Men	Women
<5 years	51%	8%	0%	0%	5%	13%
5-9 years	52%	12%	0%	5%	6%	12%
10-14 years	56%	20%	5%	7%	13%	7%
15-19 years	50%	21%	10%	14%	15%	13%
20-24 years	39%	28%	13%	20%	26%	40%
25- 29 years	39%	32%	12%	26%	15%	24%
30-34 years	39%	32%	12%	24%	13%	21%
35- 39 years	42%	32%	11%	22%	12%	19%
40-44 years	44%	31%	13%	24%	11%	17%
45-49 years	46%	30%	10%	23%	17%	23%
50-54 years	44%	40%	21%	32%	18%	24%
55-59 years	41%	53%	40%	47%	16%	23%
60-64 years	36%	69%	46%	59%	17%	26%
65-69 years	31%	86%	53%	81%	18%	31%
70-74 years	27%	105%	-83%	103%	18%	34%
75-79 years	23%	123%	87%	103%	25%	43%
>80 years	19%	141%	110%	136%	32%	50%

Source: Chugh et al., 2014: 71-74.

Percentage growth in Incidence of Atrial fibrillation and flutter between 1990 and 2010 in four regions								
	North America		Western Europe		Central Europe		South Sub Saharan Africa	
	Men	Women	Men	Women	Men	Women	Men	Women
<5 years	9%	8%	0%	0%	5%	13%	13%	5%
5-9 years	8%	12%	0%	5%	6%	12%	14%	5%
10-14 years	10%	20%	5%	7%	13%	7%	9%	7%
15-19 years	18%	21%	10%	14%	15%	13%	8%	13%
20-24 years	31%	28%	13%	20%	26%	40%	25%	8%
25- 29 years	30%	32%	12%	26%	15%	24%	23%	12%
30-34 years	30%	32%	12%	24%	13%	21%	24%	13%
35- 39 years	26%	32%	11%	22%	12%	19%	21%	11%
40-44 years	22%	31%	13%	24%	11%	17%	18%	10%
45-49 years	19%	30%	10%	23%	17%	23%	18%	9%
50-54 years	28%	40%	21%	32%	18%	24%	20%	11%
55-59 years	39%	53%	40%	47%	16%	23%	21%	12%
60-64 years	56%	69%	46%	59%	17%	26%	23%	14%
65-69 years	78%	86%	53%	81%	18%	31%	25%	16%
70-74 years	100%	105%	-83%	103%	18%	34%	28%	24%
75-79 years	123%	123%	87%	103%	25%	43%	32%	33%
>80 years	134%	141%	110%	136%	32%	50%	34%	38%

Source: Adapted from Chugh *et al.,* 2014: 71-74.

APPENDIX I:

Estimated age standardized prevalence rates of Atrial Fibrillation with 95% uncertainty interval for men and women in North America, Western Europe, Central Europe and Sub Saharan Africa for 1990 and 2010. (Per 100 000 person years)

Estimated age standardised prevalence rated ot Atrial Fibrillation with 95% uncertainty intervals 1990

	North America		Western Europe		Central Europe		South Sub Saharan Africa	
	Men	Women	Men	Women	Men	Women	Men	Women
<5 years	4.3	2.7	3.4	2.2	4.4	2.6	4.0	2.7
5-9 years	31.9	19.4	24.5	16.2	31.5	18.7	29.2	19.5
10-14 years	51.5	31.8	41.0	27.1	51.3	30.6	49.0	32.4
15-19 years	59.7	36.7	47.3	31.3	59.6	35.7	57.8	37.9
20-24 years	65.4	40.2	50.0	32.8	64.8	38.6	62.9	41.3
25- 29 years	82.3	50.6	59.4	38.5	79.3	46.4	75.7	50.8
30-34 years	115.6	71.0	79.3	50.9	107.3	61.4	101.3	69.7
35- 39 years	172.2	105.4	113.9	72.1	154.7	87.2	145.3	101.9
40-44 years	307.5	185.4	201.8	127.0	271.4	153.5	256.5	182.3
45-49 years	545.0	328.8	355.7	222.5	481.4	274.8	456.8	325.7
50-54 years	900.2	528.2	584.7	363.8	799.3	459.5	756.5	538.3
55-59 years	1,481.4	855.2	978.5	608.4	1,325.5	764.8	1,254.0	894.7
60-64 years	2,332.9	1,330.0	1,556.8	960.4	2,164.7	1,222.5	1,996.3	1,429.5
65-69 years	3,558.4	2,038.9	2,428.6	1,456.0	3,256.7	1,871.9	3,067.8	2,204.4
70-74 years	5,189.6	3,005.5	3,641.3	2,154.0	4,818.2	2,755.8	4,496.6	3,215.8
75-79 years	7,266.3	4,296.2	5,014.8	3,086.0	6,821.1	3,890.9	6,314.7	4,429.9
>80 years	11,632.0	6,758.7	7,216.5	4,602.0	10,824.0	6,282.7	10,091.0	6,643.3

Comprison of South Aub Saharan Africa with North America and Western and Central Europe

	SS Africa vs NA		SS Africa vsWE		SS Africa vs CE	
	Men	Women	Men	Women	Men	Women
<5 years	93%	100%	118%	123%	91%	104%
5-9 years	92%	101%	119%	120%	93%	104%
10-14 years	95%	102%	120%	120%	96%	106%
15-19 years	97%	103%	122%	121%	97%	106%
20-24 years	96%	103%	126%	126%	97%	107%
25- 29 years	92%	100%	127%	132%	95%	109%
30-34 years	88%	98%	128%	137%	94%	114%
35- 39 years	84%	97%	128%	141%	94%	117%
40-44 years	83%	98%	127%	144%	95%	119%
45-49 years	84%	99%	128%	146%	95%	119%
50-54 years	84%	102%	129%	148%	95%	117%
55-59 years	85%	105%	128%	147%	95%	117%
60-64 years	86%	107%	128%	149%	92%	117%
65-69 years	86%	108%	126%	151%	94%	118%
70-74 years	87%	107%	123%	149%	93%	117%
75-79 years	87%	103%	126%	144%	93%	114%
>80 years	87%	98%	140%	144%	93%	106%

Estimated age standardised prevalence rated ot Atrial Fibrillation with 95% uncertainty intervals 2010

	North America		Western Europe		Central Europe		South Sub Saharan Africa	
	Men	Women	Men	Women	Men	Women	Men	Women
<5 years	4.6	2.9	3.4	2.3	4.4	2.8	4.6	2.9
5-9 years	33.6	21.1	24.5	16.1	31.9	20.2	33.6	20.7
10-14 years	54.9	34.7	40.1	26.5	52.9	33.0	55.6	34.4
15-19 years	63.5	39.8	46.4	30.1	62.0	38.3	65.0	40.2
20-24 years	69.4	42.5	49.5	31.5	67.6	41.5	70.8	43.6
25- 29 years	88.5	53.2	60.0	37.4	83.2	50.5	86.2	53.4
30-34 years	126.7	75.0	81.3	49.9	113.2	67.6	117.0	73.3
35- 39 years	190.1	111.2	116.3	70.5	164.9	97.2	169.8	107.6
40-44 years	340.1	199.4	204.4	124.4	293.4	171.6	298.7	192.7
45-49 years	595.2	347.5	359.5	217.7	527.0	308.3	528.1	342.0
50-54 years	966.9	558.9	596.7	355.6	870.2	508.3	869.9	561.3
55-59 years	1,626.2	931.8	1,052.0	614.2	1,435.9	838.1	1,441.8	931.7
60-64 years	2,644.5	1,494.3	1,768.9	1,012.6	2,282.5	1,331.3	2,307.4	1,488.5
65-69 years	4,284.0	2,389.2	2,827.3	1,631.0	3,543.1	2,066.3	3,574.3	2,287.3
70-74 years	6,497.3	3,561.7	4,150.9	2,427.1	5,233.0	3,045.0	5,260.6	3,301.3
75-79 years	9,012.7	4,988.1	5,791.2	3,606.5	7,315.7	4,246.8	7,397.6	4,505.6
>80 years	12,340.0	6,865.1	7,671.3	4,997.2	11,264.3	6,481.8	11,479.2	6,172.5

Comprison of South Aub Saharan Africa with North America and Western and Central Europe

	SS Africa vs NA		SS Africa vsWE		SS Africa vs CE	
	Men	Women	Men	Women	Men	Women
<5	100%	100%	135%	126%	105%	104%
5-9 years	100%	98%	137%	129%	105%	102%
10-14 years	101%	99%	139%	130%	105%	104%
15-19 years	102%	101%	140%	134%	105%	105%
20-24 years	102%	103%	143%	138%	105%	105%
25- 29 years	97%	100%	144%	143%	104%	106%
30-34 years	92%	98%	144%	147%	103%	108%
35- 39 years	89%	97%	146%	153%	103%	111%
40-44 years	88%	97%	146%	155%	102%	112%
45-49 years	89%	98%	147%	157%	100%	111%
50-54 years	90%	100%	146%	158%	100%	110%
55-59 years	89%	100%	137%	152%	100%	111%
60-64 years	87%	100%	130%	147%	101%	112%
65-69 years	83%	96%	126%	140%	101%	111%
70-74 years	81%	93%	127%	136%	101%	108%
75-79 years	82%	90%	128%	125%	101%	106%
>80 years	93%	90%	150%	124%	102%	95%

Source: Chugh et al., 2014: 65-69.

APPENDIX J:

Age-specific projections of the South African male population, 2000-2040 (With-AIDS projections) (000's)

Year/ Cohort	2000	2005	2010	2015	2020	2025	2030	2035	2040
0-4	2 592	2 508	2 451	2 414	2 358	2 259	2 186	2 108	2 012
5-9	2 625	2 529	2 454	2 402	2 367	2 315	2 219	2 149	2 075
10-14	2 522	2 629	2 525	2 441	2 382	2 349	2 294	2 200	2 130
15-19	2 371	2 536	2 636	2 528	2 435	2 378	2 342	2 289	2 193
20-24	2 045	2 335	2 475	2 572	2 466	2 390	2 345	2 321	2 270
25-29	1 883	1 983	2 213	2 333	2 418	2 332	2 273	2 252	2 241
30-34	1 649	1 774	1 815	2 007	2 116	2 191	2 124	2 088	2 084
35-39	1 522	1 544	1 606	1 619	1 799	1 890	1 953	1 903	1 882
40-44	1 301	1 439	1 424	1 462	1 477	1 637	1 708	1 751	1 709
45-49	1 044	1 249	1 356	1 332	1 372	1 385	1 527	1 581	1 605
50-54	810	999	1 186	1 281	1 263	1 303	1 314	1 443	1 485
55-59	603	759	934	1 109	1 200	1 187	1 225	1 235	1 353
60-64	497	547	690	850	1 013	1 099	1 089	1 125	1 136
65-69	358	428	474	601	744	890	969	964	999
70-74	253	286	345	386	492	613	739	809	809
75-79	147	181	208	253	286	368	463	562	619
80+	115	133	162	194	236	280	353	449	559
Total	**22 345**	**23 867**	**24 961**	**25 790**	**26 433**	**26 874**	**27 130**	**27 238**	**27 168**

APPENDIX K:

Age-specific projections of the South African female population, 2000-2040

(With-AIDS projections) (000s)

Cohort	2010	2015	2020	2025	2030	2035	2040
0-4	2,411	2,373	2,318	2,221	2,149	2,071	1,976
5 to 9	2,419	2,362	2,327	2,276	2,182	2,113	2,039
10 to 14	2,500	2,410	2,347	2,314	2,260	2,168	2,097
15-19	2,633	2,512	2,412	2,350	2,314	2,262	2,167
20-24	2,497	2,558	2,441	2,358	2,311	2,290	2,240
25-29	2,218	2,302	2,357	2,261	2,201	2,185	2,182
30-34	1,824	1,936	2,014	2,058	1,986	1,954	1,962
35-39	1,630	1,559	1,665	1,725	1,756	1,704	1,689
40-44	1,463	1,434	1,372	1,462	1,499	1,509	1,464
45-49	1,404	1,338	1,313	1,258	1,332	1,349	1,336
50-54	1,232	1,319	1,258	1,238	1,186	1,247	1,251
55-59	988	1,162	1,245	1,190	1,172	1,121	1,174
60-64	746	921	1,086	1,167	1,117	1,100	1,051
65-69	561	679	841	995	1,072	1,029	1,014
70-74	470	485	592	737	875	946	909
75-79	321	375	391	482	605	723	786
80+	286	364	415	467	559	693	849
Total	**25,612**	**26,098**	**26,401**	**26,569**	**26,584**	**26,471**	**26,193,**

APPENDIX L:

Age-specific projections of AF

Age-specific projections of AF in the male South African population 2010-2040

Age-specific projections of AF in the South African male population, 2000-2040 (With-AIDS projections)														
Cohort	2010	Estimated Prevalence	2015	Estimated Prevalence	2020	Estimated Prevalence	2025	Estimated Prevalence	2030	Estimated Prevalence	2035	Estimated Prevalence	2040	Estimated Prevalence
0-4	2,451,720		2,414,317		2,358,841		2,259,449		2,186,475		2,108,675		2,012,188	
5 to 9	2,454,153		2,402,149		2,367,722		2,315,363		2,219,233		2,149,615		2,075,257	
10 to 14	2,525,391		2,441,434		2,382,849		2,349,561		2,294,673		2,200,664		2,130,149	
15-19	2,636,177		2,528,452		2,435,333		2,378,863		2,342,798		2,289,762		2,193,514	
20-24	2,475,718		2,572,182		2,466,919		2,390,085		2,345,435		2,321,907		2,270,414	
25-29	2,213,211		2,333,393		2,418,069		2,332,047		2,273,345		2,252,201		2,241,134	
30-34	1,815,348		2,007,325		2,116,378		2,191,855		2,124,644		2,088,097		2,084,837	
35-39	1,606,717		1,619,541		1,799,159		1,890,796		1,953,739		1,903,655		1,882,704	
40-44	1,424,516		1,462,524		1,477,375		1,637,446		1,708,159		1,751,838		1,709,033	
45-49	1,356,395		1,332,646		1,372,834		1,385,495		1,527,747		1,581,375		1,605,940	
50-54	1,186,606		1,281,697		1,263,933		1,303,693		1,314,906		1,443,769		1,485,467	
55-59	934,322	8,091	1,109,473	10,088	1,200,718	11,464	1,187,259	11,902	1,225,139	12,896	1,235,562	13,656	1,353,240	15,704
60-64	690,433	18,887	850,443	24,660	1,013,241	31,143	1,099,374	35,818	1,089,229	37,616	1,125,733	41,210	1,136,353	44,094
65-69	474,724	26,130	601,113	35,072	744,017	46,014	890,362	58,368	969,564	67,374	964,338	71,032	999,595	78,046
70-74	345,426	25,490	386,245	30,497	492,716	41,627	613,931	55,499	739,186	71,500	809,460	83,778	809,286	89,623
75-79	208,144	29,292	253,242	38,489	286,046	46,953	368,737	65,368	463,450	88,731	562,570	116,325	619,851	138,423
80+	162,826	31,760	194,214	41,291	236,987	54,920	280,194	70,777	353,100	97,220	449,177	134,804	559,946	183,171
Total	**24,961,827**	139,649	**25,790,390**	180,097	**26,433,137**	232,121	**26,874,510**	297,732	**27,130,822**	375,337	**27,238,398**	460,804	**27,168,908**	549,062

Age-specific projections of AF in the female South African population 2010-2040

Age-specific projections of AF in the South African female population, 2000-2040 (With-AIDS projections)														
Cohort	**2010**	**Estimated Prevalence**	**2015**	**Estimated Prevalence**	**2020**	**Estimated Prevalence**	**2025**	**Estimated Prevalence**	**2030**	**Estimated Prevalence**	**2035**	**Estimated Prevalence**	**2040**	**Estimated Prevalence**
0-4	2,411,517		2,373,128		2,318,501		2,221,429		2,149,069		2,071,668		1,976,170	
5 to 9	2,419,221		2,362,177		2,327,343		2,276,592		2,182,788		2,113,475		2,039,389	
10 to 14	2,500,103		2,410,903		2,347,558		2,314,743		2,260,741		2,168,811		2,097,922	
15-19	2,633,677		2,512,721		2,412,261		2,350,764		2,314,348		2,262,125		2,167,086	
20-24	2,497,764		2,558,760		2,441,370		2,358,004		2,311,510		2,290,140		2,240,404	
25-29	2,218,468		2,302,541		2,357,050		2,261,221		2,201,732		2,185,511		2,182,358	
30-34	1,824,325		1,936,875		2,014,353		2,058,955		1,986,932		1,954,538		1,962,677	
35-39	1,630,355		1,559,677		1,665,312		1,725,673		1,756,120		1,704,367		1,689,376	
40-44	1,463,913		1,434,073		1,372,634		1,462,966		1,499,695		1,509,123		1,464,132	
45-49	1,404,949		1,338,695		1,313,953		1,258,569		1,332,463		1,349,117		1,336,335	
50-54	1,232,320		1,319,792		1,258,348		1,238,560		1,186,350		1,247,918		1,251,350	
55-59	988,839	5,910	1,162,087	7,014	1,245,956	7,596	1,190,611	7,331	1,172,347	7,291	1,121,602	7,045	1,174,685	7,452
60-64	746,956	7,630	921,522	9,507	1,086,599	11,323	1,167,758	12,290	1,117,298	11,877	1,100,365	11,813	1,051,911	11,406
65-69	561,015	16,329	679,394	19,973	841,246	24,978	995,675	29,859	1,072,910	32,497	1,029,114	31,482	1,014,757	31,353
70-74	470,936	25,634	485,758	26,626	592,418	32,700	737,229	40,978	875,428	49,000	946,071	53,325	909,852	51,642
75-79	321,120	41,065	375,522	48,214	391,534	50,471	482,581	62,456	605,187	78,637	723,778	94,423	786,439	103,008
80+	286,853	49,211	364,605	61,424	415,371	68,716	467,736	75,987	559,570	89,269	693,728	108,680	849,071	130,621
Total	**25,612,331**	145,779	**26,098,230**	172,758	**26,401,807**	195,784	**26,569,066**	228,901	**26,584,488**	268,571	**26,471,451**	306,768	**26,193,914**	335,484

