

ACCURACY OF RISK PREDICTION TOOLS FOR ACUTE CORONARY SYNDROME: A SYSTEMATIC REVIEW

JOHET ENGELA VAN ZYL

Thesis presented in partial fulfilment of the requirements

for the degree of Master of Nursing Science

in the Faculty of Medicine and Health Science

at Stellenbosch University



Supervisor: Dr Oswell Khondowe

Department of Nursing

March 2015

Declaration

By submitting this thesis electronically, I, Johet Engela van Zyl, declare that the entirety of the work contained therein is my own original work, that I am the owner of the copyright thereof (unless to the extent explicitly otherwise stated) and that I have not previously in its entirety or in part submitted it for obtaining any qualification.

December 2014

Abstract

Background: Coronary artery disease is a form of cardiovascular disease (CVD) which manifests itself in three ways: angina pectoris, acute coronary syndrome and cardiac death. Thirty-three people die daily of a myocardial infarction (cardiac death) and 7.5 million deaths annually are caused by CVD (51% from strokes and 45% from coronary artery disease) worldwide. Globally, the CVD death rate is a mere 4% compared to South Africa which has a 42% death rate. It is predicted that by the year 2030 there will be 25 million deaths annually from CVD, mainly in the form of strokes and heart disease. The WHO compared the death rates of high-income countries to those of low- and middle-income countries, like South Africa, and the results show that CVD deaths are declining in high-income countries but rapidly increasing in low- and middle-income countries. Although there are several risk prediction tools in use worldwide, to predict ischemic risk, South Africa does not use any of these tools. Current practice in South Africa to diagnose acute coronary syndrome is the use of a physical examination, ECG changes and positive serum cardiac marker levels. Internationally the same practice is used to diagnose acute coronary syndrome but risk assessment tools are used additionally to this practise because of limitations of the ECG and serum cardiac markers when it comes to NSTEMI-ACS.

Objective: The aim of this study was to systematically appraise evidence on the accuracy of acute coronary syndrome risk prediction tools in adults.

Methods: An extensive literature search of studies published in English was undertaken. Electronic databases searched were Cochrane Library, MEDLINE, Embase and CINAHL. Other sources were also searched, and cross-sectional studies, cohort studies and randomised controlled trials were reviewed. All articles were screened for methodological quality by two reviewers independently with the QUADAS-2 tool which is a standardised instrument. Data was extracted using an adapted Cochrane data extraction tool. Data was entered in Review Manager 5.2 software for analysis. Sensitivity and specificity was calculated for each risk score and an SROC curve was created. This curve was used to evaluate and compare the prediction accuracy of each test.

Results: A total of five studies met the inclusion criteria of this review. Two HEART studies and three GRACE studies were included. In all, 9 092 patients participated in the selected studies. Estimates of sensitivity for the HEART risks score (two studies, 3268 participants) were 0,51 (95% CI 0,46 to 0,56) and 0,68 (95% CI 0,60 to 0,75); specificity for the HEART risks score was 0,90 (95% CI 0,88 to 0,91) and 0,92 (95% CI 0,90 to 0,94). Estimates of sensitivity for the GRACE risk score (three studies, 5824 participants) were 0,03 (95% CI

0,01 to 0,05); 0,20 (95% CI 0,14 to 0,29) and 0,79 (95% CI 0,58 to 0,93). The specificity was 1,00 (95% CI 0,99 to 1,00); 0,97 (95% CI 0,95 to 0,98) and 0,78 (95% CI 0,73 to 0,82). On the SROC curve analysis, there was a trend for the GRACE risk score to perform better than the HEART risk score in predicting acute coronary syndrome in adults.

Conclusion: Both risk scores showed that they had value in accurately predicting the presence of acute coronary syndrome in adults. The GRACE showed a positive trend towards better prediction ability than the HEART risk score.

Keywords: acute coronary syndrome, coronary artery disease, risk assessment tools, diagnosis, serum cardiac markers, ECG, QUADAS-2.

Opsomming

Agtergrond: Koronêre bloedvatsiekte is 'n vorm van kardiovaskulêre siekte. Koronêre hartsiekte manifesteer in drie maniere: angina pectoris, akute koronêre sindroom en hartdood. Drie-en-dertig mense sterf daaglik aan 'n miokardiale infarsie (hartdood). Daar is 7,5 miljoen sterftes jaarliks as gevolg van kardiovaskulêre siektes (51% deur beroertes en 45% as gevolg van koronêre hartsiektes) wêreldwyd. Globaal is die sterfte syfer as gevolg van koronêre vaskulêre siekte net 4% in vergelyking met Suid Afrika, wat 'n 42% sterfte syfer het. Dit word voorspel dat teen die jaar 2030 daar 25 miljoen sterfgevallen jaarliks sal wees, meestal toegeskryf aan kardiovaskulêre siektes. Die hoof oorsaak van sterfgevallen sal toegeskryf word aan beroertes en hart siektes. Die WHO het die sterfgevallen van hoe-inkoms lande vergelyk met die van lae- en middel-inkoms lande, soos Suid Afrika, en die resultate het bewys dat sterfgevallen as gevolg van kardiovaskulêre siekte is besig om te daal in hoe-inkoms lande maar dit is besig om skerp te styg in lae- en middel-inkoms lande. Daar is verskeie risiko-voorspelling instrumente wat wêreldwyd gebruik word om isgemiese risiko te voorspel, maar Suid Afrika gebruik geen van die risiko-voorspelling instrumente nie. Huidiglik word akute koronêre sindroom gediagnoseer met die gebruik van 'n fisiese ondersoek, EKG verandering en positiewe serum kardiaal merkers. Internasionaal word die selfde gebruik maar risiko-voorspelling instrumente word adisioneel by gebruik omdat daar limitasies is met EKG en serum kardiaal merkers as dit by NSTEMI-ACS kom.

Doelwit: Die doel van hierdie sistematiese literatuuroorsig was om stelselmatig die bewyse te evalueer oor die akkuraatheid van akute koronêre sindroom risiko-voorspelling instrumente vir volwassenes.

Metodes: 'n Uitgebreide literatuursoektog van studies wat in Engels gepubliseer is was onderneem. Cochrane biblioteek, MEDLINE, Embase en CINAHL databases was deursoek. Ander bronne is ook deursoek. Die tipe studies ingesluit was deurneestudies, kohortstudies en verewekansigde gekontroleerde studies. Alle artikels is onafhanklik vir die metodologiese kwaliteit gekeur deur twee beoordeelaars met die gebruik van die QUADAS-2 instrument, 'n gestandaardiseerde instrument. 'n Aangepaste Cochrane data instrument is gebruik om data te onttrek. Data is opgeneem in Review Manager 5.2 sagteware vir ontleding. Sensitiwiteit en spesifisiteit is bereken vir elke risiko instrument en 'n SROC kurwe is geskep. Die SROC kurwe is gebruik om die akkuraatheid van voorspelling van elke instrument te evalueer en te toets.

Resultate: Twee HEART studies en drie GRACE studies is ingesluit. In total was daar 9 092 pasiënte wat deelgeneem het in die gekose studies. Skattings van sensitiwiteit vir die

HEART risiko instrument (twee studies, 3268 deelnemers) was 0,51 (95% CI 0,47 to 0,56) en 0,68 (95% CI 0,60 to 0,75) spesifisiteit vir die HEART risiko instrument was 0,89 (95% CI 0,88 to 0,91) en 0,92 (95% CI 0,90 to 0,94). Skattings van sensitiviteit vir die GRACE risiko instrument (drie studies, 5824 deelnemers) was 0,28 (95% CI 0,13 to 0,53); 0,20 (95% CI 0,14 to 0,29) en 0,79 (95% CI 0,58 to 0,93). Die spesifisiteit vir die GRACE risiko instrument was 0,97 (95% CI 0,95 to 0,99); 0,97 (95% CI 0,95 to 0,98) en 0,78 (95% CI 0,73 to 0,82). Met die SROC kurwe ontleding was daar 'n tendens vir die GRACE risiko instrument om beter te vaar as die HEART risiko instrument in die voorspelling van akute koronêre sindroom in volwassenes.

Gevolgtrekking: Al twee risiko instrumente toon aan dat albei instrumente van waarde is. Albei het die vermoë om die teenwoordigheid van akute koronêre sindroom in volwassenes te voorspel. Die GRACE toon 'n positiewe tendens teenoor beter voorspelling vermoë as die HEART risiko instrument.