Age-Specific projections of AF in the Total South African population 2010-2040

Age-specific projections of AF in the South African female population, 2000-2040 (With-AIDS projections)														
Cohort	**2010**	**Estimated Prevalence**	**2015**	**Estimated Prevalence**	**2020**	**Estimated Prevalence**	**2025**	**Estimated Prevalence**	**2030**	**Estimated Prevalence**	**2035**	**Estimated Prevalence**	**2040**	**Estimated Prevalence**
0-4	4,863,237	-	4,787,445	-	4,677,342	-	4,480,878	-	4,335,544	-	4,180,343	-	3,988,358	
5 to 9	4,873,374	-	4,764,326	-	4,695,065	-	4,591,955	-	4,402,021	-	4,263,090	-	4,114,646	
10 to 14	5,025,494	-	4,852,337	-	4,730,407	-	4,664,304	-	4,555,414	-	4,369,475	-	4,228,071	
15-19	5,269,854	-	5,041,173	-	4,847,594	-	4,729,627	-	4,657,146	-	4,551,887	-	4,360,600	
20-24	4,973,482	-	5,130,942	-	4,908,289	-	4,748,089	-	4,656,945	-	4,612,047	-	4,510,818	
25-29	4,431,679	-	4,635,934	-	4,775,119	-	4,593,268	-	4,475,077	-	4,437,712	-	4,423,492	
30-34	3,639,673	-	3,944,200	-	4,130,731	-	4,250,810	-	4,111,576	-	4,042,635	-	4,047,514	
35-39	3,237,072	-	3,179,218	-	3,464,471	-	3,616,469	-	3,709,859	-	3,608,022	-	3,572,080	
40-44	2,888,429	-	2,896,597	-	2,850,009	-	3,100,412	-	3,207,854	-	3,260,961	-	3,173,165	
45-49	2,761,344	-	2,671,341	-	2,686,787	-	2,644,064	-	2,860,210	-	2,930,492	-	2,942,275	
50-54	2,418,926	-	2,601,489	-	2,522,281	-	2,542,253	-	2,501,256	-	2,691,687	-	2,736,817	
	-	-	-	-	-	-	-	-	-	-	-	-	-	
55-59	1,923,161	14,001	2,271,560	17,103	2,446,674	19,060	2,377,870	19,233	2,397,486	20,187	2,357,164	20,701	2,527,925	23,156
60-64	1,437,389	26,517	1,771,965	34,167	2,099,840	42,465	2,267,132	48,108	2,206,527	49,493	2,226,098	53,023	2,188,264	55,501
65-69	1,035,739	42,459	1,280,507	55,044	1,585,263	70,992	1,886,037	88,227	2,042,474	99,871	1,993,452	102,514	2,014,352	109,400
70-74	816,362	51,124	872,003	57,123	1,085,134	74,327	1,351,160	96,477	1,614,614	120,500	1,755,531	137,103	1,719,138	141,265
75-79	529,264	70,357	628,764	86,703	677,580	97,424	851,318	127,825	1,068,637	167,369	1,286,348	210,748	1,406,290	241,431
80+	449,679	80,970	558,819	102,715	652,358	123,636	747,930	146,763	912,670	186,489	1,142,905	243,483	1,409,017	313,792
Total	**50,574,158**	**285,428**	**51,888,620**	**352,855**	**52,834,944**	**427,904**	**53,443,576**	**526,633**	**53,715,310**	**643,908**	**53,709,849**	**767,572**	**53,362,822**	884,545.88

ANNEXURE A: Article for submission to EP Europace

RADIOFREQUENCY VERSUS CRYOABLATION FOR TREATING PATIENTS WITH PAROXYSMAL ATRIAL FIBRILLATION: AN OVERVIEW OF SYSTEMATIC REVIEWS

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STRUCTURED ABSTRACT AND KEYWORDS

AIMS: This overview of systematic reviews summarized findings of current systematic reviews on freedom from atrial fibrillation (AF) at 12 months following either radio-frequency ablation (RFA) or cryoablation (CB).

METHODS: Based on pre-specified eligibility criteria, a comprehensive search was undertaken to identify systematic reviews comparing RFA versus CB for the treatment of patients aged 18 to 70 years, with all patients having had paroxysmal atrial fibrillation or persistent atrial fibrillation and being refractory to at least one anti-arrhythmic drug. Eleven systematic reviews published between 2014 and 2018 were identified. These consisted of 57 unique studies with 18,408 participants. Data were extracted and the methodological quality was assessed using AMSTAR.

RESULTS: No difference was found between CB and RFA, with moderate certainty of the evidence (7 RCTs OR 0.98, 95%-CI [0,67 to 0,43]). Procedural time was on average shorter with CB than with RFA, with a high degree of heterogeneity among the studies. No difference was found for both fluoroscopy time and overall procedural complications. More patients developed phrenic nerve palsy when CB was performed compared to those who underwent RFA. Similarly, more patients who underwent RFA developed cardiac tamponade/pericardial effusion than those who underwent CB.

CONCLUSION: This overview of systematic reviews found that there is little or no difference between CB and RFA in freedom from AF at 12 months.

KEY WORDS: Pulmonary vein isolation for paroxysmal atrial fibrillation, cryoballoon and radio frequency ablation.

INTRODUCTION

Atrial fibrillation (AF) is the most commonly found and sustained cardiac arrhythmia of clinical significance.(1) New estimates suggest that the prevalence of AF in patients of 20 years and older is approximately 3%. The prevalence of AF increases as patients age. It is expected that

25% of all middle-aged adults in Europe and the USA will develop AF.(2) Atrial fibrillation is associated with debilitating symptoms and an impaired quality of life. Atrial fibrillation increases morbidity risk, such as through heart failure and stroke.(3) There is also an associated 1.5-fold to two-fold increased risk of all-cause mortality in men and woman. The worldwide estimate for AF in 2010 was 33.5 million people. Men accounted for 62% of this statistic.(4) Based on the incidence rates of 2010, the estimated number of new AF cases per year is 2.7 million for men and 2.0 million for women.(1) Higher incidence and prevalence rates are found in developed countries.(5)

Atrial fibrillation is associated with cardiac disease, with coronary artery disease, valvular-heart disease and cardiomyopathy being the most common. Hypertension, diabetes, heart failure, chronic obstructive pulmonary disease and renal failure are among the most frequent co-morbidities. Table 1 defines atrial fibrillation according to the 2016 AHA/ACC atrial fibrillation guidelines.(2)

Atrial fibrillation poses a significant public health problem, accounting for 1% of the National Health System (NHS) budget in the UK and between $16-26 billion in the USA each year.(1,3,6) It is suggested that between 10 and 40% of patients who have atrial fibrillation will be hospitalized each year.(7) According to a study published in 2015,(8) the mean per capita medical spending for working adults with AF was $38,861 (95%-CI) compared to similar patients without AF which was $28,406 (95%-CI). This difference of $10,355 is statistically significant ($p<0.001$). The estimated prevalence of undiagnosed people with AF in the USA is

596,000, with an incremental cost burden of undiagnosed non-valvular AF of 3.1 billion US dollars.(8)

The most recent AF guidelines recommend the use of anti-arrhythmic and anti-coagulant drugs for treating patients with symptomatic AF.(2) However, some large studies have shown anti-arrhythmic drugs to be ineffective in many instances, based on the evidence that up to 85% of these patients are in AF again within one year.(9) This has led to the introduction of catheter-based ablation (CB) as a Class IA level of evidence indication to maintain sinus rhythm in patients with symptomatic paroxysmal atrial fibrillation who are refractory or intolerant to at least one Vaughn-Williams Class I or III drug. It is important to assess patients for procedural risks, which, if present , makes ablation a Class IC level of evidence indication.(2,5,10,11)

Both RFA and CB are used to electrically isolate the pulmonary vein (PVI) in people with PAF who are refractory to drug therapy. Point-by-point radiofrequency ablation is associated with long procedural and fluoroscopy times, as well as increased peri-procedural complications. RFA causes denaturing of the tissue as the tissue surrounding the catheter tip heats up, while a cryoablation placed in the pulmonary vein ostium electrically isolates the veins through means of freezing the surrounding tissue.(12-14)

To date, a number of systematic reviews have been done to assess and compare RFA and CB for the treatment of PAF. This paper identifies and summarizes the most current evidence to allow for better decision-making processes, as well as to pinpoint gaps in research that need to be addressed. The aim was to provide an up-to-date overview of the effects of RFA vs CB for treating patients with PAF and to synthesize the current evidence of effects of RFA compared

to CB regarding freedom from AF at 12 months, as well as secondary outcomes such as procedural time, fluoroscopy time and adverse events during the time periods reported in the systematic reviews.

METHODS

A protocol was developed according to the Cochrane guidance for overviews of systematic reviews[15] and registered with PROSPERO (registration number CRD42019135439).

Criteria for Considering Reviews for Inclusion

The overall aim was to assess the effects of CB vs RFA for PAF by summarizing the evidence from systematic reviews. A systematic review is characterized as having clearly stated objectives with pre-defined eligibility criteria for studies and a methodology that is explicit and reproducible, showing an attempt to identify all studies that meet the eligibility criteria. The risk of bias pertaining to included studies is assessed; and there is a clear and systematic demonstration and synthesis of the characteristics and findings of the identified studies.(15)

Systematic reviews evaluating RFA compared to CB were identified. Both Cochrane and non-Cochrane systematic reviews were included.(15) The participants in the studies were adults (aged 18 years to 70 years old) with paroxysmal and persistent atrial fibrillation, all of whom had already failed on at least one anti-arrhythmic drug. The primary endpoint was reported freedom from AF at 12 months, while the secondary endpoints included procedural and fluoroscopy time, as well as adverse events.

Search Methods, Identification and Selection of Reviews

A comprehensive search using Epistemonikos, PROSPERO, Embase (OVID), Medline (OVID) and Medline (Pubmed) was undertaken up until 18 April 2019.

Systematic reviews from searches in Cochrane Library including DARE, HTA reviews, and economic assessments were also included. The literature was searched using the terms 'atrial fibrillation', 'paroxysmal atrial fibrillation and catheter ablation' OR 'radiofrequency ablation' OR 'RF ablation' OR cryoablation OR 'catheter ablation' OR 'radiofrequency ablation' OR 'RFA ablation' OR 'RFCA ablation' OR 'cryoablation' OR 'cryoballoon'. Medical Subject Headings (MeSH) descriptor: atrial fibrillation. Detailed information on the combinations of search terms used in the search strategy is available in Supplementary Table S1. We imported all retrieved reviews into the EndNote Web reference management software (Thomson Reuters, Carlsbad, CA, USA). Two reviewers (HHL and DL) independently screened and selected reviews. Any discrepancies were resolved by the consensus of authors of this paper. A third person Patricia McCarthy (PMC) was available to resolve any issues where authors HHL and DL did not reach consensus. Included and excluded reviews can be found on Tables 2 and 3 respectively.

Data Extraction

Data of all eligible systematic reviews were extracted and examined independently by two reviewers (HHL and DL). Extracted data included information on the following: authors, year of publication, publication title, publication type, study characteristics, population and setting,

methods used in the systematic reviews, type of interventions, participants in the studies, results and outcomes, and the quality assessment of the original studies.

Quality Assessment of Systematic Reviews

Two independent reviewers (HHL and DL) used the 'Assessing the Methodological Quality of Systematic Reviews' (AMSTAR) tool to review all included studies.[16] The AMSTAR tool uses an 11-point system to appraise the methodological aspects of the systematic reviews where the scoring system is as follows: yes=1 point; and no, can't answer or not applicable=0 points. The total final score ranges from 0 to 11. The AMSTAR assessment can be found in Table 4.

Data Synthesis

The main results of the included reviews by primary and secondary outcomes were summarised and presented. Summary tables from the extracted data for each outcome reported the number and types of included studies, measure of effect, 95%-CI and tests for heterogeneity. For the primary outcome, freedom from AF at 12 months, a GRADE assessment was completed using GRADEpro version 3.6. The GRADEpro software was developed as part of a larger initiative led by the GRADE Working Group. GRADE offers a system for rating quality of evidence (ims.cochrane.org/revman/other-resources/gradepro/about-gradepro). In determining the certainty of evidence for the primary outcome, both the effects of the intervention and an assessment of the risk of bias in a final assessment of the level of evidence were examined.

RESULTS

From the databases searched, 1639 potentially relevant articles were initially retrieved. Of these 1639 articles, 115 were retrieved from the Cochrane Library, 225 from Epistemonikos, 49 from PROSPERO, 365 from Medline (OVID), 428 from Embase (OVID), and 457 from Medline (PubMed). After the exclusion of duplicate entries, 1117 articles remained. After screening the titles and abstracts, 26 full text articles were identified to be read in their entirety. Of those, only 11 met the criteria for inclusion in this overview (Figure 1) (17-27), while 15 studies were excluded (28-41) (Table 3).

Description of Systematic Reviews

Eleven systematic reviews (Table 2) met the inclusion criteria. All of these systematic reviews were published between 2015 and 2018. The inclusion criteria and methods used in these systematic reviews varied considerably, particularly with regard to the secondary outcomes such as adverse events, procedural time and fluoroscopy time.

The 11 systematic reviews addressed 187 studies with 77,486 patients. The number of unique primary studies was 57, involving 18,408 patients. Seventeen of the studies were randomised control trials (RCTs), including one RCT pilot study. The remaining studies were non-randomised trials including cohort studies, retrospective reviews or observational studies. Many of the primary studies were included in more than one of the systematic reviews. Details are reflected on the matrix of included studies (Table 5).

All patients included in the reviews had PAF, with a few reviews including patients with persistent atrial fibrillation. The patients were typically refractory to one or more anti-arrhythmic drugs. The patient population averaged at between 55 and 60 years of age.

The systematic reviews lacked a common approach regarding how interventions were categorised. In many instances, a large amount of detail was given about the cryoballoon technology, including manufacturer, size of balloon and whether first- or second-generation balloons were used. Little information about the RFA catheters was provided. In many instances, no mention was made about whether the RFA was done with or without a 3D mapping system, who the manufacturer of the catheters was, or details of the catheter and technology used. Some of the studies indicated the use of contact force RFA catheters but no further detail was provided. One of the systematic reviews (17) provided details of all the catheters used. In this review, it was found that in five of the 40 included studies patients received a contact force catheter. In a further 26 out of 40 studies it was only indicated that they were irrigated with 'Thermocool™ catheters', with no further information being provided as to whether a 3-D mapping system was used. The remaining nine studies included, as part of the RFA group, four ablations done with a high-density Mesh ablation catheter (MESH) and one that was done with a multi-electrode phased-RF/duty cycled (PhRF/DC) pulmonary vein ablation catheter (PVAC). Neither of these therapies is used frequently for RFA.(17)

The outcomes that the systematic reviews studied were: freedom from atrial fibrillation, procedural time, fluoroscopy time and post-operative complications. All the primary outcomes were based on freedom from atrial tachycardia (AT) in broad terms and, more specifically,

atrial fibrillation (AF) for between four months and 16.5 months, with or without a blanking period. Primary outcomes were also defined as a recurrence of either AT or AF during the follow-up on the original study with one review referring specifically to acute pulmonary vein isolation.

For secondary outcomes, the systematic reviews made mention of phrenic nerve palsy as transient, persistent, permanent or unresolved. Pericardial effusion and tamponade were recorded. These were reported in some of the reviews as two separate incidents, while other reviews reported on them as a single event, regardless of whether the effusion required any intervention or not. The 11 reviews also measured procedural time , with two of the reviews defining how this measurement was made. Two reviews also defined how they arrived at the time for fluoroscopy and procedural time. (17,18) Three reviews reported on major vascular complications, but did not qualify these. (20,21,23) Two reviews measured all-cause mortality, while another only mentioned death.(21,27) Four reviews reported on stroke or transient ischaemic attack (TIA).(20,21,23,27) Two reviews reported re-do ablation as a complication.(18,25) Three reviews (23,25,27) included groin site injury and major bleeding as complications, while the following were referred to as complications in one instance: pulmonary and bronchial complications, pulmonary vein stenosis, gastrointestinal complications, anxiety, local oedema, dyspnoea, contusion, haematuria, and post-operative atrial flutter.(23) One review referred to hospitalisation as a complication.(18)

Methodological Quality

Table 4 illustrates the AMSTAR assessment of the methodological quality of the reviews. One systematic review scored 10/11, with the list of excluded studies not reported on.(18) Eight systematic reviews (73%) scored 7 points. (17,19-21,23,25,40) These eight systematic reviews included confirmation of duplicate study selection and data extraction, comprehensive literature searches, the inclusion of grey or unpublished literature, documented characteristics of included studies, methods of combining studies (for example, homogeneity tests), effect model used and sensitivity analysis, an assessment of publication bias demonstrated graphically or with a statistical test, and potential conflict of interest statement.

The reason two (18%) of the systematic reviews scored 6 (22,26) was because neither included a list of excluded studies. Two of the reviews, scoring seven and ten respectively (18,25), provided a priori designs. Other reviews performed poorly in their methodological quality for failing to report on the following: a priori design (17,19,20,21,22,23,26,27), the lists of included and excluded studies (17,18,19,20,21.22,23,25,26,27,40), documented scientific quality assessment (17,19,20,21,22,23,25,26,27,40), appropriate formulation of conclusions (methodological rigor and scientific quality) (17,19,20,21,22,23,25,26,27,40), information on the status of publication as an inclusion criteria (22,25), and an assessment of publication bias. (25)

Effects of Intervention

Primary Outcome

Four of the 11 reviews reported on freedom from AF at 12 months as found in Table 6. [18,21,23,25] Cheng X, Hu Q. *et al* [22] reported on 11 studies, three of which were RCTs and the other eight non-RCTs. The pooled measure of effect had a risk ratio of 1.01, 95%-CI [0.94 to 1.07]. The Cheng X, Hu Q. *et al* review did sub-group analyses on non-RCT-only studies that evaluated PAF and studies that compared the 28mm CB with RFA.[22] The results of these sub-group analyses did not change the measure of effect. Two reviews included RCTs only, with the first by Murray MI, Arnold A. *et al* including four RCTs [25] and the second, by Hachem AH, Marine JE. *et al* including seven RCTs all of which were included in the other 10 systematic reviews. This indicated a moderate certainty of evidence as per the GRADE assessment .[23]

The odds ratio were 0.98, 95%-CI [0.67 to 1.43], (I^2=56%)[25] and 1.13, 95%-CI [0.72 to 1.77] (I^2=60,3%) [23] respectively. Maltoni S, Negro A. *et al* included 14 studies (3 RCTs and 11 non-RCTs) that demonstrated a risk ratio of 1.04, 95%-CI [0.98 to 1.10] (I^2=23%). A sub-group analysis of this review found a risk ratio of 1.03, 95%-CI [0.97 to 1.09] (I^2=23%), when comparing CB with multi-polar catheters.[18]

Two reviews reported on freedom from any atrial tachycardia including AF (see Table 7).[20,27] Cardoso R, Mendirichaga R. *et al* [20] examined 19 studies (5 RCTs and 14 non-RCTs) and reported the odds ratio as 1.12, 95%-CI [0.97 to 1.29] (I^2=30%). The same review performed two sub-group analyses, the first looking at RCTs only (five studies) and found the OR to be 1.00, 95%-CI [0.65 to 1.56] (I^2=60%); and the second, comparing CB 2nd generation with RFA

contact force technology (4 reviews), found the OR to be 1.04, 95%-CI [0.71 to 1.51] (I^2=0).[20] Garg J, Chaudhary R. *et al.* [27] examined nine studies (three RCTs and six non-RCTs), and found an odds ratio of 1.13, 95%-CI [0.96 to 1.33] (I^2=26%).[27] Finally, one review including 16 studies (four RCTs and 12 non-RCTs) examined freedom from AF/AT at 12 months, (see Table 8) and found a risk ratio of 1.05, 95%-CI [0.98 to 1.13] (I^2 =72.5%).[21]

Secondary Outcomes

Procedural Time

All of the reviews reported on procedural time as reported in Table 9. Two of the 11 systematic reviews defined procedural time as starting with the administration of local anaesthetic to the withdrawal of the catheters, [17,18] while nine reviews did not define procedural time.[19-23,25-27,42] Nine of the 11 reviews reported the procedural times as being less in the CB group when compared with the RFA group,[17-23,26,40] while two reviews [25,27] and one sub-group analysis comparing CB_1 with multipolar catheters[17] found the procedural time shorter in the RFA group. Three reviews, including one sub-group analysis with RCTs, found no statistical significance in the difference in procedure time between CB and RFA. In a sub-group analysis of three RCTs, Garg J, Chaudhary R *et al.* [27] found a standard mean difference (SMD) of 0.37 min, 95%-CI [-0.52 to 1.26] (I^2 =93%, $\chi 2$ =29.58, p value, <0.00001).[27]

Hachem AH, Marine JE. *et al.* [23] and Murray MI, Arnold A. *et al.* [25] each included only RCTs in their reviews, being eight and four respectively. All of the studies included in the Hachem review [12-14, 43-47] were also found in the Murray review. [12-14,43] The Hachem review found a mean difference (MD) of -4.08 min, 95%-CI [-19.47 to 11.30] (I^2 = 89%; $\chi 2$= 64.58; p

value<0.00001),[23] while Murray MI, Arnold A. *et al.* in their review of four RCTs found a WMD of 12.91 min, 95%-CI [-5.59 to 31.31] (I^2 =86.8 %, no $\chi 2$ reported).

Fluoroscopy Time

Table 10 illustrates that only two of the 11 systematic reviews defined fluoroscopy time as being from start to end of the procedure.[17,18] There was very little overall difference in fluoroscopy time between the CB and the RFA groups, varying from a WMD of -27.66 min to 1.17min.[19-23,25-27,42,48] Two reviews did sub-group analyses.[17,27] The first examined ten studies, of which two were RCTs and eight were non-RCTs, and found a SMD of 0.01min, 95%-CI [-0.34 to 0.35] (I^2 95%, $\chi 2$ not reported).[27] Their second analysis looked at RCTs only, and reported a SMD of 0.28 min, 95%-CI[0.06 to 0.49] (I^2 = 16%; $\chi 2$= 1.19; *p*-value= 0.28).[17] The final sub-group analysis of two non-RCTs studies compared CB_2 with RFA using contact force technology. In this instance, the SMD was 0.10 min, 95%-CI [-0.47 to 0.68] (I^2 = 89%; $\chi 2$= 9.05; *p*-value= 0.003).[27]

Liu XH, Chen CF *et al.* did four sub-analyses comparing CB with RFA. In 30 of the 40 included studies, they found the SMD for fluoroscopy time was 0.15 min, 95%-CI [0.42 to 0.13] (I^2 =97% no $\chi 2$ reported).[17] The first sub-group analysis of 15 studies comparing CB_1 with RFA found an overall SMD equal to -0.07min, 95%-CI [-0.38 to 0.24] (I^2 of 96% no $\chi 2$ reported).[17] The SMD in the second sub-group analysis, comparing CB_2 with RFA in six studies, was -0.076min, 95%-CI [-1.36 to -0.16] (I^2 of 97% $\chi 2$ not reported) . The third sub-group analysis compared both CB_1 and CB_2 with RFA in three studies; and reported the SMD as -0.49 min,

95%-CI [-1.05 to 0.08] (I^2 = 94%, $\chi 2$ not reported). The final sub-group analysis comparing CB_1 with MTCA had a SMD of 0.43 min, 95%-CI [0.18 to 0.68] (I^2 = 13%, $\chi 2$ not reported).

Fluoroscopy time was reported on in six [12-14,44,45,47] of the eight RCTs in Hachem *et al.* [23]. The reported WMD was 1.17 min, 95%-CI [-4.94 to 7.2] (I^2 =87%, $\chi 2$= 39.74 , p *value*< 0.00001). In their review of four RCTs, Murray MI, Arnold A. *et al.* found a WMD of -12.91 min, 95%-CI [-31.31 to 5.59] (I^2 = 65.5% no $\chi 2$ reported).

Procedure Related Complications

Adverse events were reported as procedural related complications and these are found in Table 11. These included groin site injuries, [23,25,27] stroke and/or thromboembolism,[20,21,23,27] major bleeding,[21,25,27] all-cause mortality/death, [21,27] and vascular complications. [20,21,23] These events were reported on as overall procedural related complications. The two most frequently reported adverse events were phrenic nerve palsy [18-23,25-27,40] and pericardial effusion/cardiac tamponade [18-21,23,25-27,40]. Sub-group analyses were performed on these two adverse events.

Nine of the 11 reviews reported on procedural related complications. [17,19,21-23,25-27,40] One of two reviews that included only RCTs found an odds ratio for procedural related complications of 1.20, 95%-CI [0.58 to 2.52] (I^2=52.2%, χ^2 not reported) [25], while the other RCT-focused review reported 1.34, 95%-CI [0.91 to 1.95] (I^2=50%, χ^2 =12.03, *p value*= 0.06).[23] Over all the RCTs reported on in these nine reviews, [17,19,21-23,25-27,40], an overlap was found in seven of the studies. [12-14, 43-45,47]

Cardiac Tamponade/ Pericardial Effusion

Eight of the eleven reviews reported on cardiac tamponade (Table 12), [18-20, 23, 40] pericardial effusion (Table 13) [18,20] or cardiac tamponade/effusion (Table 14).[26,27] Of the 14 RCTs listed on Table 12, five were reported on in only the Hachem AH, Marine JE. *et al* review,[13,44-47] while the other nine reviews included the same RCTs. [12,14,43] The results from all the reviews showed that the incidence of cardiac tamponade and/or pericardial effusion was statistically significantly lower in the patients who underwent ablation with CB, with an odds ratio of between 0.31-0.44 at its lowest and highest. Results were similar for the reviews that reported on pericardial effusion alone or with cardiac tamponade. The RCTs from the reviews that evaluated the incidence of pericardial effusion only, were the same as those used in detecting cardiac tamponade. [12-14,43-45] Only one sub-group analysis was done, this being in a single non-RCT study and looking at CB vs multiparty catheters. In this study, the risk ratio of pericardial effusion was more than six times higher in RFA compared to all the other studies that reported on the same outcome. [49] The final two reviews, neither of which distinguished between cardiac tamponade and pericardial effusion [26,27], showed similar results, with CB having lower odds ratio OR=0.43, 95%-CI [0.26 to 0.72] (I^2=0, χ^2=6.11, *p value*= 0.87) and OR 0.62 , 95%-CI [0.41 to 0.93] (I^2 =0, χ^2=9.65 , p *value*=0.65) respectively. [12,14,26,27,43,45]

Phrenic Nerve Palsy (PNP)

Ten of the 11 reviews reported on phrenic nerve palsy as seen in Table 15. Overall CB was associated with a higher risk of PNP when compared with RFA and was the most commonly found post-operative complication in patients undergoing PVI with CB. PNP was reported as

either transient (<12 months) or unresolved. Most of the PNP was reported as transient but at discharge, PNP was significantly more common in the CB group than in the RFA group (*P* <0.01); and in eight studies, three of which were RCTs, the odds ratio was 7.40, 95%-CI [2.56 to 21.34] (I^2 =0%, χ^2=1.89 , p-*value*=0.97).[20]

Chen *et al.* reported that the incidence of PNP was 3.3% for CB vs 0.1% for RFA and that PNP accounted for 41% of all post-operative complication in the CB group, [21] while Hachem *et al.* in their review of four RCTs found that CB had a 10.3 times greater odds of PNP at 12 months follow-up compared to RFA with an odds ratio equal to 10.3, 95%-CI [3.09 to 34.6] (I^2=0, χ^2 not reported). [23] Five studies [14,43-45,47] found the PNP to be transient, while one study reported permanent phrenic nerve injury. [12] Murray *et al.* [25] in their review of four RCTs found 22 patients with phrenic nerve palsy lasting less than 12 months [12,14,43] and one patient with unresolved phrenic palsy. [12] Data from a review of 18 studies, five of which were RCTs, found the odds ratio of 10.72, 95%-CI [2.67 to 11.04] (I^2 =0%, χ^2=2.86, *p-value*=0.99). [26]

A review of three RCT and two non-RCT studies found a risk ratio of 13.60, 95%-CI [3.87 to 47.81] (I^2 =6% χ^2=4.26, *p-value*=0.37).[19] Investigating eight non-RCTs, Jiang *et al.* [23] found the odds ratio equal to 17.35, 95%-CI [6.57 to 45.85] (I^2 =7%, χ^2=7.56, *p-value*=0.37). PNP was only found in patients who underwent PVI with CB (5.4% vs 0%, *p*<0.00001) with a RR 6.29, 95%-CI [2.44 to 16.21] (I^2 =0, and χ^2 not reported).[22] Lastly, the review by Garg *et al.* [27] reporting on 13 studies that measured transient PNP (four of which were RCTs) found an odds ratio of 14.19, 95%-CI [6.92 to 29.10] (I^2 =0, χ^2=9.23, *p-value*=0.68). Reporting on three

RCT and four non-RCT studies that found unresolved PNP, Garg *et al.* found that the odds ratio was 4.62, 95%-CI [1.97 to 10.81] (I^2 of 0, χ^2=1.11, *p-value*=0.98). [27]

DISCUSSION

Summary of Main Results

This overview included 11 systematic reviews published between 2015 and 2018 comparing cryoablation with radiofrequency ablation for the treatment of atrial fibrillation. All of these studies were conducted in high income countries. All patients included in the reviews had paroxysmal or persistent atrial fibrillation, and were refractory to one or more anti-arrhythmic drugs. In general, the description of the interventions was very detailed with regard to the cryoballoon technology, with the name, size, 1st or 2nd generation and the manufacturer details included, while details relating to RFA were lacking. There was no difference in freedom from AF at 12 months (moderate certainty of evidence) and freedom from atrial tachycardia at 12 months. Only two of the 11 systematic reviews did not include procedural and fluoroscopy time as an outcome. [17,18] There was very little difference among the reviews regarding procedural and fluoroscopy time. There was no difference in procedural related complications, including groin site injuries, [23,25,27] stroke/thromboembolism, [20,21,23,27] major bleeding, [21,25,27] all-cause mortality/death, [21,27] and vascular complications. [20,21,23] Of the two major adverse events that were documented, phrenic nerve palsy [18-23, 25-27,40] was associated with CB, while pericardial effusion/cardiac tamponade [18-21,23,25-27,40] was associated with RFA.

Overall Completeness and Applicability of Evidence

The incidence and prevalence of atrial fibrillation is increasing, and so is the demand for treatment. Both CB and RFA as technologies have grown worldwide and continue to grow significantly. This overview included systematic reviews published between 2015 and 2018. Studies included in the systematic reviews were conducted in high income countries. This may limit the degree to which the evidence is applicable to low and middle income countries. However, all relevant types of participants, interventions and outcomes were investigated as non-valvular atrial fibrillation does not typically appear in people <18 years old. The comparison in all the reviews was CB vs RFA and all the relevant outcomes were addressed. Only four of the 11 reviews used the definition of freedom from AF at 12 months as their primary outcome, while the other reviews referred to a more general term of freedom from atrial tachycardia (AT) or freedom from atrial tachycardia and AF. All the reviews reported on the secondary outcomes of procedural and fluoroscopy time, with only two defining how this was measured. Overall post-operative procedural complications were reported in nine of the 11 reviews, while cardiac tamponade/pericardial effusion was reported in seven of the reviews and phrenic nerve palsy in eight reviews.

An unpublished survey of South African electrophysiologists who performed AF ablation was undertaken by the primary author in 2010. The survey found that many of their practices were similar to those of electrophysiologists elsewhere, as documented in internationally published studies. (9) Most AF ablations are done in the private sector in South Africa, with only a limited number taking place in the public sector due to a lack of resources and the scarcity of skill. The

overview fits well into the context of current practice in South Africa, where both RFA and Cryo are available and, in many instances, where both RFA and Cryo are available and used by the same electrophysiologist in the same hospital. Patient selection is important. Although both technologies can be utilized for PVI procedures, some electrophysiologists only use RFA with 3-D mapping, while others may choose to perform ablation with the cryoballoon for the first procedure, and RFA with 3D mapping when re-do ablation is required or where other complex arrhythmia are expected.

Quality of the Evidence

Among the reviews there were very few *a priori* designs. There was also poor attention to detail with regard to assessment of scientific quality and methodological rigor. However, all of these reviews did comprehensive literature searches, with search strategies being clearly stated. Many of the RCTs were included in more than one of the reviews. From the original 187 studies, there were only 57 that were unique. All the reviews shared the characteristics of having included studies and being assessed for publication bias. From the data presented, we were able to summarise the primary and secondary outcomes.

Potential Biases in the Overview Process

The protocol was registered on PROSPERO. An information specialist conducted a comprehensive search. The two authors independently applied pre-specified eligibility criteria and completed data extraction and assessment of methodological quality. The literature review and inclusion of systematic reviews was extensive and exhaustive. While all data relating to the primary and secondary outcomes were present, the definitions were in some instances vague,

such as, for example defining atrial fibrillation as both AF and an atrial tachycardia , the latter including a number of other supra-ventricular tachycardias. There was a lack of information regarding skill of the operators and specifics on the type of RFA catheters used.

Agreements and Disagreements with Other Studies or Reviews

Phrenic nerve injury can lead to diaphragmatic paralysis or dysfunction. Phrenic nerve injury is common in cardiothoracic surgery [(50)] and cryoablation of atrial fibrillation, with up to 11.2% of patients developing this as an adverse event that is associated with pulmonary vein stenosis.[(51)] The data shows that most of the phrenic nerve injuries resolves within one year. This would not have much impact for healthy patients; however, for patients with marginal respiratory reserve, having phrenic nerve palsy lasting up to 12 months may have a significant impact on their ventilation and oxygenation. Some of the reviews did not place much emphasis on this adverse event, despite the fact that it is not benign.

Published data comparing either RFA versus drug therapy or cryoablation versus drug therapy showed similar results with regard to efficacy of ablation and adverse events. This indicates a consistency in the data with regard to the primary and secondary outcomes.

Authors' Conclusions

The results of this overview of systematic reviews found that there is little or no difference between CB and RFA in freedom from AF at 12 months. The technology used to treat patients with PAF should be based on patient selection, operator choice and experience. Further research is likely to have an important impact on the confidence in the estimate of effect and may change the estimate. Further research could better define the technology used, particularly related to

RFA, by expanding on types of catheters used and the use of 3D mapping, including 3D mapping programs designed to decrease exposure to radiation.

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Contributions of authors

Taryn Young (TY) and Heather Henry-Lines (HHL)were responsible for the conceptualization and design of the work. All authors of this overview of meta-analysis made substantial contributions to the acquisition, analysis and interpretation of data, revising the work critically for important intellectual content and final approval of the version to be published. There was agreement with regards to the contributors' accountability for all aspects of the work done to ensure that questions related to the accuracy and integrity of any part of the work were appropriately investigated and resolved. The body of the article was written by HHL under guidance of TY.