Sleutel woorde: akute koronêre sindroom, koronêre hartsiekte, risiko-assessering instrumente, diagnose, serum kardiaale merkers, EKG, QUADAS-2.

Acknowledgements

“Every great dream begins with a dreamer. Always remember, you have within you the strength, the patience, and the passion to reach for the stars to change the world.”

(Harriet Tubman)

I would like to acknowledge and express my sincere gratitude to:

- God who placed this dream in my heart and for carrying me through the development of this thesis.
- I wish to extend great regards to my husband Gideon van Zyl who stood by me and encouraged me constantly, his interest in what I do and for believing in my abilities.
- I wish to thank my parents, Mrs. H. Ras and Mr J. Ras who raised me, supported my educational path, loved and taught me responsibility.
- I wish to express my warm and sincere thanks to my family for supporting me during this time.
- I want to thank my supervisor, Dr Oswell Khondowe, for the support, help and patience in development of this thesis.
- I want to thank my editor, Ruth Coetzee, for all her hard work.
- I wish to thank my friends and colleagues for their prayers, kind words and constant encouragement during this study.
- Lastly, I wish to thank all the other people not mentioned but who played a role in the success of this project.

Table of contents

Declaration	ii
Abstract	iii
Opsomming	v
Acknowledgements	vii
List of abbreviations	ix
List of tables	x
List of figures	xi
CHAPTER ONE: FOUNDATION OF THE STUDY	1
1.1 BACKGROUND	1
1.2 MAGNITUDE OF THE PROBLEM	1
1.3 DESCRIPTION OF CORONARY ARTERY DISEASE	1
1.4 COMPLICATIONS OF ACUTE CORONARY SYNDROME	2
1.5 DESCRIPTION OF INTERVENTION FOR ACUTE CORONARY SYNDROME	2
1.6 PROBLEM STATEMENT	3
1.7 RESEARCH QUESTION	5
1.8 RESEARCH AIM	5
1.9 RESEARCH OBJECTIVES	5
1.10 RESEARCH METHODOLOGY	5
1.10.1 Research design	5
1.10.2 Selection criteria	5
1.10.3 Search strategy	7
1.10.4 Study selection	7
1.10.5 Critical appraisal	7
1.10.6 Data extraction	7
1.10.7 Data analysis and synthesis	7
1.11 ETHICAL CONSIDERATIONS	8
1.12 OPERATIONAL DEFINITIONS	8
1.12.1 Acute coronary syndrome	8
1.12.2 Evidence	9
1.12.3 Index test	9
1.12.4 Reference standard	9
1.12.5 Risk assessment	9
1.13 CHAPTER OUTLINE	9
1.14 SUMMARY	10
CHAPTER TWO: LITERATURE REVIEW	12
2.1 INTRODUCTION	12
2.2 LITERATURE REVIEW	12
2.3 METHOD USED TO IDENTIFY LITERATURE	12
2.4 DEFINING CONCEPTS	13
2.5 FINDINGS FROM THE LITERATURE	13
2.5.1 Anatomy: coronary circulation	13

2.5.2	Aetiology: acute coronary syndrome	15
2.5.3	Pathophysiology of acute coronary syndrome	15
2.5.3.1	<i>Atherosclerosis</i>	15
2.5.3.2	<i>Myocardial perfusion</i>	16
2.5.3.3	<i>Acute coronary syndrome spectrum</i>	16
2.5.3.4	<i>Signs and symptoms</i>	18
2.5.4	Epidemiology of acute coronary syndrome	18
2.5.4.1	<i>Prevalence</i>	18
2.5.4.2	<i>Prognosis</i>	19
2.5.5	Standard to diagnose acute coronary syndrome in South Africa	19
2.5.6	Standard to diagnose acute coronary syndrome internationally	21
2.5.6.1	<i>GRACE</i>	22
2.5.6.2	<i>HEART</i>	23
2.5.7	Physician risk estimation versus risk assessment tool	25
2.6	SUMMARY	28
2.7	CONCLUSION	28
CHAPTER THREE: RESEARCH METHODOLOGY		29
3.1	INTRODUCTION	29
3.2	RESEARCH DESIGN	29
3.2.1	Systematic review	29
3.2.2	Purpose of doing a systematic review	30
3.3	RESEARCH METHOD	31
3.3.1	Systematic review protocol	31
3.3.2	Research question	32
3.3.3	Searching for evidence	32
3.3.3.1	<i>Search strategy</i>	33
3.3.3.2	<i>Selection criteria</i>	34
3.3.3.3	<i>Study selection</i>	36
3.3.4	Critical appraisal	37
3.3.5	Data extraction	37
3.3.6	Data analysis and synthesis	38
3.4	SUMMARY	41
CHAPTER FOUR: RESULTS		42
4.1	INTRODUCTION	42
4.2	SEARCH RESULTS	42
4.2.1	Sources	42
4.2.2	Search terms	43
4.2.3	Documentation of search	45
4.3	QUALITY ASSESSMENT	47
4.4	DATA EXTRACTION	49
4.5	DATA SYNTHESIS	54
4.6	SUMMARY	62

CHAPTER FIVE: DISCUSSION, CONCLUSIONS AND RECOMMENDATIONS	63
5.1 INTRODUCTION	63
5.2 DISCUSSION	63
5.3 LIMITATIONS OF THE STUDY	68
5.4 RECOMMENDATIONS	69
5.5 SUMMARY	69
REFERENCE LIST	70
APPENDIX A: ETHICS APPROVAL LETTER	78
APPENDIX B: QUADAS 2 TOOL	79
APPENDIX C: COCHRANE DATA EXTRACTION TOOL (ADAPTED)	82

List of abbreviations

CVD	Cardiovascular disease
CABG	Coronary Artery Bypass Graft
CINHAL	Cumulative Index of Nursing and Allied Health
CKMB	Creatine Kinase MB Isoenzyme
ECG	Electrocardiogram
EMBASE	Excerpta Medica Database
GRACE	Global Registry of Acute Coronary Events
HEART	History, Electrocardiogram, Age, Risk factors, Troponin
HEARTS3	History, Electrocardiogram, Age, Risk factors, Troponin, Sex, Serial 2-hour Serial 2-hour Troponin
MACE	Major Adverse Cardiac Events
MEDLINE	Medical Literature Analysis and Retrieval Systems Online
NSTEMI	Non-ST-elevation Myocardial infarction
NSTE-ACS	Non ST-elevation Acute Coronary Syndrome
PCI	Percutaneous Coronary Intervention
PICO	Patient, Intervention, Comparison, Outcomes
PURSUIT	Platelet glycoprotein IIb/IIIa in unstable angina: receptor suppression using Integrilin
QUADAS-2	Quality Assessment of Diagnostic Accuracy Studies
SROC	Summary Receiver Operating Characteristics
STEMI	ST-elevation Myocardial infarction
STE-ACS	ST- elevation acute coronary syndrome
TIMI	Thrombolysis in Myocardial Infarction
WHO	World Health Organisation

List of tables

Table 4.1:	Sources used in search strategy	43
Table 4.2:	Search strings for Cochrane Library, MEDLINE & CINAHL	43
Table 4.3:	Search strings for Embase	44
Table 4.4:	Summary of search	45
Table 4.5:	Excluded full text articles	47
Table 4.6:	Excluded studies after critical appraisal	47
Table 4.7:	QUADAS 2 risk of Bias	48
Table 4.8:	Characteristics of articles for inclusion	49
Table 4.9:	Summary of study	51
Table 4.10:	Summary of findings for HEART risk score	52
Table 4.11:	Summary of findings for GRACE risk score	53
Table 4.12:	MACE findings of HEART risk score	54
Table 4.13:	MACE findings of GRACE risk score	54
Table 4.14:	Backus et al., 2010 2x2 contingency table	55
Table 4.15:	Backus et al., 2013 2x2 contingency table	55
Table 4.16:	Lee et al., 2011 2x2 contingency table	55
Table 4.17:	Lyon et al., 2007 2x2 contingency table	56
Table 4.18:	Ramsay et al., 2007 2x2 contingency table	56

List of figures

Figure 3.1:	ROC curve diagram	41
Figure 4.2:	Flow of studies identified in literature search for systematic review	46
Figure 4.3:	Forest plot for HEART risk score	56
Figure 4.4:	SROC curve for HEART risk score	57
Figure 4.5:	Forest plot for GRACE risk score	58
Figure 4.6:	SROC curve for GRACE risk score	59
Figure 4.7:	Comparison of GRACE and HEART forest plot	60
Figure 4.8:	Comparison of HEART and GRACE SROC curve	61

CHAPTER ONE: FOUNDATION OF THE STUDY

The aim of this chapter is to orientate the reader to the study in terms of the background and complications related to the accuracy of risk prediction tools for acute coronary syndrome. An overview regarding the research question, objectives, research design and methodology will also be given.