Declarations of interest

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Figure 1: Systematic review selection flow chart

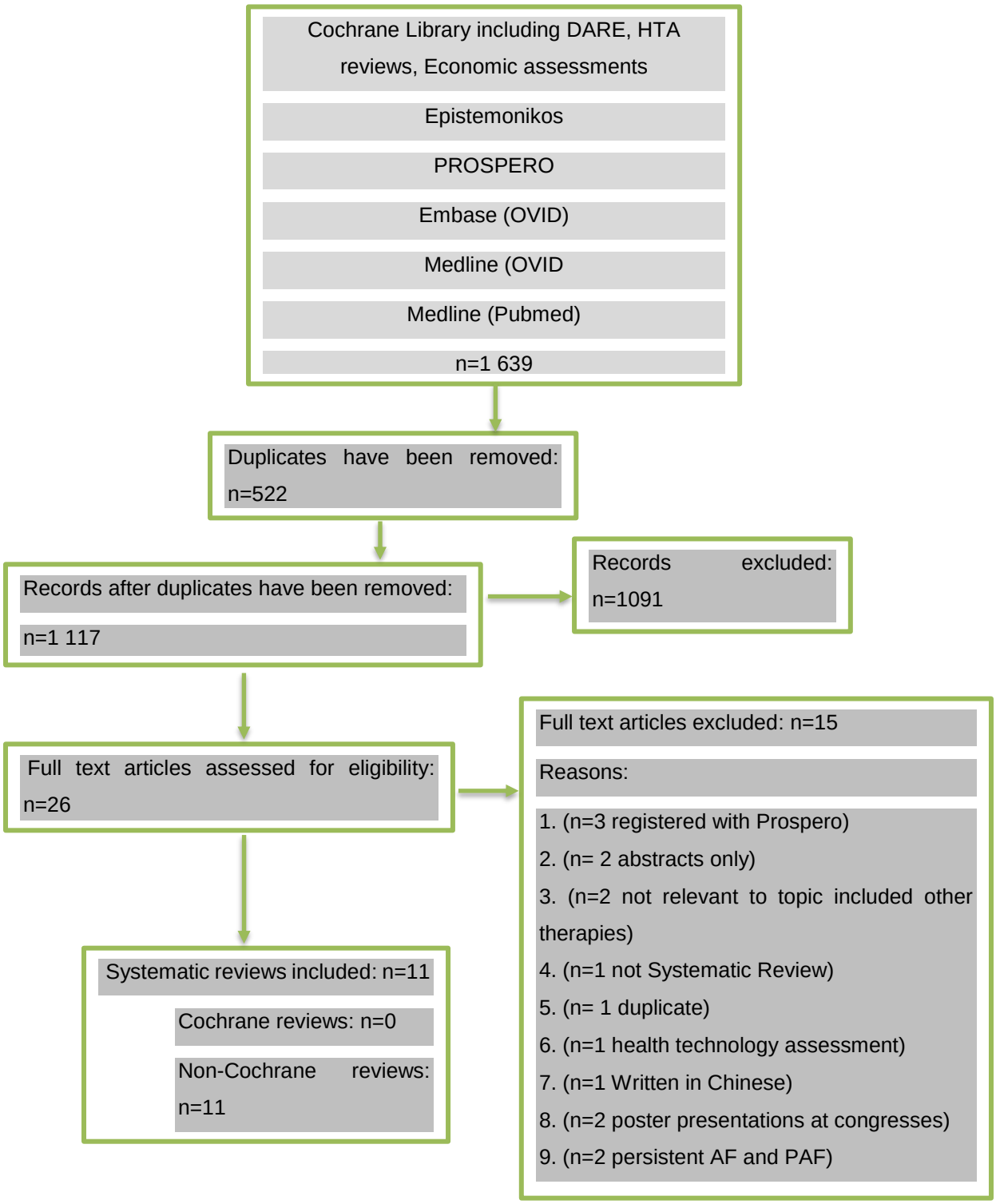

Table 1: Definition of atrial fibrillation [2]

First diagnosed AF	AF that has not been diagnosed before, irrespective of the duration of the arrhythmia or the presence and severity of AF-related symptoms.
Paroxysmal AF	Self-terminating, in most cases within 48 hours. Some AF paroxysms may continue for up to 7 days.[a] AF episodes that are cardioverted within7 days should be considered paroxysmal.[a]
Persistent AF	AF that lasts longer than 7 days, including episodes that are terminated by cardioversion, either with drugs or by direct current cardioversion, after 7 days or more.
Long-standing persistent AF	Continuous AF lasting for ≥1 year when it is decided to adopt a rhythm control strategy.
Permanent AF	AF that is accepted by the patient (and physician). Hence, rhythm control interventions are, by definition, not pursued in patients with permanent AF. Should a rhythm control strategy be adopted, the arrhythmia would be re-classified as 'long-standing persistent AF'.

AF ¼ atrial fibrillation; AHRE ¼ atrial high rate episodes; ECG ¼ electrocardiogram; ICD ¼ implantable cardioverter defibrillator; TIA ¼ transient ischaemic attack.[a]Class of recommendation.[b]Level of evidence. [c]Reference(s) supporting recommendations.

Table 2. Characteristics of Included Systematic Reviews

Review	Date of Search	Objectives	Inclusion Criteria	Interventions	Comparison	Settings	Number included studies and participants	Outcomes reported
Buiatti, A. *et al* (2016) [19]	April 2016	Primary outcome- recurrence of any AT excluding the 3-month blanking period. Without use of any AAD's	Data procedure success with CB vs irrigated RF catheter. Recurrence of AT during follow-up after 3-month blanking period. studies with ≥6month follow-up	PVI either by means of CB or RFA.	23 and 28mm CB^1 and CB^2 or conventional irrigated RFA catheters	France, Germany, Switzerland, Spain, USA.	Ten studies Participants n=6473	Primary outcome recurrence of any AT. Secondary outcomes - Adverse events - Procedure time - Fluoroscopy time
Cardoso, R. *et al* (2016) [20]	April 2016	Comparing safety and efficacy of CB vs RFA for PVI	Patients with PAF with or without prior use of AAD's.	RFA with an irrigated tip catheter and Cryoballoon	CB, CB^1 & CB^2 Non-CF and CF RFA	Among others, UK, Germany, Spain, French,	Twenty-two studies Participants n= 8668	Freedom for AT 12 months Rate of repeat ablations after 3-

		in patients with PAF.				Belgium, USA		month blanking period CB Procedural time Adverse events
Chen, Y. *et al* 2017[21]	July 2016	Evaluate the safety and efficacy of CB vs RFA for AF.	RCTs or Observational studies; Only PAF; CB vs RFA	RFA using an irrigated tip catheter and CB.	CB using CB[1] or CB[2] RFA- Irrigated tip no with or without CF	Germany, UK, Spain, Hungary, France, USA, Belgium, Switzerland	-Sixteen studies were included -Participants n=7195	-Freedom for AT at 12 months -Procedural time - Fluoroscopy time - adverse events
Cheng, X. *et al* 2015[22]	Oct 2014	Long-term efficacy and safety of AF ablation by means of either RFA or CB	Avoid the 3-month blanking period; Follow-up period of 3 or more months; Studies with a sample size of > 20; Information on how the AF	PVI with either CB or RFA	Medtronic Arctic in 23 or 28mm CB compared with RFA – no detail	Among others Spain and Switzerland	-Eleven studies included. -Participants n=1216	Freedom from AF at mean of 16.5 months Secondary outcomes: adverse events

			recurrence was assessed					
Garg, J. *et al* 2016 [27]	April 14, 2016	Efficacy, procedural characteristics and complications of both CB and RFA for the treatment of AF.	Human subjects undergoing catheter ablation for AF; Published in English; Reported clinical outcomes, procedure time and complications; Either RCT or prospective cohort studies.	Irrigated RFA with CB[1] and CB [2]	CB[1] studies (7 studies), CB [2] (2 studies). CB[1] & CB [2] (3 studies) RFA. - Conventional Irrigated catheters (13 studies) - Conventional irrigated catheters and -Contact sensing	Among others Germany, UK, Spain, France, USA, Switzerland, Belgium	-Sixteen studies -Participants n=16 545	Efficacy -Freedom from AF -Recurrent atrial arrhythmias -Repeat ablation Procedure time Fluoroscopy time Safety and Complications

					catheters (2studies), -Duty-cycled phased RFA catheters (1 study)			
Jiang, J. *et al* 2017[40]	May 31, 2016	Assess the efficacy and safety of CB^2 compared with RFA for ablation of PAF.	Patients with PAF refractory to at least one AAD's who were undergoing ablation for PAF; Use of CB^2 vs standard irrigated RFA catheter with or without Contact Force; Studies provided	Irrigated Radiofrequency catheter ablation with or without Contact Force vs 2nd generation CB	CB vs RFA for PVI	Among others Germany, France, USA,	Nine studies Participants n=2 336	Primary Outcomes Recurrence rate AT Secondary Outcomes Procedure time Fluoroscopy time Complication rate

			primary and secondary clinical outcomes; Mean follow-up of more than 3-months -Sample size >20					
Liu, X.H. *et al* 2016 (17)	April 2016	Evaluate the clinical benefits of CB ablation compared with RFA for treating AF.	Patients with PAF refractory to at least one AAD's undergoing ablation for PAF; receiving catheter ablation for first time; comparison RFA and CB; Sample size ≥20; Follow-up of more than 3-months; studies	Radiofrequency catheter ablation and CB ablation for AF.	CB 1st generation vs RFCA CB2nd Generation vs RFCA CB 1st and 2nd generation vs RFCA CB1st generation vs Multi-electrode	Among others Germany, UK, Spain, France, USA, Switzerland, Belgium.	Forty Trials were included Participants n=11 395	Primary Outcomes Recurrence rate AT Secondary Outcomes Procedure time Fluoroscopy time Complication rate

			measured procedure time, fluoroscopy time, ablation time, energy time, success rate of PVI.		catheters ablation			
Ma, H. *et al* 2017[26]	Dec 2016	Compare the efficacy and safety between CBA and RFCA for the treatment of AF.	Contained data regarding procedural time, fluoroscopy time, total procedure related, had at least 20 patients in each arm, freedom from AF, duration of follow up of at least six months including a 3-month blanking period.	PVI with either CB or RFCA	Medtronic Arctic CB in either 23 or 28mm compared with Irrigated RFA catheter no mention of names, size, or whether mapping was used.	Among others Germany, UK, Spain, France, USA, Switzerland, Belgium.	Twenty Studies were included Participants n=9141	Primary Outcomes: -freedom of AF - Procedural time and fluoroscopy time. Secondary Outcomes: -complications

Murray, M.I. *et al.* 2018 [25]	June,16 2016	Evaluate the clinical efficacy and safety of CB vs traditional irrigated RFA for PVI in patients with PAF who are refractory to AAD	Clear definitions of study population and outcome assessment; type of ablation catheter used;	PVI with either CB or RFA	Medtronic Arctic first and second-generation CB in either 23 or 28mm compared with Irrigated RFA catheter with Carto 3D mapping system.	Germany, UK and Spain	Four RCTs N= 1284.	Primary Outcomes -Freedom from AF at 1 year. -Complications and re-do ablation rate
Hachem, A.H. *et al* 2018 [23]	May 10, 2016	Comparing RFA versus CB for patients with AF	Studies that randomly allocated adult patients ≥ 18 years old to received either CB or RFA for AF	PVI with either CB or RFA	Medtronic Arctic first and second generation CB compared with Irrigated RFA catheter.	Spain, Russia, France, UK, Germany and Sweden	Studies included n=8 Participants n= 1598	Freedom from AF at 1 year. Procedure Duration. Fluoroscopy Time Ablation Time Post-operative complications

Maltoni, S. *et al* 2018 (18)	Sept 2018	Assessing efficacy, safety and technical performance of PVI with CB and RFA in patients with persistent and paroxysmal AF	Contained data regarding procedural time, fluoroscopy time, had at least ten patients with AF, freedom from AF, duration of follow up of at least 12 months including a 3-month blanking period. At least one outcome of interest.	PVI with either CB or RFA	Medtronic Arctic first and second-generation CB compared with Irrigated RFA catheter, multi-pole catheters (Mesh) and pulmonary vein ablation catheters (PVAC)	Among others Germany, UK, Spain, France, USA, Switzerland	RCT n=31, observational controlled studies n=23 Participants n=11 635** Data varies please see data extraction tool	Freedom from AF at 1 year. Total Procedural time. Fluoroscopy Time Post-operative complications

List of abbreviations

AF = Atrial Fibrillation, CB = Cryoballoon, Cryoablation, RFA = Radiofrequency Ablation, AAD's = Anti-arrhythmic Drug, PAF = Paroxysmal Atrial Fibrillation, PVI = Pulmonary Vein Isolation, RF=Radiofrequency, AT= Atrial tachycardia, EP Centre= Electrophysiology centre, RCT= Randomized Clinical Trial, NA=Not applicable, CF=contact force, RFCA, Radiofrequency catheter ablation, MTCA=Multi-electrode catheters. CB^1= Cryoballoon ^{1st} generation. CB^2= Cryoballoon ^{2nd} generation.

Table 3: List of Excluded Studies

Authors' Year	Reason for exclusion
Banga S. *et al*. 2018[28]	Abstract/Poster at a congress
Patel L. *et a*l. 2018[29]	Protocol registered with Prospero
Parwani S. *et al*. 2017[30]	Persistent Atrial Fibrillation
Patel N. *et al.* 2018[31]	Abstract at congress
Chen C. *et al.* 2018[32]	Persistent atrial fibrillation
Desai Y. *et al*. 2017[33]	Management of AF in the elderly
Gasparini M. *et al*. 2018[34]	Atrial fibrillation and cardiac resynchronisation therapy
Junjie Z. *et al.* 2017[35]	Catheter ablation vs Surgical ablation
Hussain N. *et al.* 2017[36]	Conference Abstract
Cai Q. *et al.* 2017[37]	Written in Chinese
Sousa PA. *et al.* 2015[38]	Not a Systematic review/Meta-analysis
Cay S. *et al.* 2015[39]	Abstract in Journal supplement
Jiang J. *et al.* 2017[24]	Duplicate
Boriani G. *et al.* 2013[41]	HTA Assessment

Table 4: Methodological Quality Assessment of Systematic Reviews Using the AMSTAR Tool

Methodological Quality Assessment of the included studies Systematic Reviews - AMSTAR Items												
Study	*a priori* design	Duplicate study	Comprehensive literature search	Inclusion criteria i.e., grey or unpublished literature	List of studies included/excluded	Characteristics of included studies	Scientific quality assessed	Methodological rigor and scientific quality	Methods of combining studies	Assessment of publication bias	Conflict of interest statement	Rating
Buiatti *et al* 2017 [19]	**No**	**Yes**	**Yes**	**Yes**	**No**	**Yes**	**No**	**No**	**Yes**	**Yes**	**Yes**	**7**
Cardoso *et al* 2016 [20]	**No**	**Yes**	**Yes**	**Yes**	**No**	**Yes**	**No**	**No**	**Yes**	**Yes**	**Yes**	**7**
Chen *et al* 2017[21]	**No**	**Yes**	**Yes**	**Yes**	**No**	**Yes**	**No**	**No**	**Yes**	**Yes**	**Yes**	**7**
Cheng *et al* 2015[22]	**No**	**Yes**	**Yes**	**No**	**No**	**Yes**	**No**	**No**	**Yes**	**Yes**	**Yes**	**6**
Garg *et al* 2016[27]	**No**	**Yes**	**Yes**	**Yes**	**No**	**Yes**	**No**	**No**	**Yes**	**Yes**	**Yes**	**7**

Hachem *et al* 2018[23]	**No**	**Yes**	**Yes**	**Yes**	**No**	**Yes**	**No**	**No**	**Yes**	**Yes**	**Yes**	**7**
Jiang *et al* 2017[40]	**No**	**Yes**	**Yes**	**Yes**	**No**	**Yes**	**No**	**No**	**Yes**	**Yes**	**Yes**	**7**
Liu *et al* 2016[17]	**No**	**Yes**	**Yes**	**Yes**	**No**	**Yes**	**No**	**No**	**Yes**	**Yes**	**Yes**	**7**
Ma *et al* 2017[26]	**No**	**Yes**	**Yes**	**Yes**	**No**	**Yes**	**No**	**No**	**Yes**	**No**	**Yes**	**6**
Murray *et al* 2018[25]	**Yes**	**Yes**	**Yes**	**No**	**No**	**Yes**	**No**	**No**	**Yes**	**Yes**	**Yes**	**7**
Maltoni, *et al* 2018 [18]	**Yes**	**Yes**	**Yes**	**Yes**	**No**	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**10**

Eleven items were scored as “Yes”, “No”, “Can’t Answer” or “Not Applicable”

Table 5: Matrix of Primary Studies Included in the Systematic Reviews

Systematic reviews														
				Primary studies within systematic reviews										
Incl. study #	Included study	Type of study	Sample size	Buiatti *et al* 2017 (19)	Cardoso *et al* 2016 (20)	Chen *et al* 2017 (21)	Cheng *et al* 2015 (22)	Garg *et al* 2016 (27)	Jiang *et al* 2017 (40)	Liu *et al* 2016 (17)	Ma *et al* 2017 (26)	Murray *et al* 2018 (25)	Hachem *et al* 2018 (23)	Maltoni *et al* 2018 (18)
(12)	Kuck 2016	RCT	762	(12)	(12)	(12)		(12)		(12)	(12)	(12)	(12)	(12)
(13)	Pérez-Castellano 2014	RCT	50	(13)	(13)	(13)	(13)	(13)		(13)	(13)	(13)	(13)	(13)
(14)	Hunter 2015	RCT	237		(14)	(14)		(14)			(14)	(14)	(14)	
(43)	Luik 2015	RCT	315	(43)	(43)	(43)		(43)		(43)	(43)	(43)	(43)	(43)
(44)	Pokushalov 2013	RCT	80				(44)			(44)			(44)	
(45)	Siklódy 2012	RCT	60	(45)	(45)		(45)			(45)	(45)		(45)	(45)
(46)	Schmidt 2013	Pilot RCT	99					(46)		(46)			(46)	
(47)	Malmborg 2013	RCT	110							(47)			(47)	

(51)	Amin 2014	Abstract	-		(51)									(51)
(52)	Linhart 2009	Case Control	40				(52)			(52)				
(53)	Wasserlauf 2015	Cohort	201	(53)	(53)	(53)		(53)	(53)	(53)				(53)
(54)	Kojodjojo 2010	Cohort study	295		(54)		(54)	(54)		(54)	(54)			(54)
(55)	Schmidt 2014	Cohort Study	3775	(55)				(55)		(55)	(55)			
(56)	Straube 2016	Cohort Study	373	(56)	(56)	(56)		(56)	(56)	(56)	(56)			(56)
(57)	Schmidt 2016	Cohort study	2306		(57)	(57)		(57)						(57)
(58)	Juliá 2015	Cohort Study	286		(58)	(58)				(58)				(58)
(59)	AkerstrÖm 2014	Cohort study	630		(59)					(59)				
(60)	Siklódy 2011	Cohort Study	74							(60)				
(61)	Mugnai 2015	Cohort Study	1352							(61)				
(62)	Sauren 2009	Cohort study	30							(62)				
(63)	Wasserlauf 2014	Cohort study	201								(63)			
(64)	Squara 2015	Cohort study,	376		(64)	(64)		(64)	(64)	(64)	(64)			(64)
(65)	Dulac 2014	Non RCT	49		(65)				(65)					(65)
(66)	Kardos 2015	Non RCT	96						(66)					
(67)	Miyazaki 2016	Non RCT	82						(67)					(67)

(68)	Khoueiry 2016	Non- RCT	687	(68)	(68)	(68)		(68)			(68)			(68)
(69)	Gaita 2011	Non- RCT	108					(69)		(69)				
(70)	Kühne 2010	Non-RCT	50	(70)		(70)	(70)			(70)	(70)			(70)
(71)	Mugnai 2014	Non-RCT	396		(71)	(71)	(71)	(71)		(71)	(71)			(71)
(72)	Jourda 2015	Non-RCT	150	(72)	(72)	(72)		(72)		(72)	(72)			(72)
(73)	Ciconte 2015	Non-RCT	100		(73)					(73)				(73)
(74)	Aryana 2015	Non-RCT	1196		(74)				(74)	(74)	(74)			(74)
(75)	Mokrani 2012	Non-RCT	79		(75)									(75)
(76)	Kardos 2016	Non-RCT	98			(76)								(76)
(77)	Jourda 2014	Non-RCT	150						(77)					
(78)	Defaye 2010	Non-RCT	60							(78)				
(79)	Hofmann 2010	Non-RCT	79							(79)				
(80)	Kiss 2014	Non-RCT	89							(80)				
(81)	Schmidt 2012	Non-RCT	243							(81)				
(82)	Chierchia 2010	Non-RCT	133							(82)				
(83)	Neumann 2011	Non-RCT	89							(83)				

(84)	Wissner 2014	Non-RCT	86							(84)				
(85)	Boveda 2016	Non-RCT												(85)
(86)	Ferretto 2015	Non-RCT.	63		(86)									(86)
(87)	Knecht 2014	Prospective	327	(87)	(87)	(87)		(87)		(87)	(87)			(87)
(88)	Herm 2013	Prospective	37							(88)				
(90)	Kuck 2016	RCT	750	(90)										(90)
(91)	Providencia 2017	RCT	860			(91)								(91)
(92)	Koch 2012	RCT	32							(92)				
(93)	Malmborg 2013	RCT	30							(93)	(93)			
(94)	Nagy-Baló 2013	RCT	34							(94)				
(95)	Tse 2005	RCT	30							(95)				
(96)	Gunawardene 2016	RCT	60								(96)			
(97)	Bittner 2011	RCT	80								(97)			
(98)	Sorgente 2010	Retrospective Study	94				(98)			(98)				(98)

(99)	Nagy 2016	Retrospective Study	96						(99)		(99)			
(100)	Mandell 2013	Retrospective Study	124				(100)			(100)				

Table 6: CB vs RFA Freedom from AF at 12 Months

Review	Types of studies	Study (n)	Measure of effect	Statistical Heterogeneity
Cheng X. *et al.* 2015.[22]	3 RCTs 8 Non-RCTs	11	RR 1.01 95%-CI [0.94 to 1.07]	I^2=5%; χ^2 =10.54, *p value* = 0.39
Cheng X. *et al.* 2015.[22]	Non-RCTs	8	RR 1.03 95%-CI [0.97 to 1.09]	I^2=0%; χ^2=4.34, *p value* = 0.74
Cheng X. *et al.* 2015.[22]	1 RCT 7 Non-RCTs (PAF Only)	8	RR 0.99 95%-CI [0.88 to 1.11]	I^2=20%; χ^2=7.48, *p value* = 0.28
Cheng X. *et al.* 2015.[22]	1 RCT 5 Non-RCTs	6	RR 1.04 95%-CI [0.95 to 1.14]	I^2=0%; χ^2=4.36, *p value* = 0.50
Murray MI. *et al.* 2018.[25]	4 RCTs	4	OR 1.13 95%-CI [0.72 to 1.77]	I^2=60.3%
Hachem AH. *et al* 2018[23]	7 RCTs	7	OR 0.98 95%-CI [0.67 to 1.43]	I^2=56%; χ^2=13.7, *p value* = 0.03
Maltoni S. *et al.* 2018[18]	3 RCTs 11 Non=RCTs	14	RR 1.03 95%-CI [0.97 to 1.09]	I^2=23%; χ^2=16.99, *p value* = 0.20
Maltoni S. *et al.* 2018[18]	1 RCT 1 Non-RCT	2	RR 1.26 95%-CI [0.97 to 1.63]	I^2=0%; χ^2=0.00, *p value* = 0.08

Table 7: CB vs RFA Freedom from AT at 12 Months

Review	Types of studies	Study (n)	Measure of effect	Statistical Heterogeneity
Cardoso R. *et al.* (2016)[20]	5 RCTs and 14 Non-RCTs	19	OR 1.12 95%-CI [0.97 to 1.29]	I^2=30%; χ^2=25.56, *p value* = 0.11
Cardoso R. *et al.* (2016)[20]	RCTs only	5	OR 1.00 95%-CI [0.65 to 1.56]	I^2=60%; χ^2=10.08, *p value* = 0.04
Cardoso R. *et al.* (2016)[20]	4 Non-RCTs (CB_2 vs Contact force)	4	OR 1.04 95%-CI [0.71 to 1.51]	I^2=0%; χ^2=1.23, *p value* = 0.75
Garg J. *et al.* 2016[27]	3 RCTs 6 Non-RCT	9	OR 1.13 95%-CI [0.96 to 1.33]	I^2=26%; χ^2=10.84, *p value* = 0.21

Table 8: CB vs RFA Freedom from AF/AT at 12 Months

Review	Types of studies	Study (n)	Measure of effect	Statistical Heterogeneity
Chen Y. *et al.* 2017[21]	4 RCTs12 Non-RCTs	16	RR 1.05 95%-CI [0.98 to 1.13]	I^2 72.5%, χ^2not reported

Table 9: CB vs RFA Procedural Time

Review	Types of studies	Study (n)	Measure of effect	Statistical Heterogeneity
Buiatti, A. *et al.* (2016)[19]	2 RCTs 8 Non-RCTs (112-215 min vs 111-284 min)	10	WMD -14.44min CI – 95% [-32.91 to 4.02]	I^2=98% (no χ^2 reported)
Cardoso R. *et al.* (2016)[20]	5 RCTs 17 Non-RCTs	22	WMD -28.9 min 95%-CI [-49 to -8.8]	not reported
Chen Y. *et al.* 2017[21]	4 RCTs 11 Non-RCTs	15	WMD -0.37 min 95%-CI [-2.78 to 2.04]	I^2=89%, *p value* =0.00 (no χ^2 reported)
Cheng X. *et al.* 2015.[22]	3 RCTs 8 Non-RCTs (149.4min vs 183.6min)	11	WMD -31.94 min 95%-CI [-60.43 to-3.45]	I^2=96% (no χ^2 reported)
Garg J. *et al.* 2016[27]	3 RCTs 8 Non-RCTs	11	SMD 0.02 min 95%-CI [-0.52 to 0.88]	I^2=93%; χ^2=29.58, *p value*< 0.00001
Garg J. *et al.* 2016[27]	3 RCTs	3	SMD 0.37 min 95%-CI [-0.52 to 1.26]	I^2 =93%; χ^2= 29.58; *p value* <0.00001
Garg J. *et al.* 2016[27]	2 Non-RCTs (CB_2 vs Contact force)	2	SMD 0.12 min 95%-CI [-0.76 to 0.99]	I^2= 95%; χ^2= 20.71; *p value* <0.00001
Jiang J. *et al.* 2017[40]	6 Non-RCTs	6	WMD -.39.72 min 95%-CI [-61.36 to -18.08]	I^2 =97%; χ^2=197.21; *p value* <0.00001
Liu XH. *et al.* 2016[17]	1 RCT 7 Non-RCTs (CB_2 vs Irrigated RFA)	8	SMD -0.067 min	I^2 =97%; χ^2= 241.87; *p value* <0.00001

			95%-CI [-1.15 to -0.18]	
Liu XH. *et al.* 2016[17]	3 Non-RCTs ($CB_{1\&2}$)	3	SMD -1.43 min 95%-CI [-1.62 to -1.23]	I^2 =35%; χ^2= 3.09 *p value* = 0.21
Liu XH. *et al.* 2016[17]	4 RCTs 4 Non-RCTs (CB_1 vs MTCA)	8	SMD 0.30 min 95%-CI [0.06 to 0.54]	I^2 =31%; χ^2= 10.11; *p value* =0.18;
Ma H. *et al.* 2017[26]	5 RCTs 11 Non-RCTs	16	MD -30.38 min 95%-CI [-46.43 to-14.33]	I^2 =98%; χ^2= 626.74; *p value* <0.00001;
Murray MI. *et al.* 2018.[25]	4 RCTs	4	WMD 12.91 min 95%-CI [-5.59 to 31.31]	I^2 =86.8 % (no χ^2 reported)
Hachem AH. *et al* 2018[23]	8 RCTs	8	WMD -4.08 min 95%-CI [-19.47 to11.30]	I^2 = 89%; χ^2= 64.58; *p value* <0.00001
Maltoni S. *et al.* 2018[18]	3 RCTs 18 Non-RCTs	21	WMD -23.48min 95%-CI [-37.97 to -9.02]	I^2 = 98% (no χ^2 reported)

Table 10: CB vs RFA Fluoroscopy Time

Review	Type of Study	Study (n)	Measure of effect	Statistical Heterogeneity
Buiatti, A. *et al.* (2016)[19]	2 RCTs 8 Non RCTs (17-61min vs 18-73 min)	10	WMD -1.05min 95%-CI [-2.89 to -4.99]	I^2 =95% I^2 = 89%; χ^2= 9.05, *p value* = 0.003
Cardoso R. *et al.* (2016)[20]	5 RCTs 17 Non-RCTs	22	WMD -2.6min 95%-CI [-6.4 to1.3]	I^2= 95%, (no χ^2 reported)
Chen Y. *et al.* 2017[21]	4 RCTs 11 Non-RCTs	15	WMD -27.66min 95%-CI [-45.24 to -10.08]	I^2 =97%, (no χ^2 reported)
Cheng X. *et al.* 2015.[22]	3 RCTs 8 Non-RCTs (35.8min vs 39.9 min)	11	WMD -8.6min 95%-CI [-18.29 to 3.69]	I^2 =96%, (no χ^2 reported)
Garg J. *et al.* 2016[27]	2 RCTs 8 Non-RCTs	10	SMD 0.01min 95%-CI [-0.34 to 0.35]	I^2= 95%; χ^2= 171.70, *p value* <0.00001
Garg J. *et al.* 2016[27]	2 RCTs	2	SMD 0.28 95%-CI [0.06 to 0.49]	I^2 = 16%; χ^2= 1.19, *p value* = 0.28
Garg J. *et al.* 2016[27]	2 Non-RCTs (CB_2 vs Contact force)	2	SMD 0.10 95%-CI [-0.47 to 0.68]	I^2 = 89%; χ^2= 9.05, *p value* = 0.003
Jiang J. *et al.* 2017[40]	7 Non-RCTs	7	WMD -2.86min 95%-CI [-7.02 to 1.30]	I^2 = 96%; χ^2= 136.71, *p value* < 0.00001

Liu XH. *et al.* 2016[17]	Not stated	15	SMD -0.07min 95%-CI [-0.38 to 0.24]	I^2 = 96%, (no χ^2 reported)
Liu XH. *et al.* 2016[17]	Not stated	6	SMD -0.076min 95%-CI [-1.36 to -0.16]	I^2 =97%, (no χ^2 reported)
Liu XH. *et al.* 2016[17]	Not stated	3	SMD -0.49min 95%-CI [-1.05to 0.08]	I^2= 94%, (no χ^2 reported)
Liu XH. *et al.* 2016[17]	Not stated	6	SMD 0.43min 95%-CI [0.18 to 0.68]	I^2 =13%, (no χ^2 reported)
Liu XH. *et al.* 2016[17]	Not stated	30	SMD 0.15min 95%-CI [0.42 to 0.13]	I^2 =97%, (no χ^2 reported)
Ma H. *et al.* 2017[26]	5 RCTs 11 Non-RCTs	16	MD -3.18min 95%-CI [-6.43 to 0.07]	I^2 = 95%; χ2= 273.42, *p value* < 0.00001
Murray MI. *et al.* 2018.[25]	4 RCTs	4	WMD -12.91mon 95%-CI [-31.31 to 5.59]	I^2 = 65.5%, (no χ^2 reported)
Hachem AH. *et al* 2018[23]	6 RCTs	6	WMD 1.17min 95%-CI [-4.94 to 7.2]	I^2 =87%; χ2= 39.74; *p value* < 0.00001
Maltoni S. *et al.* 2018[18]	1 RCTs 17 Non-RCTs	18	WMD -1.92min 95%-CI [-4.89 to 1.05]	I^2 =94%, (no χ^2 reported)

Table 11: Overall Procedural Related Complications

Review	Type of Study	Study (n)	Measure of effect	Statistical Heterogeneity
Buiatti, A. *et al.* (2016)[19]	2 RCTs 8 Non-RCTs	10	Risk Ratio 0.92 95%-CI [0.66 to 1.28]	I^2=22%, χ^2 =11.53, *p value*= 0.24
Chen Y. *et al.* 2017[21]	4 RCTs 11 Non-RCTs	15	RR 1.08 95%-CI [0.86 to 1.35]	I^2=26.9%, (χ^2 not reported)
Cheng X. *et al.* 2015.[22]	3 RCTs 8 Non-RCTs	11	RR 1.3 95%-CI [0.91 to 1.85]	I^2=0%, (χ^2 not reported)
Garg J. *et al.* 2016[27]	4 RCTs 11 Non-RCTs	15	OR 1.06 95%-CI [0.84 to 1.34]	I^2=31%, χ^2=20.17, *p value*= 0.12
Jiang J. *et al.* 2017[40]	7 Non-RCTs	7	OR 2.01 95%-CI [0.91 to 4.43]	I^2=62%, χ^2=15.65, *p value*= 0.02
Liu XH. *et al.* 2016[17]	7 RCTs and 21 Non-RCTs	28	RR 0.72 95%-CI [0.58 to 0.90]	I^2=13%, χ^2 =30.93, *p value*= 0.27
Ma H. *et al.* 2017[26]	4 RCTs 9 Non-RCTs	13	OR1.56 95%-CI [1.05 to 2.31]	I^2=39%, χ^2=19.53, *p value*= 0.08
Murray MI. *et al.* 2018.[25]	4 RCTs	4	OR1.20 95%-CI [0.58 to 2.52]	I^2=52.2%, χ^2not reported

Hachem AH. *et al* 2018[23]	7 RCTs	7	OR 1.34 95%-CI [0.91 to 1.95]	I^2=50%, χ^2=12.03, *p value*= 0.06

Table 12: Cardiac Tamponade

Review	Type of study	Study (n)	Measure of effect	Statistical Heterogeneity
Buiatti, A. *et al.* (2016)[19]	2 RCTs 5 Non-RCTs	7	RR 0.48 95%-CI [0.25 to 0.89]	I^2 =0, χ^2= 5.69, *p value*= 0.46
Cardoso R. *et al.* (2016)[20]	2 RCTs 6 Non-RCTs	8	OR 0.31 95%-CI [0.15 to 0.64]	I^2 =0, χ^2= 0.62, *p value*= 1.00
Jiang J. *et al.* 2017[40]	5 Non-RCTs	5	OR 0.32 95%-CI [0.13 to 0.78]	I^2 =0, χ^2= 0.38, *p value*=0.98
Maltoni S. *et al.* 2018[18]	2 RCTs 7 Non-RCTs	9	RR 0.33 95%-CI [0.18 to 0.62]	I^2 =0, χ^2= 0.75, *p value*= 1.00
Hachem AH. *et al* 2018[23]	8 RCTs	8	OR 0.39 95%-CI [0.11 to 1.4]	I^2 =0

Table 13: Pericardial Effusion

Review	Type of study	Study (n)	Measure of effect	Statistical Heterogeneity
Cardoso R. *et al.* (2016)[20]	3 RCTs 10 Non-RCTs	13	OR 0.44 95%-CI [0.28 to 0.69]	I^2 =0, χ^2= 5.06 *p value*= 0.96
Cheng X. *et al.* 2015.[22]	3 RCTs 8 Non-RCTs	11	RR 0.58 95%-CI [0.30 to 1.06]	I^2 =0 (χ^2= not reported)
Maltoni S. *et al.* 2018[18]	3 RCTs 6 Non-RCTs (CB vs RFA)	9	RR 0.53 95%-CI [0.31 to 0.91]	I^2 =0, χ^2=4.55 *p value*= 0.80
Maltoni S. *et al.* 2018[18]	Sub-group 1 Non-RCT	1	RR 0.31 95%-CI [0.02 to 6.24]	N/A

Table 14: Cardiac Tamponade/Pericardial Effusion

Review	Type of study	Study (n)	Measure of effect	Statistical Heterogeneity
Garg J. *et al.* 2016[27]	3 RCTs 9 Non-RCTs	12	OR 0.43 95%-CI [0.26 to 0.72]	I^2 =0, χ^2=6.11 *p value*= 0.87
Ma H. *et al.* 2017[26]	4 RCTs 9 Non-RCTs	13	OR 0.62 95%-CI [0.41 to 0.93]	I^2 =0, χ^2=9.65 *p value*=0.65

Table 15: Phrenic Nerve Palsy

Review	Type of study	Study (n)	Measure of effect	Statistical Heterogeneity
Buiatti, A. *et al.* (2016)[19]	3 RCTs 2 Non-RCTs	5	Risk ratio 13.60 95%-CI [3.87 to 47.81]	I^2 =6% χ^2=4.26, *p value*=0.37
Cardoso R. *et al.* (2016)[20]	3 RCTs 5 Non-RCTs	8	OR 7.40 95%-CI [2.56 to 21.34]	I^2 =0%, χ^2=1.89, *p value*=0.97
Cheng X. *et al.* 2015.[22]	3 RCTs 8 Non-RCTs	11	RR 6.29 95%-CI [2.44 to 16.21]	I^2 =0%, (χ^2 not reported)
Garg, J. 2016 [28]	4 RCTs 9 Non-RCTs	13	OR 14.19 95%-CI [6.92 to 29.10]	I^2 =0%, χ^2=9.23, *p value*=0.68
Garg, J. 2016 [28]	3 RCTs 4 Non-RCTs	7	OR 4.62 95%-CI [1.97 to 10.81]	I^2 =0%, χ^2=1.11, *p value*=0.98
Hachem AH. *et al* 2018[23]	5 RCTs	6	OR 10.3 95%-CI [3.09 to 34.6]	I^2=0%, (χ^2not reported)
Jiang J. *et al.* 2017[40]	8 Non-RCTs	8	OR 17.35	I^2 =7%, χ^2=7.56, *p value*=0.37

			95%-CI [6.57 to 45.85]	
Ma, H. 2017[27]	5 RCTs 13 Non-RCTs	18	OR 10.72 95%-CI [5.59 to 20.55]	I^2 =0%, χ^2=15.89, *p value*=0.53
Maltoni S. *et al.* 2018[18]	3 RCTs 9 Non-RCTs	12	RR 5.43 95%-CI [2.67 to 11.04]	I^2 =0%, χ^2=2.86, *p value*=0.99

SUPPLEMENTARY TABLE S1: SEARCH STRATEGY

Search strategy up to 18 April 2019

Total- 1639

Duplicates- 522

SEARCH HISTORIES:

Search No.	Date	Database searched	Hits (before duplicate removal)
1	15/04/2019	Cochrane Library	115
2	15/04/2019	Epistemonikos	225
3	16/04/2019	PROSPERO	49
4	16/04/2019	Embase (OVID)	365
5	16/04/2019	Medline (OVID)	428
6	16/04/2019	Medline (PubMed)	457
FINAL NUMBER OF REFERENCES IN ENDNOTE AFTER DELETING DUPLICATES = 1117			