1.1 BACKGROUND

Coronary artery disease is a form of cardiovascular disease (CVD) which manifests itself in three ways: angina pectoris, acute coronary syndrome and cardiac death (Lewis, Heitkemper & Dirksen, 2004:809–810). It is estimated that 33 people die daily of a myocardial infarction (Heart and Stroke Foundation of South Africa, 2007: 2). There were 25 827 deaths in South Africa from heart disease in 2010, making it the fourth leading cause of death that year (Statistics South Africa, 2010:38). Of that total, ischemic heart disease caused 12 044 deaths (Statistics South Africa, 2010:83).

1.2 MAGNITUDE OF THE PROBLEM

There are 7.5 million deaths annually from CVD where 51% are caused by strokes and 45% are caused by coronary artery disease (WHO, 2012). It is predicted that by the year 2030, there will be 25 million deaths annually due to CVD. These deaths will mainly be caused by strokes and heart disease (WHO, 2012). Globally the death rate of CVD is a mere 4% compared to South Africa with a 42% death rate (WHO, 2011). The World Health Organisation (WHO, 2011) compared the death rates of high-income countries against middle- and low-income countries, like South Africa, over the past two decades. The results show that CVD deaths in high-income countries are declining, but in low- and middle-income countries, they are increasing at a rapid rate.

1.3 DESCRIPTION OF THE CORONARY ARTERY DISEASE

Acute coronary syndrome occurs as a result of myocardial ischemia, which is the lack of oxygen to the myocardium (Lewis et al., 2004:809–810). Acute coronary syndrome is a term used to denote the acute phase of ischemic coronary artery disease which can be with or without the presence of myocardial cell necrosis (Hamm, Heeschen, Falk & Fox, 2006:333).

It refers to a spectrum of conditions, namely unstable angina pectoris, ST-elevation myocardial infarction (STEMI) and non-ST elevation myocardial infarction (NSTEMI) (Kohli, Parajuli, Maskey & Acharya, 2010: 125). In unstable angina pectoris, there is no elevation in cardiac markers. A positive ECG can only be noted during an ischemic episode as ischemia is reversible (Houghton & Gray, 2003:186). A STEMI develops as a result of an untreated ST-segment elevation acute coronary syndrome. An NSTEMI develops as a result of an untreated ST-segment elevation acute coronary syndrome (Lewis et al., 2004:810). In an NSTEMI, the ECG shows no abnormality, hence the term “non-ST elevation myocardial infarction”. The World Health Organisation (2012) attributes the high percentage of deaths to the fact that the low- and middle-income countries are more exposed to risk factors such as the use of tobacco, unhealthy diet and stress. In South Africa it has been proven that South Africans follow a sedentary lifestyle and this leads to the development of other risk factors that can cause heart disease, such as obesity and hypertension (The Heart and Stroke Foundation, 2007). The Heart and Stroke Foundation (2007) explains that the magnitude of the risk for heart disease should be determined for each individual by assessing the risk factors for that individual. Every risk factor increases ones possibility for a future myocardial infarction.

1.4 COMPLICATIONS OF ACUTE CORONARY SYNDROME

There are many complications that can arise from a myocardial infarction, the most common being arrhythmias which occur in 80% of patients and this is the most common cause of death in myocardial infarction patients (Lewis et al., 2004:814). There are different arrhythmias which are described as the disruption of the intrinsic rhythm of the heartbeat (American Heart Association, 2012). Congested heart failure is also a frequent complication after a myocardial infarction. Congested heart failure occurs when the pumping effort of the heart is diminished due to the injury caused to the heart muscle by the myocardial infarction (Lewis et al., 2004:814). Other complications are cardiogenic shock which is an acute form of heart failure (Ashley & Niebauer, 2004). In cardiogenic shock there is a lack of oxygen and nutrients being pumped to tissues as a result of severe left ventricular failure (Lewis et al., 2004: 814).

1.5 DESCRIPTION OF INTERVENTION FOR ACUTE CORONARY SYNDROME

There are several different tools used globally, in combination with history taking and physical examination, to assess ischemic risk when a patient presents at a facility with chest pain. These risk assessment tools are: global registry of acute coronary events (GRACE)

and thrombolysis in myocardial infarction (TIMI); platelet glycoprotein IIb/IIIa in unstable angina; receptor suppression using integrilin (PURSUIT); the history, electrocardiogram, age, risk factors, troponin (HEART); and added sex, serial 2-hour ECG, serial 2-hour delta troponin (HEARTS3).

The GRACE and TIMI risk assessment tools are most commonly used internationally (Hamm et al., 2011:3009). The reason for this is that both tools have been validated in multiple clinical environments (D'Ascenzo, Biondi-Zoccai, Moretti, Bollati, Omede, Sciuto, et al., 2012: 508). Research indicates that the GRACE tool is superior to the TIMI because it has a greater ability to risk-stratify a patient, thus indicating the long-term risk for recurrent ischemia (Carmo, Ferreira, Aguiar, Ferreira, Raposo, Goncalves, et al., 2011: 247). The GRACE risk assessment tool assesses the entire spectrum of acute coronary syndrome and it has been validated internally and externally (Yusufali, Zubaid, Alsheikh, Al-Mallah, Suwaidi, Rashed, et al., 2011:508). Therefore it is seen as the gold standard internationally. The HEART risk assessment tool is a newer tool developed in the Netherlands (Fesmire, Martin, Cao & Heath, 2012:1829). It was developed to predict all forms of acute coronary syndrome, but was found to have drawbacks and so was revised and adjusted to become the HEARTS3. The triple-S that was added refers to sex, serial 2-hour electrocardiogram (ECG) and serial 2-hour delta troponin (Fesmire et al., 2012:1830). The HEARTS3 was developed to identify acute coronary syndrome and myocardial infarction in a 30-day period (Fesmire et al., 2012:1829). The HEART tool was found to outperform the TIMI and GRACE tools because it assessed patients with undifferentiated chest pain, whereas the TIMI and GRACE tools assess patients diagnosed with acute coronary syndrome (Fesmire et al., 2012:1834). The HEARTS3 risk assessment tool has not been validated to the same extent as the GRACE and TIMI tools. A study of the HEARTS3 recommended that the tool needs to be tested further.

Two risk assessment tools, the GRACE and HEART/HEARTS3 are the focus of this study as they assess all forms of acute coronary syndrome. PURSUIT and TIMI were not selected for study as they only assess unstable angina pectoris and NSTEMI (Chin, Chua & Lim, 2010: 218).

1.6 PROBLEM STATEMENT

In South Africa, the reference standard for diagnosing acute coronary syndrome is elevated serum cardiac markers (creatinine kinase, MB band and troponin) and a positive ECG. Both these reference standards have limitations which makes it risky to rely on them only. ECGs do not adequately represent the apical, posterior and lateral walls of the left ventricle which

may cause a myocardial infarction in these areas being missed (Kumar & Cannon, 2009: 921). A normal ECG does not exclude the possibility of unstable angina pectoris and NSTEMI (Kumar & Cannon, 2009:921). In 20 to 50% of cases, the initial ECG is non-diagnostic of an acute myocardial infarction (Kellett, Hirschl, Derhaschnig, Collinson, Gaze, Haass, et al., 2004:159). Two thirds of ischemic episodes are clinically silent, hence they are unlikely to be detected by an ECG (Hamm, Bassand, Agewall, Bax, Boersma, Bueno, et al., 2011: 3005). This makes diagnosing unstable angina pectoris difficult at times. It is important to make a quick diagnosis because patients benefit significantly from early treatment (Six, Backus & Kelder, 2008:192). A missed diagnosis could result in a wrongful discharge and ultimately lead to an out-of-hospital sudden death if unstable angina pectoris progresses to a myocardial infarction (Six et al., 2008:192). Troponin I and T measurements also have limitations as they do not increase for at least six to twelve hours after the onset of a patient's symptoms (Kumar & Cannon, 2009:921). Patients consulting their general practitioners with these symptoms during this period could therefore be missed.