Search Name: Cochrane library issue up to 18 April 2019

Date Run: 17 April 2019

#12 MeSH descriptor: [Atrial Fibrillation] explode all trees 3473

#13 "Paroxysmal atrial fibrillation ":ti,ab,kw (Word variations have been searched) 705

#14 MeSH descriptor: [Catheter Ablation] explode all trees 1585

#15 "catheter ablation":ti,ab,kw (Word variations have been searched) 2126

#16 "radiofrequency ablation":ti,ab,kw (Word variations have been searched) 1212

#17 "RF ablation":ti,ab,kw (Word variations have been searched) 184

#18 MeSH descriptor: [Cryosurgery] explode all trees 356

#19 "cryosurgery":ti,ab,kw (Word variations have been searched) 441

#20 "cryoablation":ti,ab,kw (Word variations have been searched) 193

#21 #12 or #13 3842

#22 #14 or #15 or #16 or #17 or #18 or #19 or #20 3151

#23 #21 and #22 847

Epistemonikos

(title:((title:("Atrial Fibrillation" OR "Paroxysmal atrial fibrillation ") OR abstract:("Atrial Fibrillation" OR "Paroxysmal atrial fibrillation ")) AND (title:("catheter ablation" OR "radiofrequency ablation" OR "RF ablation" OR cryoablation) OR abstract:("catheter ablation" OR "radiofrequency ablation" OR "RF ablation" OR cryoablation))) OR abstract:((title:("Atrial Fibrillation" OR "Paroxysmal atrial fibrillation ") OR abstract:("Atrial Fibrillation" OR "Paroxysmal atrial fibrillation ")) AND (title:("catheter ablation" OR "radiofrequency ablation" OR "RF ablation" OR cryoablation) OR abstract:("catheter ablation" OR "radiofrequency ablation" OR "RF ablation" OR cryoablation))))

PROSPERO

#1	MeSH DESCRIPTOR Atrial Fibrillation EXPLODE ALL TREES	121
#2	Paroxysmal atrial fibrillation	11
#3	#1 OR #2	122
#4	catheter ablation	22
#5	radiofrequency ablation	47
#6	Cryoablation	23
#7	MeSH DESCRIPTOR Cryosurgery EXPLODE ALL TREES	8
#8	#4 OR #5 OR #6 OR #7	78
#9	#8 AND #3	25

Database: Embase 1947-Present, updated daily

Search Strategy:

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1 Paroxysmal Atrial Fibrillation.mp. or paroxysmal atrial fibrillation/ or paroxysmal heart atrium fibrillation/ (7870)

2 PAF.ab. or PAF.ti. (13890)

3 1 or 2 (20149)

4 catheter ablation/ or Catheter Ablation.mp. (30675)

5 radiofrequency ablation.mp. or radiofrequency ablation/ (31814)

6 RF ablation.ab. or RF ablation.ti. (3833)
7 Cryosurgery.mp. or cryosurgery/ (11440)
8 cryoablation.mp. or cryoablation/ (6711)
9 4 or 5 or 6 or 7 or 8 (69774)
10 3 and 9 (2999)
11 exp review/ (2342082)
12 (literature adj3 review$).ab. or (literature adj3 review$).ti. (303286)
13 exp meta-analysis/ (133186)
14 exp "Systematic Review"/ (148437)
15 11 or 12 or 13 or 14 (2588764)
16 (systematic$ adj2 (review$ or overview)).ab. or (systematic$ adj2 (review$ or overview)).ti. (146423)
17 (meta?anal$ or meta anal$ or meta-anal$ or metaanal$ or metanal$).ab. or (meta?anal$ or meta anal$ or meta-anal$ or metaanal$ or metanal$).ti. (154304)
18 (medline or medlars or embase or pubmed or cinahl or amed or psychlit or psyclit or psychinfo or psycinfo or scisearch or cochrane).ab. or (medline or medlars or embase or pubmed or cinahl or amed or psychlit or psyclit or psychinfo or psycinfo or scisearch or cochrane).ti. (192334)
19 RETRACTED ARTICLE/ (8656)
20 18 or 19 (200848)
21 15 and 20 (150594)
22 16 or 17 or 21 (300279)
23 10 and 22 (76)
24 15 or 16 or 17 (2635226)
25 10 and 24 (265)

Database: Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <1946 to Present>
Search Strategy:
---

1 Paroxysmal Atrial Fibrillation.mp. or paroxysmal atrial fibrillation/ or paroxysmal heart atrium fibrillation/ (48139)
2 PAF.ab. or PAF.ti. (11343)
3 1 or 2 (58528)
4 catheter ablation/ or Catheter Ablation.mp. (31986)
5 radiofrequency ablation.mp. or radiofrequency ablation/ (12626)
6 RF ablation.ab. or RF ablation.ti. (2228)

7 Cryosurgery.mp. or cryosurgery/ (13108)

8 cryoablation.mp. or cryoablation/ (13362)

9 4 or 5 or 6 or 7 or 8 (48201)

10 3 and 9 (9421)

11 exp review/ (2364271)

12 (literature adj3 review$).ab. or (literature adj3 review$).ti. (246024)

13 exp meta-analysis/ (85370)

14 exp "Systematic Review"/ (0)

15 11 or 12 or 13 or 14 (2504058)

16 (systematic$ adj2 (review$ or overview)).ab. or (systematic$ adj2 (review$ or overview)).ti. (120553)

17 (meta?anal$ or meta anal$ or meta-anal$ or metaanal$ or metanal$).ab. or (meta?anal$ or meta anal$ or meta-anal$ or metaanal$ or metanal$).ti. (122472)

18 (medline or medlars or embase or pubmed or cinahl or amed or psychlit or psyclit or psychinfo or psycinfo or scisearch or cochrane).ab. or (medline or medlars or embase or pubmed or cinahl or amed or psychlit or psyclit or psychinfo or psycinfo or scisearch or cochrane).ti. (162514)

19 RETRACTED ARTICLE/ (0)

20 18 or 19 (162514)

21 15 and 20 (126924)

22 16 or 17 or 21 (252923)

23 10 and 22 (211)

Pubmed History

Search	Query	Items found
#33	Search (#32) OR #21 Field: Title/Abstract Sort by: PublicationDate	343
#32	Search (#31) AND #20 Field: Title/Abstract Sort by: PublicationDate	195
#21	Search (#6) AND #19 Sort by: PublicationDate Filters: Systematic Reviews; Field: Title/Abstract	323
#31	Search ((#30) OR #29) OR #28 Field: Title/Abstract Sort by: PublicationDate	203260
#20	Search (#6) AND #19 Field: Title/Abstract Sort by: PublicationDate	8915
#28	Search meta-analysis or meta-analysis or metaanalysis Field: Title/Abstract Sort by: PublicationDate	106023

Search	Query	Items found
#30	Search systematic review Field: Title/Abstract Sort by: PublicationDate	119671
#29	Search "Meta-Analysis" [Publication Type] Field: Title/Abstract Sort by: PublicationDate	78730
#23	Search systematic review Sort by: PublicationDate Filters: Systematic Reviews; Field: Title/Abstract	111300
#25	Search "Meta-Analysis" [Publication Type] Sort by: PublicationDate Filters: Systematic Reviews; Field: Title/Abstract	78065
#27	Search meta-analysis or meta-analysis or metaanalysis Sort by: PublicationDate Filters: Systematic Reviews; Field: Title/Abstract	86852
#26	Search meta analysis Sort by: PublicationDate Filters: Systematic Reviews; Field: Title/Abstract	86119
#19	Search ((((((#18) OR #16) OR #15) OR #13) OR #12) OR #9) OR #8 Field: Title/Abstract Sort by: PublicationDate	47323
#6	Search (#5) OR "Atrial Fibrillation"[Mesh] Field: Title/Abstract Sort by: PublicationDate	55690
#8	Search "Catheter Ablation"[Mesh] Field: Title/Abstract Sort by: PublicationDate	26823
#18	Search cryoablation Field: Title/Abstract Sort by: PublicationDate	2913
#16	Search "Cryosurgery" Field: Title/Abstract Sort by: PublicationDate	3359
#15	Search "Cryosurgery"[Mesh] Field: Title/Abstract Sort by: PublicationDate	11857
#13	Search rf ablation Field: Title/Abstract Sort by: PublicationDate	3495
#12	Search radiofrequency ablation Field: Title/Abstract Sort by: PublicationDate	17513
#9	Search Catheter Ablation Field: Title/Abstract Sort by: PublicationDate	13050

Search	Query	Items found
#5	Search paroxysmal atrial fibrillation or PAF Field: Title/Abstract Sort by: PublicationDate	17052
#4	Search paroxysmal atrial fibrillation Field: Title/Abstract Sort by: PublicationDate	6916
#3	Search paroxysmal atrial fibrillation Sort by: PublicationDate	65878
#2	Search "Atrial Fibrillation"[Mesh] Sort by: PublicationDate	43991

Appendix A: EP Europace Instructions to authors

https://academic.oup.com/europace/pages/General_Instructions#Submission%20of%20manuscripts

EP Europace - The European Journal of Pacing, Arrhythmias and Cardiac Electrophysiology - is an official Journal of the European Heart Rhythm Association (EHRA), a branch of the European Society of Cardiology (ESC), and the ESC Working Group on Cardiac Cellular Electrophysiology. The journal aims to provide an international avenue of communication for top quality original scientific work and reviews in the fields of arrhythmias, cardiac electrophysiology, and pacing. Clinical investigations, basic science translational research, technical issues, short case reports, comprehensive reviews, editorial comments, educational articles, images in pacing and electrophysiology, book reviews and correspondence are included.

Papers that do not adhere to the following instructions will be returned for revision before assessment.

Submission of manuscripts

EP Europace operates a web-based system for submission and peer-review, Editorial Manager. This system is intended to reduce manuscript processing times. The Journal does not require the first submission of an article to be formatted to the *EP Europace* style. Further details can be found under "First submission of articles". Text, tables and figures should be prepared in accordance with the instructions given under "Preparation of Manuscripts" below.

Authors must specify the category for which their submission is intended.

If you need help with the electronic submission process please contact the editorial office (europace.editorialoffice@oup.com). Enquiries about the review process and other journal matters should also be directed to the Editorial Office.

Online submission

Please go to the Editorial Manager website for *EP Europace*, and follow the instructions given on screen. First-time users must click 'Register' on the navigation menu at the top of the screen, and enter the required information. The system will send you an automatic e-mail with your username and password. Detailed guidelines are available at the Editorial Manager site, by clicking on 'Help' or viewing the author or reviewer tutorials.

You will be asked to supply information about your manuscript and then attach your files containing the text and any figures and tables. Editorial Manager will create a PDF from your data, which is the format in which the manuscript will be made available to the editors and referees during the peer-review process.

The manuscript text, references and figure legends should be prepared in a single file; if at any point in the process a manuscript with tracked changes is uploaded as well, this should be uploaded as a supplementary file. Papers should be submitted as Microsoft Word documents where possible, although other standard word-processing formats may be acceptable. The manuscript must not be submitted in .pdf format.

Any appendices must be supplied separately, and will be published as online-only supplementary data. Please change any references to Appendices in the manuscript to 'Supplementary', e.g. Supplementary Table S1, Supplementary Appendix 2.

Tables and figures may be included in the manuscript file, but must appear at the end of the text on separate sheets (and not embedded in the text).

If preferred, tables and illustrations may be prepared and submitted in separate files. Electronically submitted figures should be in high resolution and in one of the following formats: tiff, bitmap (.bmp), jpeg (.jpg), postscript (.ps or .eps) or as PowerPoint or Excel files. (Should the manuscript be accepted, the original photographs may be required for use in the production process.) Tables may be submitted as Word tables, or in .rtf format.

You will be required to enter the Abstract, Representative Figure and Keywords during the submission process. These may be copied and pasted from the manuscript document, but must still appear in the manuscript itself. Please supply the names and addresses of three referees to whom your manuscript may be sent for review in the 'Enter Comments' section of your electronic submission.

When completing the 'Add Authors' section, please enter the names of the all the authors listed on the manuscript.

First submission of articles

We will consider initial Original Article and Review Article submissions in which the manuscript file is not formatted according to the *EP Europace* journal style. Manuscripts can be submitted in any common document format that can be easily opened and read by others. A single PDF or Word file is usually reliable.

- All elements must be completed within the online submission form including manuscript title, author names, affiliations, and address (including email).
- Manuscript file must contain page numbers and figures may be embedded within the manuscript or in separate files.
- Supplementary Material files must be uploaded separately.

- References can be formatted in any readable style at submission. Authors are responsible for the accuracy of the references. Later, authors will be asked to comply with the journal's citation convention.
- Include acknowledgements, details of funding sources and grant numbers at the end of the text. Use author initials to indicate which authors were in receipt of grants.

Upon request, authors should be prepared to provide high-resolution figures separately, in a common image format (e.g. tif, jpg).

Those papers that are revised or ultimately accepted will be required to be formatted by the authors according to *Europace* format requirements.

Manuscript preparation

Text

The manuscript should be typed on one side only of A4 paper, double spaced using 2.5 cm wide margins all round. The text should be arranged as follows: Title page, Structured Abstract and Keywords, Introduction, Methods, Results, Discussion, Acknowledgements, References, Appendices, Tables, Figure legends. (For review articles, the format may be altered, if necessary; an abstract is not required but keywords should be supplied.) References, figures and tables should be numbered in the order in which they are cited in the text. Generic names should be used for drugs and instruments whenever possible.

Title page

The title page should bear: (a) title, (b) name(s) of authors, (c) institution(s) where work was done, (d) addresses of all authors, (e) name of author to whom proofs should be sent, with complete postal address, telephone and fax numbers, and e-mail details.

Abstracts and keywords

An abstract (maximum 250 words) should be typed double spaced. The abstract should be structured under the headings (1) Aims, (2) Methods (3) Results (4) Conclusion, followed by a list of three to six keywords.

Authors of Clinical Research and Basic Science articles are encouraged to submit a graphical abstract (schematic figure) as part of the article, in addition to the text abstract. The graphical abstract should clearly summarize the focus and findings of the article, and will be published as part of the article online and in PDF. The graphical abstract should be submitted for peer review as a separate file, selecting the appropriate file-type designation in the journal's online submission system. The file should be clearly named, e.g. *graphical_abstract.tiff*. See this pagefor guidance on appropriate file format and resolution for graphics. Please ensure graphical abstracts are in landscape format.

Acknowledgements

Acknowledgements and details of support in the form of grants, equipment or drugs are typed at the end of the text before References.

References

References are identified in the text by arabic numerals and numbered in the order cited. References are typed double spaced on sheets separate from the text in the Vancouver style. Complete information should be given for each reference, including title of article, abbreviated journal title and inclusive page numbers. The first six authors should be listed, followed by et al.

Please note: where a paper cited in the references of your paper has been published jointly in *EP-Europace* and another publication, authors are requested to cite the *EP-Europace* version of the paper.

Examples:

Gianfranchi L, Brignole M, Menozzi C, Lolli G, Bottoni N. Determinants of development of permanent atrial fibrillation and its treatment. Europace 1999; 1: 30–46.

Abello M, Merino JL, Peinado R, Gnoatto M, Arias MA, Gonzalez-Vasserot M, et al. Syncope following cardioverter defibrillator implantation in patients with spontaneous syncopal monomorphic ventricular tachycardia. Eur Heart J 2006; 27:89-95.

Ebels T, Elzenga NJ, Brenken U. Right atrial auricle as inter-caval tunnel in the cavopulmonary connexion: method to avoid the sinus node and its blood supply. In: Minami K, Korfer R, Wada J, eds. Cardiothoracic Surgery. Amsterdam: Elsevier Excerpta Medica 1992: 9–16.

ESC Knowledge Centre Surveys Program, Heart Failure II. http://www.escardio.org/guidelines-surveys/ehs/heart-failure/Pages/survey-hf2.aspx#.VDewJvldXTo (10 October 2014, date last accessed).

Personal communications, manuscripts in preparation and other unpublished data are not cited in the reference list but are mentioned in the text in parentheses. Titles of journals should be abbreviated in accordance with Index Medicus (see list printed annually in the January issue of Index Medicus).

Figures

There is no charge for colour figures in *EP- Europace*.

Authors are asked to use the journal's colour scheme in charts and diagrams as much as possible. PowerPoint allows the specification of custom colour according to the RGB definition.

Details of the journal's colour scheme

The Publisher may re-draw any charts or graphs using the colour palette where necessary during the production process. Authors will have the opportunity to correct any inappropriate changes at the proof correction stage.

All illustrations should be referred to as figures and should be numbered in a single sequence in the order in which they are mentioned in the text.

Electronically submitted figures should be in high resolution and in one of the following formats: tiff, bitmap (.bmp), jpeg (.jpg), portable data format (.pdf) or postscript (.ps or .eps). The resolution required for publication is 300-500 dpi.

If there is difficulty in submitting figures electronically, they may be sent by post to the Editorial Office. (Consideration of the manuscript will not begin until all materials have been received).

Useful information on preparing your figures for publication.

Representative Figure

Authors should designate a single figure that best summarizes their techniques, their results or the impact of their work. This figure (generally in colour) may be used as a cover illustration for *EP Europace* or appear in its table of contents.

Tables

Tables are typed on separate sheets with the table number (in arabic numerals) and title above and any explanatory notes below.

Supplementary data

Supporting material that is not essential for inclusion in the full text of the manuscript, but would nevertheless benefit the reader, can be made available by the publisher as online-only content, linked to the online manuscript. The material should not be essential to understanding the conclusions of the paper, but should contain data that is additional or complementary and directly relevant to the article content. Such information might include more detailed methods, extended data sets/data analysis, list of Investigators, or additional figures.

All text and figures must be provided in suitable electronic formats (instructions for the preparation of Supplementary data can be viewed here). All material to be considered as Supplementary data must be submitted at the same time as the main manuscript for peer review. It cannot be altered or replaced after the paper has been accepted for publication. Please indicate clearly the material intended as Supplementary data upon submission. Also ensure that the Supplementary data is referred to in the main manuscript where necessary.