The use of physical examination, history taking and reference standards to diagnose acute coronary syndrome are not sufficient, as cardiac markers and ECG findings have limitations and drawbacks. These limitations can lead to a false negative result, missed diagnosis and subsequent advanced disease and even death. This has been the experience of the researcher who noticed that patients who were admitted to a critical cardiac unit for a myocardial infarction, had a history of prior visits to their general practitioners. Most patients related that they had been physically examined and sent home following negative cardiac markers results and a negative ECG. To ensure effective and targeted treatment, appropriate prediction tools are needed in addition to the current practice of physical examination, history taking and use of reference standards to confirm the presence of the disease. The World Health Organisation (WHO, 2012) identifies a need to reduce the burden of CVD in low- and middle-income countries and suggests the implementation of several interventions. One of these is to identify high risk patients early in the primary phase with the use of simple tools like risk prediction charts. Identifying people early may foster inexpensive treatment which can prevent many heart attacks. There is a need to increase government investment in prevention and early detection of the disease (WHO, 2012).

No previous studies could be found in South Africa regarding the implementation of these risk assessment tools. Based on this fact, on the limitations of reference standards used to diagnose acute coronary syndrome, on personal observations and on informal discussions held with various stakeholders, it was decided to undertake the current study.

1.7 RESEARCH QUESTION

The research question posed is as follows:

What is the prediction ability of risk assessment tools in predicting acute coronary syndrome in adults?

1.8 RESEARCH AIM

The research aim of this study is to systematically appraise evidence for the accuracy of risk prediction tools for acute coronary syndrome in adults.

1.9 RESEARCH OBJECTIVES

The objectives of the study are:

- To estimate the accuracy of GRACE and HEART/HEARTS3 in predicting acute coronary syndrome in adults.
- To compare the accuracy of the two tools in risk prediction of acute coronary syndrome in adults.
- To propose recommendations for a potential risk assessment tool for South Africa.

1.10 RESEARCH METHODOLOGY

1.10.1 Research design

A research design is the overall plan or blueprint used to address a research question; it includes specifications to enhance a study's integrity (Polit & Beck, 2012:741). A research study involves the performance of a systematic review followed by recommendations which are formulated to inform best practice. The research design will be discussed in further detail in Chapter three of the study.

1.10.2 Selection criteria

Types of study

The studies considered in this review are cross-sectional studies, cohort studies and randomised controlled trials investigating the prediction ability of risk assessment tools (GRACE and HEART/HEARTS3) to predict acute coronary syndrome.

Types of participants

Studies were included if they reported on participants of any gender, aged 18 years and above, with chest pain.

Setting

Study or research setting refers to the location of where a study is being conducted (Grove, Burns & Gray, 2013: 373). Studies conducted in any setting were included in the review.

Index test

The index test refers to the test whose performance is being evaluated; therefore the index test is referred to as the intervention in diagnostic test accuracy reviews (Centre for Reviews and Dissemination, 2009). In this review, the two index tests are the GRACE and HEART/HEARTS3 risk assessment tools.

Outcomes

Studies were considered which compared the results of GRACE or HEART/HEARTS3 to results of elevated serum cardiac markers and/or positive ECG. Due to the fact that both cardiac markers and ECG findings formed part of the index test, the outcome that was reported in the studies was MACE. MACE are major adverse cardiac events that are an indirect result of acute coronary syndrome being present. Therefore if one has MACE, this serves as indirect proof that acute coronary syndrome is present (Backus et al. 2010:164). Therefore elevated cardiac markers and and/or positive ECG was not used as the outcome because the results might be biased and not allow a true reflection of the index tests ability to predict or refute the presence of acute coronary syndrome. MACE was used as reference standard in the selected studies

Reference standards

The reference standard refers to the best test currently available to confirm the presence of a disease. It is the standard against which the index test is compared in a review of test accuracy (Centre for Reviews and Dissemination, 2009).

The reference standards for confirming the presence of acute coronary syndrome (STEMI, NSTEMI or unstable angina pectoris) are elevated serum cardiac markers (troponin T and I and CKMB) and/or positive ECG. In the various studies MACE is used as the reference standard for reasons identified above. MACE serves as indirect proof that acute coronary syndrome is present.

1.10.3 Search strategy

Two reviewers, namely Johet van Zyl and Oswell Khondowe, independently performed a literature review searching for articles from inception to 2014. The term inception means that since this concept of risk assessment tools has been used in the context of articles and conference proceedings. The following databases were used: Cochrane Library, Medical Literature Analysis and Retrieval Systems Online (MEDLINE), Excerpte Medica Database (Embase) and Cumulative Index of Nursing and Allied Health (CINAHL). Search terms were “acute coronary syndrome”, “chest pain”, “NSTEMI”, “STEMI”, “unstable angina pectoris”, “angina pectoris”, “risk assessment”, “risk stratification”, “risk prediction”, “predict”, “accuracy”, “GRACE”, “HEART” and “HEARTS3”.

1.10.4 Study selection

The two reviewers selected studies following a three-step study selection process. This process is discussed in Chapter Three.

1.10.5 Critical appraisal

The identified studies that met the inclusion criteria underwent independent assessment of methodology quality by the two reviewers. Differences of opinion between the two reviewers were resolved by discussion. If no consensus was reached, a third reviewer was consulted. The quality assessment was done using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool (Appendix B).

1.10.6 Data extraction

Data was extracted by both reviewers. An adapted data extraction tool (see Appendix C), which is available on the Cochrane website, was used (Cochrane Consumers and Communication Review Group, 2011:3–7). A pilot study comprised of three selected studies, was conducted to determine the feasibility of the study, search range, assessment and extraction tools to minimise errors and to ensure reliability and validity of the extraction tool.

1.10.7 Data analysis and synthesis

The study results were reported separately for each study. The statistical software Review Manager 5.2 was used to create forest plots for each set of study results. The data from each study was used to create 2 x 2 contingency tables to divide the study results into true negative, true positive, false negative and false positive. The results of the contingency tables were used to present estimates of sensitivity and specificity in a table format and

illustrated using a forest plot. Data from the forest plot was used to create graph using the summary receiver-operating characteristics space for each index test.

1.11 ETHICAL CONSIDERATIONS

A systematic review does not use the customary methods of data collection and analysis, but it is necessary for the researcher to adhere to certain ethical principles because the research project is bound to raise some or other ethical questions. The first ethical principle is permission to conduct the review. Ethical approval was sought from the Human Ethics Committee at Stellenbosch University, who granted permission to conduct the proposed systematic review (see Appendix A). The rigour of the study was ensured by ensuring validity and reliability of tools to be used. Validity is defined by Botma, Greeff, Mulaudzi and Wright (2010:174) as the degree to which a measurement represents a true value. Reliability is defined by Brink, van der Walt and van Rensburg (2012:126) as the consistency, repeatability and stability of a measure. In the systematic review, the measures were the tools (QUADAS-2 and data extraction tool) used in the critical appraisal and data extraction process. Consistency means that the two reviewers use the same appraisal tool and consider similar if not identical outcomes. This is termed “interrater-reliability” (Grove, Burns & Gray, 2013:390). Reliability is increased by the two reviewers conducting a critical appraisal of studies, thus preventing inconsistencies. Internal validity is increased with the clearly described literature search. Internal validity is further increased by updating the systematic review with any new studies to prevent omission of relevant data. Internal validity can be threatened, however, by language bias of the study. The reviewers could only consider studies written in English as a result of limited resources, introducing a possibility of language bias in the study. Publication bias can occur where there is an overemphasis of differences for the publication’s sake. In other words, positive results have priority compared to negative results (Brink et al., 2012:87). In this study, publication bias was reduced by including “grey” literature such as conference papers.

1.12 OPERATIONAL DEFINITIONS

1.12.1 Acute coronary syndrome

Acute coronary syndrome refers to a condition where there is chest pain and/or other symptoms caused by the lack of oxygen supply (ischemia) to the myocardium (Medterms, 2012). The ischemic episode is prolonged and is not immediately reversible. Acute coronary syndrome is subdivided into unstable angina pectoris, STEMI and NSTEMI depending on the severity of ischemia (Lewis et al., 2004:810).

1.12.2 Evidence

Evidence refers to information used to determine whether or not a statement or observation should be trusted (Pearson, Field & Jordan, 2007:50). LoBiondo-Wood and Haber (2010:16) identify various levels of evidence that can be used for clinical decision-making and practice recommendations. In this study, evidence is drawn from various sources including cross-sectional studies, cohort studies and randomised controlled trials, subject experts and conference proceedings.

1.12.3 Index test

The index test refers to the test whose performance is being evaluated; therefore the index test is referred to as the intervention in diagnostic test accuracy reviews (Centre for Reviews and Dissemination, 2009). In this review, the two index tests are the GRACE and HEART/HEARTS3 risk assessment tools.

1.12.4 Reference standard

The reference standard refers to the best test currently available to confirm the presence of a disease. It is the standard against which the index test is compared in a review of test accuracy (Centre for Reviews and Dissemination, 2009). In this review, the reference standard for confirming the presence of acute coronary syndrome (STEMI, NSTEMI or unstable angina pectoris) will be MACE.

1.12.5 Risk assessment

Risk assessment refers to the estimation of the likelihood of the occurrence of adverse effects that may occur from exposure to certain health hazards (Risk assessment, 2013).

1.13 CHAPTER OUTLINE

The research study is divided into the following chapters:

Chapter One: Foundation of the study

In the introductory chapter of the research study, the problem statement, research objectives, research design, method, quality of data control and ethical principles are presented.

Chapter Two: Literature review

The reader is provided with a summary of theoretical and empirical sources to identify what is known and not known about acute coronary syndrome and risk assessment tools.

Chapter Three: Research methodology

This chapter provides an in-depth discussion of the various sections introduced in Chapter One. The reader is orientated to the research design and method as applied to the research study.

Chapter Four: Results

Data that has been collected, appraised, extracted and synthesised is presented in this chapter.

Chapter Five: Discussion, conclusions and recommendations

The results of the study are discussed, together with the conclusions and limitations identified throughout the study. Recommendations related to the data findings as well as nursing practice, education and research are highlighted in this chapter.

1.14 SUMMARY

It is essential for South Africa to be able to assess whether risk assessment tools have the potential to accurately predict acute coronary syndrome in adults. Statistics indicate that the death rate due to CVD is increasing rapidly. This research study intends to create and produce evidence of the prediction ability of the GRACE and HEART tools, which will be transferred by means of recommendations to be used to inform best practice. The evidence from this study will make the assessment phase more specific, preventing some patients being 'misdiagnosed' as a result of limitations of reference standards used to diagnose the presence of acute coronary syndrome. The study thus aims to develop recommendations to help to enhance the care rendered to patients with acute coronary syndrome. In Chapter Two a summary of theoretical and empirical sources will be discussed to identify what is known and not known about acute coronary syndrome and risk assessment tools.

1.15 CONCLUSION

In Chapter One, an introduction and rationale for the research study was provided. The aim, objectives, research methodology and ethical considerations of the study were outlined.

Chapter Two will discuss the literature related to acute coronary syndrome in adults and risk assessment tools used to predict the presence of the disease.

CHAPTER TWO: LITERATURE REVIEW

2.1 INTRODUCTION

In Chapter One a basic outline of the study was provided, including the research question and the research objectives to be explored. Chapter Two will focus on discussing the existing body of knowledge concerning acute coronary syndrome and risk assessment tools.

2.2 LITERATURE REVIEW

A literature review can be described as a written presentation of what one finds when reviewing literature (Grove et al. 2013:97). A literature review provides a study with a background to the problem being studied (Grove & Burns, 2011:189). Polit and Beck (2012:732) define a literature review as a critical summary of research that is based on a topic of interest. It is prepared so that a research problem can be placed into context.

The purpose of this literature review is to examine:

- Acute coronary syndrome.
- The South African and international standards used to diagnose acute coronary syndrome.
- Which risk assessment tools are available to diagnose acute coronary syndrome.
- The strengths and limitations of studies done on these risk assessment tools.

2.3 METHOD USED TO IDENTIFY RELEVANT LITERATURE

Polit and Beck (2012:96) describe the process of conducting a literature review as similar to that of a full study. The process includes a question, a plan to gather information and a plan to analyse and interpret that information.

Establishing the question is the first step in the literature review process. The question is similar to the one created for the study (Polit & Beck, 2012:96). The question is therefore:

What is the current state of knowledge on the question about the accuracy of acute coronary syndrome risk assessment tools?

The second step of the review process is to identify databases to be used, as well as the search terms. These were the same as for the study, namely Cochrane Library, MEDLINE, Embase and CINAHL, with the addition of Google Scholar. Search terms were “acute coronary syndrome”, “chest pain”, “NSTEMI”, “STEMI”, “unstable angina pectoris”, “angina pectoris”, “risk assessment”, “risk stratification”, “risk prediction”, “predict”, “accuracy”, “GRACE”, “HEART” and “HEARTS3”. Once primary source studies were identified, they were screened for relevance and appropriateness. The applicable studies were evaluated and information retrieved for the literature review.

2.4 DEFINING CONCEPTS

Acute coronary syndrome : Lewis et al., (2004:810) define acute coronary syndrome as a lack of oxygen supply to the heart muscle which is prolonged and not immediately reversible.

Risk assessment : Risk assessment is defined as the estimation of the likelihood that an adverse effect may occur if exposed to a health hazard (Risk assessment, 2013).

Risk assessment tool : A risk assessment tool is an instrument that was designed to assist with the assessment and evaluation of risk in order to allow one to make a more informed decision (Risk assessment, 2013).

Standard : A standard refers to a rule or principles that are used as the basis for judgement (Standard, 2014).

2.5 FINDINGS FROM THE LITERATURE

The literature to be described in this chapter begins with the normal anatomy of the coronary circulation system. Acute coronary syndrome is then discussed in-depth with regard to the etiology, pathophysiology and epidemiology of the disease. The researcher then introduces the South African standard used to diagnose acute coronary syndrome, followed by a discussion of the international standard. Finally, the researcher describes the gap that was identified between physician risk estimation and risk assessment tools.

2.5.1 Anatomy: coronary circulation

The heart muscle requires a rich blood supply; this is supplied by the left and right coronary arteries. These coronary arteries separately arise from the aortic sinus at the aorta's base (Aaronson, Vard & Conolly, 2013:8). This opening (sinus) in the aorta is known as the

coronary ostium and allows blood to be supplied to the coronary arteries (Manacci, 2013:146).

The right coronary artery runs between the pulmonary trunk and the right atrium of the heart to the anterior ventricular sulcus. The right coronary artery then descends to supply the lower parts of the heart muscle by dividing into two sections, the posterior descending and right marginal branches (Aaronson et al., 2013:9). The left coronary artery runs behind the pulmonary trunk and between it and the left atrium. The left coronary artery then divides into three sections, namely circumflex, left marginal and anterior descending branches (Aaronson et al., 2013:9). Natural anastomoses occur between the left and right marginal branches and the anterior and posterior descending arteries. These anastomoses are unable to maintain myocardial perfusion in an event of one-sided occlusion of the coronary arteries (Aaronson et al., 2013:9).

Most of the left ventricle is supplied by the left coronary artery. The left ventricle supplies the greater part of the body with oxygen and nutrient rich blood. When this coronary artery becomes occluded it becomes very dangerous for a patient (Aaronson et al., 2013:9). The right coronary artery supplies the anterior ventricular node, sinus node and Bundle of His, which is part of the electrical conduction system of the heart. Therefore obstruction of the coronary artery causes defects in the cardiac conduction system (Lewis et al., 2004:758). An example of a conduction problem when the coronary artery is occluded is an anterior ventricular block or slowed heart rate (Aaronson et al., 2013:9).

The coronary circulation system can develop a good collateral system if required in a patient with ischemic heart disease, where a branch or branches of the coronary arteries become occluded (Aaronson et al., 2013: 9). This collateral circulation occurs when there are arterial anastomoses. This is when arteries and arterioles merge and form an alternative blood supply pathway due to another being occluded (Aaronson et al., 2013:11). If occlusions of coronary arteries occur slowly over time, the collateral circulation is well formed. Clinically it has been proven that younger individuals have more severe myocardial infarctions as a result of poor collateral formation (Lewis et al., 2004:801).

2.5.2 Description of acute coronary syndrome

Acute coronary syndrome is a term used for a condition brought on by a sudden and reduced blood flow to the myocardium (Hamm et al., 2006: 333). Acute coronary syndrome development starts in the coronary artery when an unstable, lipid rich substance known as plaque, ruptures or erodes. This lipid rich substance is referred to as atherosclerosis. Platelets will adhere to this area and a fibrin clot will form and thrombin formation is

activated (Manacci, 2013:253). Acute coronary syndrome encompasses a variety of clinical presentations; the manifestations follow the disruption of coronary arterial plaque. The thrombosis mobilises, causing various degrees of obstruction in the coronary artery affecting myocardial perfusion (Hamm et al., 2006:333). Total occlusion of the coronary artery by the thrombosis causes lack of oxygen supply to the myocardial cells (ischemia). The ischemia progresses to an infarction of myocardial cells if not immediately treated (Prins, Bote, Smit, Wheathes & Neetling, 2008:204). The clinical presentation of a patient depends on the extent of myocardial ischemia caused by the occlusion from the thrombosis (Hamm et al., 2006: 333).