ANNEXURE B: Article for submission to Cardiovascular Journal of Africa

THE COST-EFFECTIVENESS OF RADIOFREQUENCY ABLATION COMPARED WITH ANTI-ARRHYTHMIC DRUG THERAPY FOR PAROXYSMALATRIAL FIBRILLATION IN THE SOUTH AFRICAN PRIVATE SECTOR

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Abstract

This study, completed in 2011, measured the cost-effectiveness of radiofrequency ablation (RFA) as compared with antiarrhythmic drug therapy (ADT). A hypothetical cohort of patients with drug refractory paroxysmal atrial fibrillation (PAF) was treated with either RFA or one of three drugs, either on their own or in combination, this being projecting this over four years. Interviews were also conducted with South African electrophysiologists to determine costs associated with the two treatment options, including net treatment costs, average and incremental effectiveness in quality adjusted life-years (QALYs), average length of stay in hospital for complications, and the net monetary benefit of ADT compared with RFA for the isolation of the pulmonary veins. Results indicated that RFA may be a more cost-effective treatment for PAF patients in South African private health care than ADT. However, more evidence and analysis is needed before RFA can be established in routine care.

Keywords: paroxysmal atrial fibrillation, cost-effectiveness, radiofrequency ablation

Terminology:

In this paper, for convenience, we use the abbreviation ‘RFA’ as a short form for ‘radiofrequency ablation to isolate the pulmonary veins’ or ‘catheter ablation’, and ‘ADT’ for anti-arrhythmic drug therapy. We refer to atrial fibrillation as ‘AF’, while noting that the abbreviations ‘AF’ and ‘PAF’ are often used interchangeably, and that the type of AF is not always defined in the data. We use ‘PAF’ where we refer specifically to the paroxysmal type.

INTRODUCTION

Atrial fibrillation (AF) is the most common and sustained cardiac arrhythmia of clinical significance.[1] New estimates suggest that the prevalence of AF in patients of 20 years and older is approximately 3%. The prevalence of AF increases as patients age; and it is expected that 25% of all middle-aged adults in Europe and the USA will develop AF.[2] AF is associated with debilitating symptoms and an impaired quality of life. It increases the morbidity risk, such as heart failure and stroke.[3] There is also an associated 1.5-fold to two-fold increased risk of all-cause mortality in men and woman. In 2010, the worldwide estimate for people affected by AF was 33.5 million, with men accounting for 62% of this statistic.[4] Using the 2010 estimated incidence rates, the number of new AF cases per year is estimated at 2.7 million for men and 2.0 million for women.[1] Higher incidence and prevalence rates are found in developed countries than in the developing world.[5]

AF is associated with cardiac disease, particularly coronary artery disease, valvular heart disease, cardiomyopathy and stroke. Hypertension, diabetes, heart failure, chronic obstructive pulmonary disease and renal failure are among the other most frequent co-morbidities.[2]

AF is a significant public health problem, accounting for 1% of the National Health System budget in the UK, and between USD 16 billion and USD 26 billion in the US each year.[1, 3] It is suggested that between 10 and 40% of patients who have AF will be hospitalised each year. [6] According to a study published in 2015, the mean per capita medical spending for adults with AF was USD 38,861, CI-95% [USD 35,781 to USD 41,950] while for similar patients without AF, it was USD 28,506, CI-95% [USD 28,409 to USD 28,603]. This difference was statistically significant ($p<0.001$). It is further estimated that there are 596,000 undiagnosed non-valvular AF cases per year in the US, and that it would cost an additional USD 3.1 billion (CI-95% [USD 2.7 to USD 3.7 billion]) to treat these cases.[7]

The cost of treating AF in South Africa is unknown. A South African survey on AF completed in 2014 found that the single most prevalent clinical characteristic associated with AF was hypertension (65.9%), and that 34.4% of patients had required hospitalisation during the previous 12 months, with one third of these patients requiring multiple hospitalisations.[8] The estimated cost of treating all South African patients who suffered from sequelae of diabetes, hypertension and hypercholesterolaemia - all known risk factors for developing AF - would be USD 34.2 billion per year, this being roughly 10% of South Africa's 2017 GDP.[9]

The restoration and maintenance of sinus rhythm in patients with AF is favoured as it may provide important hemodynamic benefits not afforded by rate control, as well as subjective benefits. This is therefore an important goal for AF patients.[10]

The 2014 American College of Cardiology (ACC), American Heart Association (AHA), Heart Rhythm Society (HRS) and European Society of Cardiology (ECS) 2016 guidelines recommend anti-coagulant and anti-arrhythmic drugs for treating patients with symptomatic AF.[2] Both rate- and rhythm-control strategies are recommended, based on the individual patients' underlying pathologies.[2]

RFA offers an alternative treatment option for AF. While not the first-line therapy for AF, RFA has become first-line therapy for many other supra-ventricular arrhythmia.[11] RFA uses energy that is high-frequency but low-voltage. Radiofrequency energy causes the tissue to heat up and small uniform lesions are created. The size of the lesions are a function of the length of the distal-ablation electrode, type of catheter used (irrigated or non-irrigated), uniform contact at the catheter-tissue interface and the power used during ablation.[12,13]

While the success rates for RFA are highest in patients with common forms of supra-ventricular tachycardia (SVT) - for example, atrioventricular nodal re-entrant tachycardia (AVNRT)[11] -

as technology has improved, success rates have improved for other common types of cardiac arrhythmia, such as AF. This includes both of the following success measures: success at the end of the procedure; and no incidents of AF longer than 30 seconds at 12 months.[14, 15] The 2014 AHA guidelines recommend RFA as a strategy for maintaining sinus rhythm in patients with symptomatic AF who are refractory or intolerant to at least one Vaughan Williams Class I or III drug as a Class IA indication. Patients must, however, be assessed for procedural risks, which, if present, would then be recommended as a Class IC indication.[16]

A meta-analysis undertaken by Noheria *et al*. in 2008 showed that 75.7% of patients treated with RFA were free of AF recurrence at 12 months, compared with 18.8% treated with ADT (RR 3.73, 95%-CI [2.47-5.63], $P<0.001$).[11]In this meta-analysis,[11] reported adverse events included hospitalisation, mild to moderate pulmonary vein stenosis in the RFA group and bleeding. Pappone *et al.*'s 2011 ablation for paroxysmal atrial fibrillation (APAF) study reported seven times more hospital admissions for the ADT group than the RFA group over the same period.[17] Other reported adverse events in the RFA group included stroke, pericardial effusion and phrenic nerve palsy .[18] Of the patients treated with amiodarone, 46.7% reported adverse events.[19]

ADT remains the first-line therapy when treating patients with AF. The up-front costs of RFA are significantly higher than the cost of drugs. However, the cost of drugs excludes the cost of complications, such as re-hospitalisation.

This study is important for the South African private healthcare market as many decision-makers are not willing to extrapolate data from cost-effectiveness studies performed in other regions of the world to apply them locally.

RFA has become accepted as a strategy to treat patients with PAF in patients who are refractory to at least one anti-arrhythmic drug that has failed to provide relief.[2] It is often the case that, when new technologies are introduced into healthcare, they are considered a cost driver until proven otherwise. Patients with AF have for many years been treated with a 'pill in the pocket' and other ADT strategies,[20] costing only a few thousand rand per year, whereas the up-front cost of RFA for AF may exceed R100,000 per patient. However, to understand the cost-effectiveness of one therapy compared with another, we must measure total costs over a period of time.

METHODS

To calculate the cost-effectiveness of RFA compared with ADT, we conducted a South African-specific cost-effectiveness analysis using a decision tree analysis and a Markov simulation model for patients with AF. As a randomised control trials comparing RFA with ADT for outcome and success had not been done before in South Africa, this study modelled the analysis on an international study. The study chosen was the APAF) study by Pappone *et al*., [19,21] as it was sufficiently applicable to the South African setting and suitable for decision analytic modelling. The APAF was evaluated for possible bias, with none found. The treatment comparators in the model are pulmonary vein isolation using RFA or ADT.

Validation of the relevance of the APAF study in clinical practice in South Africa

The input and output values were taken from the APAF study.[19,21] However, it was crucial that the treatment regimen in South African practice be comparable with that followed by the APAF study. To gather information on the South African treatment regimen, 10 practicing electrophysiologists accredited by the Cardiac Arrhythmia Society of South Africa were contacted. At the time of our survey in 2011, these were only 10 practicing electrophysiologists in South Africa. Eight agreed to participate in the questionnaire survey. The purpose of the

study was explained and the patient population was described. Of the eight electrophysiologists, who were interviewed either in person or over the phone, seven performed RFA to treat AF, while the eighth chose not to treat complex arrhythmia. Information derived from the interviews indicated that the treatment regimen in South Africa was sufficiently similar to that described by the APAF study[22] to justify the use of Pappone *et al.*'s input and output values.

The overall finding from the responses to the questionnaire was that the strategies used by South African electrophysiologists to treat patients with AF compare favourably with the treatment regime in the Pappone *et al.* APAF study.

Model structure

The model used a decision tree analysis and a Markov simulation model to capture and simulate costs and outcomes at one, two, three and four-years. Four health states were created:

- 'AF' (experiencing AF – all patients enter the decision tree analysis with AF, at least one ADT treatment having failed.)
- 'No AF' (converted to sinus rhythm, or AF but no episodes of 30 seconds or longer)
- 'PAF' (paroxysmal episodes of AF lasting longer than 30 seconds); and
- 'AF controlled' (still experiencing AF but both doctor and patient felt control was adequate with regard to duration and frequency of arrhythmia recurrences).

Each cycle ran for six months over a four-year period. If a RFA patient required a second RFA procedure, this was done within six months. At the end of each six-month cycle a patient could be in any of the four health states described above.

Figure 1 shows possible transitions between health states in the Markov model.

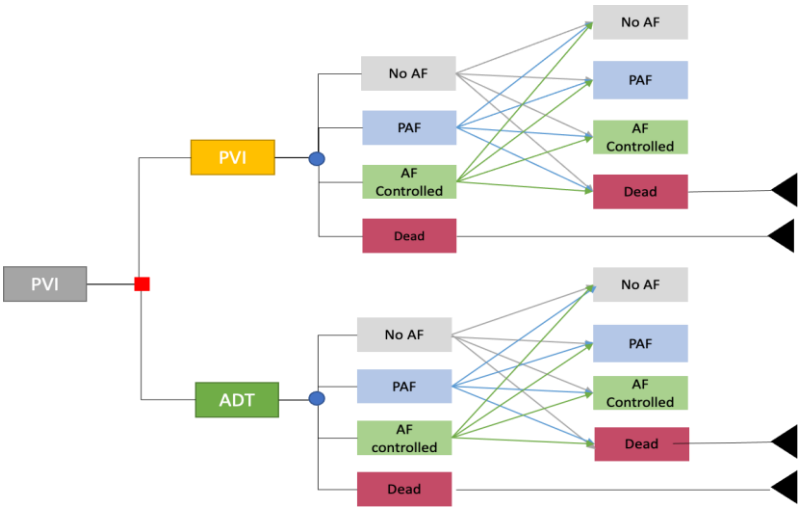

Figure 1. Transition probabilities in Markov Model.

Table 1 provides a summary of the transitions probabilities described in nine clinical studies. Pappone *et al.* investigated the probability of patients with PAF being randomised to receive either RFA or ADT (n=198).[22] Other clinical studies investigated the probability of AF recurring after one year for both RFA and ADT, as well as decrements in utilities in health states.[23] Other issues investigated for both RFA and ADT were death rate,[24] stroke rate and death rate from stroke,[25] hospitalisation rate and length of hospital stay,[26,27] one, three and five-year mortality,[28] cardiovascular hospitalisations, stroke and cardiovascular deaths,[3,29] and the number of hospital visits.[23]

Table 1: Transition probabilities applied to the Markov process for the ADT arm

The probability of:	Probability	Source
Receiving Amiodarone	0.33	Pappone *et al*, 2006
Receiving Flecainide	0.33	
Receiving Sotalol	0.33	
Amiodarone suppressing AF	0.36	
Flecainide suppressing AF	0.21	
Sotalol suppressing AF	0.15	
Receiving Amiodarone and Flecainide	0.65	
Receiving Sotalol and Flecainide	0.35	
Crossover from drug to PVI	0.56	
AF Free on Amiodarone and Flecainide	0.22	
AF control on Amiodarone and Flecainide	0.33	
AF control on Sotalol and Flecainide	0.23	
AF recurring after 1 year	0.29	McKenna *et al,* 2009
Adverse events (ADT)	0.30	Calkins *et al,* 2009
Death (ADT)	0.03	
AF free (PVI)	0.86	Pappone *et al,* 2006
Having AT (PVI)	0.03	
Being AF controlled (PVI)	0.05	
Require second PVI	0.06	
AF free after second PVI	0.83	
AF recurring after 1 year (PVI)	0.0335	McKenna *et al,* 2009
Adverse events (PVI)	0.049	Calkins *et al,* 2009
Death (PVI)	0.007	

Cost calculations

Cost data were provided by Netcare head office, as more than 80% of all RFA procedures at the time were performed in a Netcare hospital. All RFAs were done using a 3D mapping system. The sample consisted of data from 51 patients, representing 20% of all RFA procedures in 2010. The data were anonymised, so the authors could not see the identity of either the treating doctor or the patient.

The average length of hospital stay was 2.2 days, with a range of 1.5 to 5.5 days. The total average cost of the RFA was R134,411, with a median of R134,641.

Outpatient costs - applicable to both the ADT and RFA groups - included all the physicians' costs and diagnostic tests. The mean cost was R2,495 per patient, and the range was R2,363 to R2,891.

The cost of blood tests performed included 16 international normalised ratio tests (INR) with dosing. Only those patients receiving amiodarone required the following additional tests: urea, electrolytes (U&E) and creatinine; full blood count; and thyroid and liver functions.

The costs of drugs were derived from single exit prices on the Department of Health website. Calculations per drug were up to the maximum tolerable dose. For amiodarone, costs were calculated per day at each specific titrated and recommended dose. In instances where single drug therapy failed, and a combination of drugs was prescribed, the costs were calculated per day for combination 1 (flecainide and amiodarone, 200mg each) or combination 2 (flecainide, 200mg, and sotalol, 240mg).

Hospital costs included hospital stay, coronary care unit /ward fees, use of monitors, oxygen and medication. Theatre fees included a fee for the use of specialised equipment (for example, bi-plane X-ray, 3D-mapping system and ablation generator) and any drugs or disposables used in theatre, including catheters. Electrophysiology catheters were costed at the 2011 net acquisition price. All catheters were calculated as single use, as recommended by the manufacturer.

Finally, the costs for re-hospitalisation included hospital, electrophysiologist fee, blood tests and cardioversion; and were calculated at a mean cost per day.

Costs associated with re-hospitalisation for AF

The APAF study recorded 24 hospital admissions in the RFA group, nine of which were for repeat ablations, and 209 hospitalisations in the ADT group, of which 167 were for recurrence of AF and heart failure, and 42 for RFA.[23] To calculate the average cost of admissions related to heart failure or the recurrence of AF, we used a sample of non-patient- identifiable treatment costs from Netcare. The measures of interest were number of days in hospital per admission; and total cost, which included hospital, pathologist fee, cardioversion, daily coronary care unit or ward consultation with electrophysiologist fee, and one follow-up visit after discharge.

The mean length of hospitalisation was 5.1 days, with a median cost per hospital admission of R8,096, and a range of between R5,819 and R9,419. All the costs are shown on Table 2.

Table 2: Costs associated with treating PAF in South Africa

Item	Cost
Outpatient costs- average	R2 495.40
Pathology costs per year	R3 442. 26
Sotalol- per month	R508,29
Flecainide- per month	R662,12
Warfarin- per month	R45,49
Amiodarone 1st month	R866,09
Amiodarone month 2-12	R512,24
Procedure costs	R37 877,00
EP catheters	R54 101,00
Hospital stay	R11 350,00
Average fee for anaesthetist	R9 965,00
Average fee for radiographer	R1 617,00
Average fee for technologist	R2 919,00
Average fee for electrophysiologist	R16 582,00
Median costs of re-hospitalisation - Total	R31 801.66
Median costs of re-hospitalisation - Cost per day	R8 096.42

Quality of life (QoL) calculations

The QoL scores shown in Table 3 illustrate that patients who underwent PVI showed a significant long-term improvement in QoL scores. Analysis of the QoL scores of both groups on an intention-to-treat basis shows little difference between the PVI and ADT groups. However, it is noted that 90% of patients initially randomized to ADT and before crossing over to PVI showed significantly poorer QoL.

Table 3: Comparisons of QoL scores for PVI and ADT at baseline, before crossover and at 48 months

	PVI (n=99)			ADT's (n=99)			
	Baseline	**48 months**	**p-value**	**Baseline**	**Prior to crossover**	**48 months**	**p-value**
Physical functioning	69±18	85±12	<0.0001	68±21	***67±16*	82±15	<0.0001
Role physical	63±19	82±14	<0.0001	61±17	61±14	80±15	<0.0001
Bodily pain	68±19	80±17	<0.0001	66±24	***63±19*	77±21	<0.0001
General health	65±17	79±15	<0.0001	67±17	***63±17*	77±16	<0.0001
Vitality	56±22	71±23	<0.0001	55±18	***53±16*	68±21	<0.0001
Social functioning	68±22	87±14	<0.0001	66±20	***64±17*	86±14	<0.0001
Role emotional	70±24	86±18	<0.0001	70±22	***66±19*	84±19	<0.0001
Mental health	66±21	81±17	<0.0001	67±19	***62±15*	78±17	<0.0001
PCS	44.4±9	52.3±9	<0.0001	45.7±9	***44.1±7*	52.6±8	<0.0001
MCS	43.7±11	52.9±9	<0.0001	44.4±10	***42.5±10*	51.9±9	<0.0001

*Notes: Those in italics** indicate a deterioration from baseline.*

Source: Pappone et al., 2011: 20 & 21.

RESULTS

Cost-effectiveness analysis

After two years, the cost of ADT was R187,000 per patient, with a QALY of 1.53, while the cost of RFA was R168,000 per patient, with a QALY of 1.64. Figure 3 shows that RFA (a red square in the top left-hand quadrant) is both more efficacious and less costly than ADT (a blue triangle in the bottom right quadrant). The model thus estimates that RFA generates better health outcomes than ADT, including at lower cost, and can thus be considered the more cost-effective treatment option.