2.5.3 Aetiology: acute coronary syndrome

There are a series of non-modifiable and modifiable risk factors related to the development of atherosclerosis and the risk of presenting with acute coronary syndrome (Hamm, Heeschen, Falk & Fox, 2006:335).

Manacci (2013:253) identifies the risk factors increasing the likelihood of developing acute coronary syndrome as:

- Non-modifiable – family history of heart disease and menopause
- Modifiable – smoking, stress, obesity, diabetes, hypertension, hyperlipoproteinemia, sedentary lifestyle, high fat and high carbohydrate diet

Hamm et al. (2006: 336) include gender and age under non-modifiable risk factors and they describe gender and age as the most powerful and independent predictor of acute coronary syndrome development.

2.5.4 Pathophysiology of acute coronary syndrome

2.5.4.1 Atherosclerosis

The term atherosclerosis is derived from two Greek words which translate to “hard fatty mush”. This indicates that atherosclerosis starts as a soft fatty deposit but over time hardens, thus occasionally referred to as “hardening of the arteries” (Lewis, 2004:799). Hamm et al. (2006:338) describe atherosclerosis as a chronic and multifocal immune-inflammatory, fibro proliferative disease of the arteries mainly driven by lipid accumulation. Early fatty streak formation appears to be a part of normal development of a human. These fatty streaks remain until the age of 10 years old, after which they regress or remain static and pose no further harm to the individual. In a minority of individuals these fatty streaks

continue to develop into potentially destructive atheromatous plaques (Nowak & Handford, 2004:222). Coronary heart disease is caused by atherosclerosis; this is where there is a build-up of plaque in the lumen of the coronary artery (Marshall, 2011:48). Atherosclerosis is the primary cause of acute coronary syndrome.

2.5.4.2 Myocardial perfusion

Physiological changes occur when atherosclerosis is present in the coronary arteries. This causes problems with myocardial oxygen supply and demand (Rosano, Fini, Caminiti & Barbaro, 2008:2551). Myocardial metabolism is oxygen dependent and uses up to 80% of oxygen from the coronary blood supply. Coronary blood flow to the myocardium occurs during diastole (Nowak & Handford, 2004:253). Lewis et al. (2004:810) explain that atherosclerosis causes occlusion in the coronary arteries. When the myocardial oxygen demand exceeds the supply, the coronary arteries are unable to supply the heart with oxygen and this is termed ischemia (Lewis et al., 2004:810). Myocardial ischemia results from the occlusion and this causes impaired myocardial perfusion. The degree of obstruction varies and is well tolerated by the body as long as the myocardial oxygen demand is low. Ischemia occurs when the demand increases, for example, when individual exercises (Lewis et al., 2004:810). When myocardial ischemia is present the term acute coronary syndrome is used.

2.5.4.3 Acute coronary syndrome spectrum

Acute coronary syndrome is a clinical emergency and needs urgent assessment. Acute coronary syndrome is characterised by chest pain, ECG changes and – if myocardial injury has occurred – a rise in serum cardiac markers (Dalby, 2001:879). Dalby (2001:879) explains further that risk stratification is essential to allow the correct triage of a patient. Acute coronary syndrome can either be classified as a STEMI, NSTEMI or unstable angina pectoris (Lewis et al., 2004:810).

ECG

An ECG is used to diagnose the presence of a STEMI or unstable angina pectoris. In a STEMI, a positive ECG is one with an ST-segment elevation of greater than 1mm in two contiguous limb leads and 2mm in two contiguous chest leads (Marshall, 2011:53). A positive ECG for suspected unstable angina pectoris has T-wave inversion or most commonly ST-segment depression (Houghton & Gray, 2003:170–171). A patient who had a myocardial infarction before might have a permanent T-wave inversion on the ECG (Houghton & Gray, 2003: 185–186). If this patient experiences a myocardial ischemic episode, the T-wave turns upright until ischemic episode stops (Houghton & Gray, 2003:

185–186). In a NSTEMI there are no ECG changes, hence the term “non ST-elevation MI” (Lewis et al., 2004:810).

Serum cardiac markers

There are two cardiac markers that are important in diagnosing STEMI or NSTEMI. These are creatine kinase (CK), including the MB band, and troponin T and I. The normal CK level depends on one's sex; for women it is 30 to 135 units/L and for men it is 55 to 170 units/L. A MB band greater than 3% indicates a STEMI or NSTEMI. Normal values for troponin I are 0,0 - 0,05 ng/ml or 0,0-0,50 ng/l or less than 10 µg/L (Lewis et al., 2004:817). The normal values for troponin T are <0.01 ng/mL or <14 ng/L or 0–0.1 µg/L (Lewis et al., 2004: 817).

The three conditions of acute coronary syndrome are portions of the continuum of the clinical manifestations arising from a single pathogenic mechanism and therefore may overlap one another (Dalby, 2001:880). The ECG findings and results of the blood cardiac markers categorise a patient as follows: persistent acute chest pain for 20 minutes or less with ST-segment elevation on the ECG is diagnosed as ST-ACS. When the blood results of the cardiac markers return as positive, troponin I >0,07ng/ml, a diagnosis of STEMI is made (Hamm et al., 2011:3004).

For a patient with an acute chest pain but no ST-segment elevation presenting on the ECG, neither T-wave abnormality like T-wave inversion nor ST-segment depression, a diagnosis of NSTEMI-ACS is made. When the blood results of the cardiac markers return as positive, troponin >0,07ng/ml, a diagnosis of NSTEMI is made. When the blood results of cardiac markers return as negative, troponin I <0,07ng/ml, a diagnosis of unstable angina pectoris is made (Hamm et al., 2011:3004).

Angina is caused by exercise, eating and even stress and can be relieved with rest; this type of angina is referred to as chronic stable angina (Mahmoud, Hassanein, Nour, El-Din, Elbetagy & Sadaka, 2010:1). Over time the plaque in the coronary artery becomes thickened and it ruptures. This leads to platelets aggregating at site of rupture and causes a thrombosis to form (Mahmoud et al., 2010:1). The patient will note that his or her symptoms for stable angina change in their severity and duration. This state of change is then referred to as unstable angina pectoris (Mahmoud et al., 2010:1). Dalby (2001:880) describes unstable angina pectoris as a clinical state where there are changes in the pattern of angina pain caused by reversible ischemic episodes due to partial occlusion of a coronary artery. Cell injury is unlikely when an ischemic episode is reversed (Dalby, 2001:880).

2.5.4.4 Signs and symptoms

Coronary artery disease develops over years, and when symptoms appear then the disease process is already well advanced (Lewis, 2004:801).

The classic signs and symptoms are described by Lincoff (2014:234) as an intense, oppressive chest pressure that radiates to the left arm. The signs and symptoms can also be described as nearly any discomfort between the nose and navel. Therefore other symptoms include pain in the jaw, arm, epigastric and abdominal area. Associative symptoms identified by Lincoff (2014:234) include heaviness or burning chest pain radiating to the shoulder, neck or back and dyspnoea. There are atypical symptoms experienced by individual, especially older women. These symptoms include nausea, vomiting, sweating, breathlessness, light-headedness and arrhythmias (Lincoff, 2014:234).

2.5.5 Epidemiology of acute coronary syndrome

2.5.5.1 Prevalence

The Heart and Stroke Foundation of South Africa (2007) identifies the prevalence of acute coronary syndrome as three in every 1 000 people. They also describe the ratio pertaining to myocardial infarction related to gender is one female for every two males. South African white Afrikaner, Jewish and Asian populations have the highest familial hypercholesterolemia carrier rates. This affects one in eight individuals (Prins et al., 2008: 198). The highest death rates for heart and blood vessel disease occur in the Indian population and then in the coloured population. The white and black populations have the lowest death rates caused by these diseases. The disease death rate may be similar for white and black populations but the pattern is different. The white population pattern of death is mostly caused by heart attacks, while the black population death rate pattern indicates death mostly being caused by strokes (Heart and Stroke foundation of SA, 2007:4).

Hamm et al. (2011:3004) identifies NSTEMI-ACS as more prevalent than STEMI-ACS but also states that it may vary from country to country. Although NSTEMI-ACS is more prevalent, the mortality rate of STEMI-ACS is higher. When both conditions were compared at six-month intervals it was found that the mortality numbers are similar for both conditions. Hamm et al. (2007:3004) also assessed the long-term outcomes and found that the death rate for NSTEMI-ACS was higher than for STEMI-ACS.

2.5.5.2 Prognosis

The prognosis related to acute coronary syndrome depends on the occurrence and extent of myocardial damage. Patients without persistent ST-elevations and typical rise in cardiac enzymes have the lowest incidence of mortality and morbidity. Patients who have intermediate complications are those without ST-elevation but with a rise in cardiac enzymes. Patients with the worst prognosis are those with ST-elevations and substantial myocardial damage (Boersma, Pieper, Steyerberg, Wilcox, Chang, Lee et al., 2000:10).

2.5.6 Standard to diagnose acute coronary syndrome in South Africa

A diagnosis of STEMI, NSTEMI or unstable angina is made based on a comprehensive evaluation of the patient's history, clinical examination, resting 12 lead ECG and evaluation of serum cardiac markers (Dalby, 2001:881).

Dalby (2001:881) explains that history taking involves enquiring about the pain as well as the presence of certain risk factors. The pain type and severity should be assessed because pain in acute coronary syndrome is spontaneous in onset, and may vary from mild to comprehensive discomfort to a sharp severe pain. The pain location is important as acute coronary syndrome pain is usually anterior chest pain, especially substernal, and can include radiation to the jaw, shoulder, neck, arms, back and epigastrium (Dalby, 2001:881). The interval of the pain must also be assessed. The pain interval is usually brief but may be longer than 30 minutes in some individuals. Other symptoms to enquire about are shortness of breath, nausea and vomiting as well as diaphoresis (Dalby, 2001:881). Occasionally some individuals may experience minimal to no pain and have atypical symptoms with accompanying features of acute transient reduction in cardiac output. The symptoms are hypotension, tachycardia and/or lethal ventricular tachyarrhythmia's (Dalby, 2001:882). Details of gender and age also need to be recorded, as males over the age of 50 and women in menopause have a greater likelihood of developing acute coronary syndrome. History about smoking, dyslipidemia, diabetes, family history of CAD and hypertension should also be assessed (Dalby, 2001:881).

A physical examination may deliver minimal to no evidence of the presence of acute coronary syndrome as indicated by Dalby (2001:881). Dalby states that there are certain findings to consider like the presence of a fourth heart sound or mitral regurgitation murmur. Pulmonary congestion may indicate possible transient ischemic myocardial dysfunction. A new onset of heart failure, tachycardia, and hypotension with a poor perfusion of the peripheral areas as well as cardiogenic shock should increase suspicion. These signs can

indicate that a large volume of the myocardium is involved in an ischemic process (Dalby 2001:881).

Ker (2003:26) maintains that an urgent resting 12 lead ECG is the first and most important test to be performed. An ECG can assist to stratify a patient as one of the following: STEMI, NSTEMI or unstable angina pectoris. Dalby (2001:882) further explains that ECG should be repeated at intervals of four to six hours. The ECG should be assessed for presence of signs of ST-segment depression, transient ST-segment elevation and/or T-wave inversion present in two or more contiguous leads (Dalby, 2001:882). Contiguous leads refer to lead groups like the inferior leads (II,III and aVF), anterior leads (V1-V6) or the lateral leads (I and aVL) (Thygesen, Alpert & White, 2007:2530). A normal ECG does occur in 20 to 26% of patients and therefore it is important to obtain further ECG tracings as ECG changes may only appear several hours later (Dalby, 2001:882).

To make a clinical diagnosis of suspected acute coronary syndrome, one cannot rely on ECG and clinical symptoms only as they have low diagnostic accuracy (Ramsay, Podogrodzka, McClure & Fox, 2006:12). Adding a troponin I to risk-stratify a patient can aid the process to diagnose acute coronary syndrome (Ramsay et al., 2006:12). The initial evaluation of serum cardiac markers may be within normal ranges, especially when they are obtained shortly after onset of chest pain (Dalby, 2001:882). Troponin I has a negative predictive value when measured on arrival as time is required for efflux of this marker from the injured cardiomyocytes as described by Ramsay (2006:12). When a patient's cardiac markers are normal, it is necessary to obtain a second sample four to six hours, or even eight hours, after the onset of chest pain (Dalby, 2001:882). Ker (2003:28) explains that any elevation of cardiac markers, namely CKMB and troponin I and T, will increase an individual's risk of acute coronary syndrome. Even minimal elevation is associated with increased risk of adverse events (Ker 2003:28).

A myocardial infarction event can be indicated by the myoglobin cardiac blood marker but this marker has been shown to be clinically limited. It has the highest incidence of false-positive results. Therefore in practice, CKMB and troponin levels are utilised because they are specific and sensitive markers of myocardial infarction (Dalby, 2001:882). Raised amounts are present as early as four hours after initial onset of ischemic symptoms according to Dalby (2001:882). Myocardial infarction is diagnosed when the serum markers are above the 99th percentile of values during the first 24 hours after onset (Dalby, 2001:882). The cut-off value of the 99th percentile for troponin T levels is 0,01ng/ml. There is only one type of assay to measure troponin T; thus the value is universal (Mangla, 2012). Troponin I's cut-off value of the 99th percentile varies due to the fact that there are many

different assays used to measure troponin I. Here are some of the different assays used, together with their cut-off points (Mangla, 2012):

- DPC Immulite: 0.40
- Abbott AxSYM: 0.30
- Bayer ACS:Centaur: 0.15
- Ortho Vitros: 0.10
- Bayer ACS:180: 0.07
- Dade Dimension RxL, second generation: 0.07
- Beckman Access, second generation: 0.04
- Byk-Sangtec Liaison: 0.036
- Dade Status CS: 0.03
- Roche Elecsys, third generation: 0.01

To rely only on patient history, physical examination, ECG finding and/or cardiac marker results is risky. Each of these tools currently in use has certain limitations. Some symptoms patients can present with are not specific and isolated to myocardial ischemia only and can lead to misdiagnoses (Thygesen et al., 2007:2527). Thygesen et al. state that some symptoms can be attributed to neurological, gastrointestinal, pulmonary and even musculoskeletal disorders which are not necessarily cardiac. De Lemos (2008:5) explains that elevated troponin levels, even when low, can indicate possibility of other conditions like pulmonary emboli, myocarditis, congestive heart failure and even diabetes while left ventricular hypertrophy can lead to troponin elevation. Thygesen et al. (2007:2528) also point out that when cardiac troponin is elevated in the absence of clinical evidence of ischemia, there is a possibility that it can be due to something other than myocardial necrosis. The ECG can also indicate something other than myocardial ischemia or infarction when there is presence of ST deviations like acute pericarditis, left ventricle hypertrophy and left bundle branch block (Thygesen et al., 2007:2529). Other limitations related to ECG findings and serum cardiac markers have been described in Chapter One.

2.5.7 Standard to diagnose acute coronary syndrome internationally

Patients with acute coronary syndrome present with diverse clinical, ECG and cardiac enzyme characteristics. The estimation of risk based only on clinical characteristics is a challenge and is imprecise; therefore risk assessment is necessary to guide triage and management strategies (Fox, Dabbous, Goldberg, Pieper, Eagle, Van de Werf et al., 2006:1091). Quantitative assessment of risk is useful to guide clinical decision-making. Several scores have been developed to estimate ischemic risk (Hamm et al., 2011:3009).

The American College of Cardiology and American Heart Association guidelines highlight three commonly used risk assessment models to manage acute coronary syndrome patients. The three models are GRACE, TIMI and PURSUIT (Chin et al., 2010:217). For the purpose of this literature review, only the GRACE and HEART risk assessment tools were explored. TIMI and PURSUIT risk scores were excluded from this review as neither of these tools assess the entire acute coronary syndrome spectrum.

2.5.7.1 GRACE

The GRACE programme was created in 1999. The purpose of creating the programme was to attempt to resolve uncertainties regarding acute coronary syndrome and to define how a patient should be treated, as well as to describe the characteristics of the outcomes for these patients (Fox, Eagle, Gore, Steg & Anderson, 2010:1095). The GRACE tool was published in 2003 (Chin et al., 2010:217) and was created from an international registry across the acute coronary syndrome spectrum (Marshall, 2011). It was created to assess all forms of acute coronary syndrome; unstable angina pectoris, STEMI and NSTEMI (Chin et al., 2010:217) and to determine the probability of myocardial infarction or death in hospital (Chin et al. 2010:217). The originators of the GRACE programme aimed to narrow the gap that exists between evidence and clinical practice regarding acute coronary syndrome patients (Fox et al., 2010:1095).