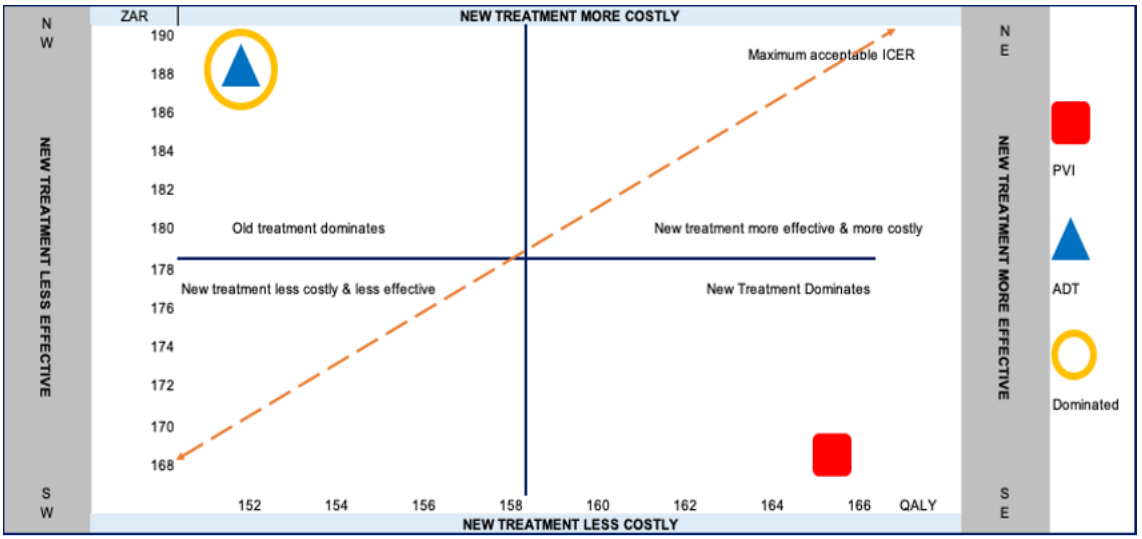

Figure 2: Cost-effectiveness analysis of PVI vs ADT for AF

Sensitivity analysis

Sensitivity analysis of the duration of the study (tDuration)

The first sensitivity analysis measured the cost-effectiveness at Years 1, 2, 3 and 4 (*tDuration*). One of the main criticisms of RFA for patients with AF is that the up-front costs are very high. However, the sensitivity analysis shows that PVI by means of RFA is less costly than ADT after Year 1 and continues to be less costly up to four years, with an incremental cost-effectiveness ratio (ICER) at two years of -R164,295 (see Table 4).

Table 4: Sensitivity analysis of duration (*tDuration*)

Strategy	Variable	Cost per patient	Eff.	CE	ICER	Dominated
PVI	1 year	R158 866	0.82059	193600.1075	552059.063	
ADT		R13 227	0.77243	171247.2542	0	
PVI	2 years	R168 437	1.64062	102667.0502	0	
ADT		R187 357	1.52545	122821.0932	-164295.3091	(Dominated)
PVI	3 years	R180 471	2.43056	74250.84062	0	
ADT		R259 999	2.19949	118208.8877	-344163.2532	(Dominated)
PVI	4 years	R194 621	3.19099	60990.94188	0	
ADT		R340 376	2.80595	121305.2412	-378547.6041	(Dominated)

Sensitivity analysis of cost

Figure 3 shows that up to 1.587 years, RFA costs more on average than ADT. After this, the cost of RFA flattens out and the cost of ADT grows exponentially. At one year, the cost of ADT is in the region of R130,000 compared with R160,000 for RFA. After four years, the cost of ADT reaches R340,000, while the cost of RFA has increased to only R190,000. This represents a cost increase of 19% for RFA and 162% for ADT.

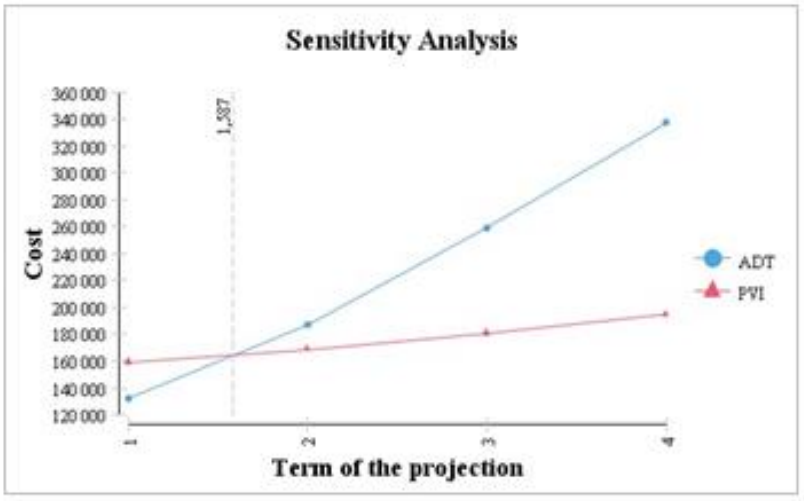

Figure 3: Measure of average cost at set intervals (one, two, three and four years after initiation of treatment)

Figure 4 shows that the incremental costs up to four years of RFA decline in Year 1. By Year 2, the line on the graph has flattened out, with the incremental cost being unchanged over Years 2 to 4. The opposite is true for ADT, which shows costs continuing to increase up to four years.

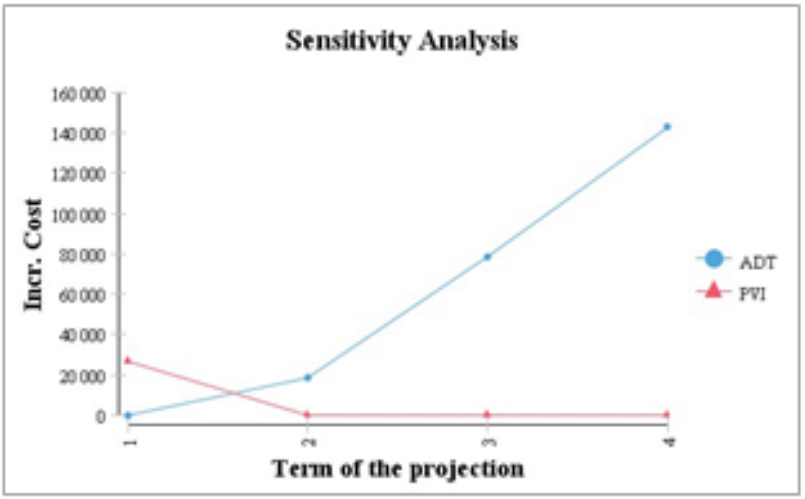

Figure 4: Measure of incremental cost at set intervals (one, two, three and four years after initiation of treatment)

Sensitivity analysis of incremental effectiveness

Figure 5 shows that the incremental effectiveness of RFA declines marginally over the first two years and thereafter remains unchanged, indicating that the efficacy remains constant up to Year 4. On the other hand, the incremental effectiveness of ADT starts declining from the inception of the study and continues to decline beyond Year 2 and up to Year 4.

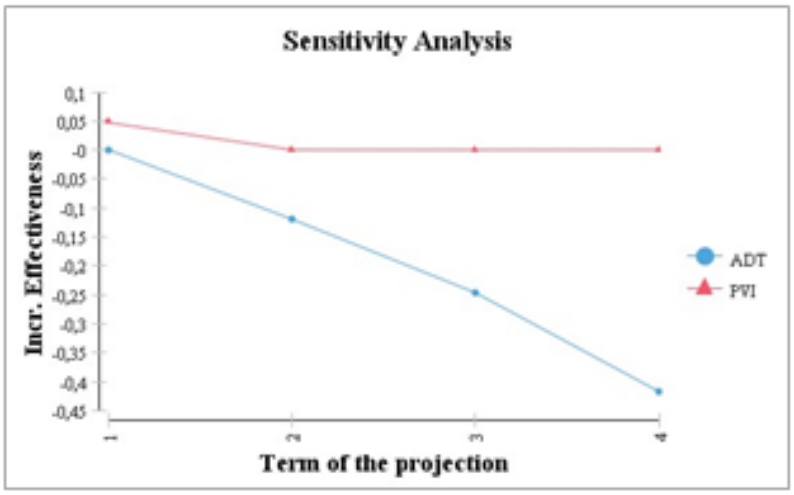

Figure 5: Measure of incremental effectiveness at set intervals (one, two, three and four years after initiation of treatment)

Sensitivity analysis of the net monetary benefits

The term 'net monetary benefits' refers to the value of an intervention in monetary terms. To calculate this, we need to know the willingness-to-pay threshold for a unit of benefit, in other words, the cost per QALY must be known. Using net monetary benefits provides a scale to compare the health outcomes and the use of resources to costs without using ratios like ICERs. To calculate the net monetary benefit, we used the formula: *([incremental benefit x threshold] - incremental cost).*

Figure 6 shows the net monetary benefit of the two treatment options over four years. Again, the net monetary benefit of the RFA group exceeds that of the ADT group from 1.3 years.

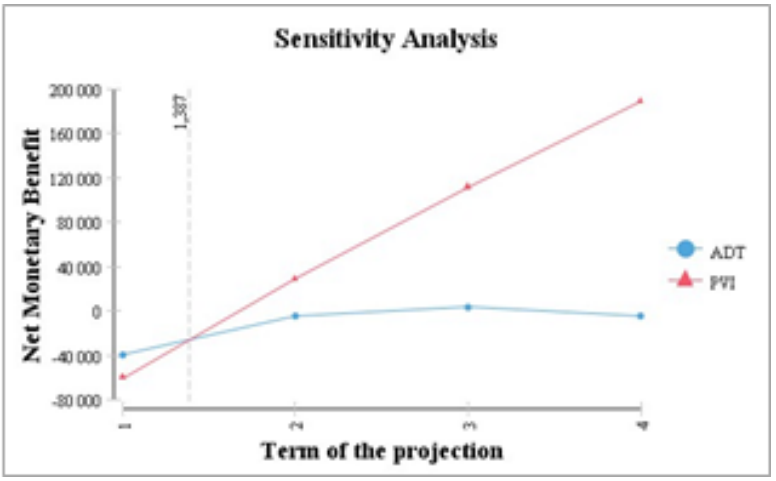

Figure 6: Measure of the net monetary benefit at set intervals (one, two, three and four years after initiation of treatment)

Sensitivity analysis of results associated with parameter change

Finally, a series of one-way sensitivity analyses was conducted on key parameters within the model to test for variation in results associated with parameter change. The Tornado diagram in Figure 7 shows ranges of results associated with particular parameters staked according to descending variation.

The one-way sensitivity analysis showed that the model was reasonably robust to the cost estimations of medicines and quality of life valuations for atrial fibrillation.

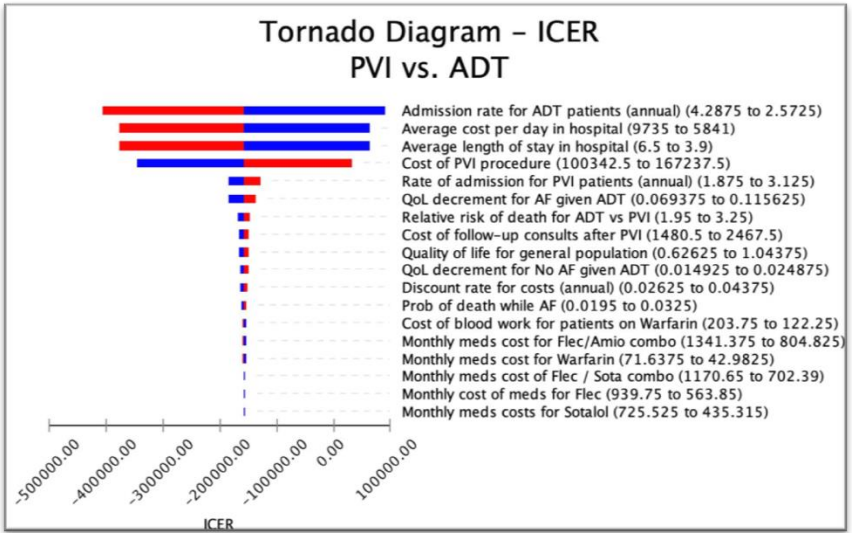

Figure 7: Tornado Diagram-ICER PVI vs ADT

The model was most sensitive to variations in annual admission rate for ADT patients, length and cost of stay in hospital for an AF-related event and the cost of the PVI procedure. However, at the extreme of the sensitivity analysis, the predicted ICER did not exceed R100,000/QALY for PVI vs ADT, providing reasonable confidence in the results of the analysis.

A one-way sensitivity analysis is limited in that it assumes parameter variation *ceteris paribus*, when in practice certain parameters are likely to vary in correlation. For instance, if medicine costs are greater, cost of hospital stay is also likely to be greater. A gold standard sensitivity analysis would have included probabilistic sensitivity analysis where all parameters are varied across a given distribution. However, given the availability of data and resources available for analysis, the authors have provided a one-way analysis to provide an indicative understanding of the implications of parameter variation.

DISCUSSION

The Cardiac Arrhythmia Society of Southern Africa, of which many of the South African electrophysiologists are members, has adopted the ACC, AHA, HRS and ESC guidelines for the treatment of AF. At the time of writing this study (2019), the South African private sector reserved RFA for patients who had failed at least one ADT.

Multiple studies have demonstrated clinical benefits of RFA for PAF, including improved maintenance of sinus rhythm and improved quality of life when compared with ADT. In our study, we used a Markov simulation model to project costs and QALY for patients with drug-refractory PAF who were treated with either RFA or ADT. Using assumptions and transitions probabilities derived from medical literature, we found that, within the South African health care system, RFA is cost-effective when compared with ADT.

RFA for AF should be considered more widely for patients with symptomatic AF as it is not only more efficacious but could also be more cost-effective in the South African context.

Study limitations

All the models used are simulations and therefore approximations of reality. The treatment of PAF is complex, as well as patient- and physician-dependent; and the models necessarily simplify treatment options and their clinical and cost impacts. However, the models do provide some indication of the relative cost-effectiveness of the treatment options. The clinical outcomes used in the models were based on a randomised controlled trial from a hospital in Milan, requiring an assumption that the clinical outcomes observed would be similar to outcomes in the South African private healthcare setting. This necessity, arising from the limited available data on RFA in South Africa, is somewhat mitigated by the use of the survey of South African clinicians who confirmed broadly similar practice in the South African private sector compared with the trial setting. The model only projects costs and treatment outcomes for a four-year period: this does not incorporate the full range of clinical and cost parameters experienced over the remaining life-time of the patients. However, as ADT incurs ongoing costs with limited relative health gain, extending the length of time incorporated within the model is likely to improve the relative cost-effectiveness of RFA. This would not change our current interpretation of our results.

Another limitation relates to the method used. Since the data in the models were only from the private healthcare sector, they therefore cannot be used for recommendations for public healthcare in South Africa. In order to do so, we would have needed access to substantially more information on public sector costs and outcomes.

Conclusion and recommendations

The economic value of RFA has not been established in South Africa. Because of this, RFA is deemed to be either highly cost-effective or not cost-effective at all, depending on whose viewpoint is being considered (usually either the treating physician's or the funder's).

Some of the biggest risk factors for heart disease and stroke are physical inactivity, smoking, excessive alcohol and an unhealthy diet, resulting in hypertension, diabetes, hyperlipidaemia and obesity.(30) These are also risk factors for AF.

In the past, the main healthcare problems in Africa and South Africa were infectious diseases. However, the global prevalence of AF increased by 49% between 1990 and 2007, and again by 31% between 2007 and 2017, including in developing nations like South Africa.(31)

There is a paucity of data on AF in South Africa in particular and sub-Saharan Africa as a whole The limited data that exist suggest the prevalence of AF is currently lower in these regions than in developed countries but is set to increase over the next two to three decades. This is because major forces driving social, cultural and economic change, such as urbanisation, globalisation, and populations living longer, result in an increase of risk factors for cardiovascular disease.(30) Patients with AF constitute a significant burden of disease and associated costs.

Despite the limitations of this study, and the fact that it was based on a small number of privately insured patients in South Africa, it still represents an important contribution to the literature and maps a way forward for future research.

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APPENDICES

Appendix A: *Cardiovascular Journal of Africa* style guidelines

https://www.cvja.co.za/authors.php

ARTICLE SUBMISSION

All categories of manuscripts for the Cardiovascular Journal of Africa must be submitted on-line to Editorial Manager. You will be assigned your own password and user name. This will allow complete interaction between the editor and authors. Internally, reviewers will be approached to review material in their field of expertise and assigned with similar interaction. All information will be entirely protected and confidential.

All submissions should be written in a clear and succinct manner, following the style of the Journal. Title page should include a descriptive title; authors' surname and forename, address of each author and full address, telephone, fax and e-mail contacts for the corresponding author. In text: tables and figures are either inserted as part of sentence, for example Table 1, or in parentheses, for example (Fig. 1). Each table should carry a descriptive heading.

Editorial Manager will clearly indicate which aspects of the submission must be supplied off-line (**download off-line document**). This must be provided to the Journal by mail (PO Box 1013, Durbanville, South Africa, 7551) or e-mail to **info@clinicscardive.com**

All images MUST be at or above intended display size, with the following image resolutions: Line Art 800 dpi, Combination (Line Art + Halftone) 600 dpi, Halftone 300 dpi Image files also must be cropped as close to the actual image as possible.

Preferred Image Format

Image Format	.tif
Image Width	Greater than or equal to intended display size
Colorspace	RGB
DPI	500+
Alpha Channels	None
Layers	Flattened

Alternative Image Format

Image Format	.jpg
Image Width	Greater than or equal to intended display size
Colorspace	RGB
DPI	500+
Compression Quality	Maximum

References numbered in the order of appearance in the text, according to Vancouver style. For articles: Author AB, Author C, Author M. The title of the article. Abbreviated journal title 1999; 14: 172–183. For book chapters: Author AB, Author CD. The title of the chapter. In: Editor A, Editor BC, ed. Title of the book, 2nd edn. Location: Publisher, 1999: 133 –139. DOI Numbers / PMID (Pubmed ID / PMC ID) must be added to all references to facilitate tagging for PubMed Central.

Original articles: Title page as above. Abstract (150 words) a short inclusive statement suitable for direct electronic abstracting, identifying the purpose of the study, key methods, the main results and the main conclusion. Keywords: maximum of six keywords for indexing. Introduction: concise description of background, sufficient for the non-specialist to appreciate the context of the work. Clear statement of the purpose of the study. Methods: a brief description of study design, procedures, analytical techniques and statistical evaluation. Results: a clear account of the study findings using quantitative language where possible and cross-referenced to tables and figures. Discussion: an interpretation of the study placed within the context of current knowledge, leading to specific conclusions where possible. Acknowledgements. References, figures and tables as above.