An observational cohort study was conducted in 123 hospitals in 14 different countries. The first 10–20 patients admitted with suspected acute coronary syndrome every month were included and traced over a period of time (Fox et al., 2010:1095). The study provided a reference standard to be used to describe the characteristics, management and outcomes of patients with acute coronary syndrome (Fox et al., 2010:1097). The study also looked at influences in the variation of care given to individuals assessing the impact on outcomes. It examined factors such as geography, resource availability and the adherence to evidence-based guidelines. The result of this study was the identification of a treatment paradox (Fox et al., 2010:1098). It was discovered that those doctors who did not use routine risk stratification had patients with lower risk receiving more evidence-based care and treatments than did those with high risk. This proved that objective risk stratification tools needed to be used and were of great importance (Fox et al., 2010:1098).

The GRACE risk model was then translated into guidance both nationally and internationally and adopted by bodies like the European Society of Cardiology, American College of Cardiology, American Heart Association, SIGN guideline and the National Institute for Health and Clinical Excellence (Fox et al., 2010:1098). Further studies conducted compared the GRACE risk assessment tool to other tools. The GRACE performed extremely well and the

National Institute for Health and Clinical Excellence proposed that the GRACE tool be applied immediately upon patient presentation (Fox et al., 2010:1098). The GRACE programme involved 247 hospitals, and 102 341 patients in 30 different countries assessing the entire spectrum of acute coronary syndrome, and was thus a well validated tool. The tool provides an opportunity for care delivery to patients with acute coronary syndrome being improved by defining patient characteristics and outcomes (Fox et al., 2010:1099). The GRACE tool was revised and a second tool was published in 2004 to determine death in a six-month period (Chin et al., 2010:217).

The GRACE tool assesses the following aspects: age, systolic blood pressure, heart rate, Killip class (to assess heart failure), creatinine levels, cardiac arrest on admission, elevated cardiac enzymes and ST-segment deviation (Marshall, 2011). It is complex to use because it requires a computer programme. According to previous research findings, the GRACE risk assessment tool is superior to the TIMI and PURSUIT tools because it has a greater ability to determine long-term risk (Carmo et al., 2011:247).

2.5.7.2 HEART

Six et al. (2008:191) found difficulties in excluding NSTEMI-ACS in the emergency room because of a lack of ECG changes and lack of increased cardiac marker levels. They believed that early diagnosis is critical for a patient to benefit from early treatment. In the Netherlands, resident doctors were evaluating patients in the emergency room. They would then discuss their findings with their supervisor regarding patient history, risk factors, ECG and cardiac marker levels. Based on this, a decision would be made to admit or discharge a patient (Six et al., 2008:191). Six et al. found that non-specific chest pain patients were being misdiagnosed when presented with NSTEMI-ACS which resulted in adverse outcomes. They wanted therefore to create a new risk assessment tool. Initially they wanted to determine the factors that made a doctor decide to admit a patient, and the predictors for acute myocardial infarction, death and the need for revascularisation (Six et al., 2008:192). All patients admitted in a three-month period were included in the study, with data gathered from a 265-bed community hospital. Six et al. (2008:92) decided that the different predictors – based on medical experience and medical literature of primary end points – would be history, ECG, age, risk factors and troponin I. The acronym HEART was created with the first letter of each of the predictors (Six et al., 2008:192).

The HEART risk assessment tool was developed in the Netherlands obtaining a score between zero and ten points based on aspects of the acronym. Each aspect was allocated zero, one or two points and the total was calculated at the end of the allocation process. It was developed to predict acute coronary syndrome (Fesmire et al., 2012:1830). The study

included 122 patients. A total of 29 patients reached one or more end points in a three-month period. Of these, 16 patients were given an acute myocardial infarction diagnosis, 14 went for percutaneous coronary intervention, six went for coronary artery bypass graft and two died (Six et al., 2008:193). Six et al. (2008:196) performed a literature search assessing the other tools used for NSTEMI-ACS and found that neither were applicable to their situation. They therefore developed a new tool to trial.

Literature shows that the common tools used were TIMI, GRACE and PURSUIT. These risk assessment tools had a scientific basis but they could not effectively differentiate chest pain of patients with low to moderate risk for adverse outcomes. According to Six et al. (2008:196), TIMI and PURSUIT are designed for high-risk patients who would benefit greatly from aggressive therapy. In addition, PURSUIT was created before the use of troponin assays. The limitation of GRACE was that it requires the use of the internet to calculate a score. Although TIMI uses a simple calculation, it uses binary choices which do not take the existence of grey areas into consideration (Six et al., 2008:196). The advantages identified by Six et al. (2008:196) of the HEART risk assessment tool were firstly, that it facilitated communication and decision-making between residents and supervisors. The findings from their study further showed that a HEART score of zero to three identified a patient as having a 2,5% risk of developing adverse outcomes and thus early discharge of patients was recommended. A HEART score of four to six indicated that a patient has a risk of 20,3% of developing an adverse outcome. These patients needed to be admitted for further investigation. A HEART score of seven or more indicated that a patient has a 72,7% risk of developing an adverse outcome and such patients would require immediate aggressive treatment (Six et al., 2008:196).

The HEART score required further validation. Backus, Six, Kelder, Mast, van den Akker, Mast et al. (2010:164) performed a study of various subgroups to confirm the findings from Six et al.'s study from 2008. A total of 2 161 patients were admitted to four different sites. There were 910 patients admitted for chest pain, of which 30 were non-evaluable, so 880 patients remained for inclusion in the study (Backus et al., 2010:166). Within six weeks, a total of 158 patients (17,95%) had an adverse outcome and 92 patients (10,45%) were diagnosed with acute myocardial infarction. Thirteen patients (1,48%) died (Backus et al., 2010:166). Backus et al. explain that, compared to the other three commonly used scores, the HEART score relies heavily on patient history. Whereas the other methods do not classify patient history at all, HEART classifies history numerically. Patients whose history is non-suspicious, thus giving a total score of zero for history, have a negative predictive value of 95,8%. A patient with a score of two for history has a positive predictive value of 44,4% (Backus et al., 2010:168).

Fesmire et al. (2012:1830) observe that the GRACE and TIMI risk assessment tools are applied to emergency room patients with great success, having been developed to predict adverse outcomes in already diagnosed acute coronary syndrome. HEART, on the other hand, was created to diagnose undifferentiated patients with chest pain. The HEART risk assessment tool was found to outperform TIMI and GRACE. These findings were reported at the Congress of the European society of Cardiology in 2010 (Fesmire et al., 2012:1834).

The HEART risk assessment tool was later found to have drawbacks and was adjusted to become the HEARTS3 (Fesmire et al., 2012:1830). This tool was developed to identify acute coronary syndrome and myocardial infarction in a 30-day period (Fesmire et al., 2012:1830). A study confirmed that the HEARTS3 outperformed HEART, and could reliably risk-stratify a patient with chest pain as acute coronary syndrome in 30 days (Fesmire et al., 2012:1863). However, according to Fesmire et al. (2012:1863), the HEARTS3 has one limitation: it uses complex scoring which makes memorising the score difficult when compared to the HEART scoring tool. Unfortunately only one study has been done on the HEARTS3 risk assessment tool.

2.5.8 Physician risk estimation versus risk assessment tool

Approximately 6% of patients are discharged from the emergency unit of a hospital with a missed diagnosed myocardial infarction (Ramsay et al., 2006:12). A study was concluded in 2009 by Yan, Yan, Huynh, Casanova, Raimondo, Fitchett et al., to examine patient risk assessment by a physician, in relation to treatment and objective risk-score evaluation. The results from their study proved that several well-established and powerful prognosticators were not considered by physicians while estimating a patient's risk. This caused a risk-treatment paradox. Those who were deemed high risk by physicians would receive aggressive therapy. But the GRACE, PURSUIT and TIMI risk scores identified certain patients as having been incorrectly risk-stratified by the physician as low risk, while they were actually intermediate to high risk. These individuals did not receive the aggressive therapy which they should have received (Yan et al., 2009:376). The researchers came to the conclusion that risk scores are superior to risk assessment by physicians, and that without the use of these risk scores, accurate and comprehensive integration of numerous prognostic factors is difficult to achieve (Yan et al., 2009:377). Therefore risk assessment tools are a valuable adjunct to clinical judgement (Yan et al., 2009:376).

A further study was done in 2013 to assess the treating physician's initial diagnostic impression of a patient of possible acute coronary syndrome versus definite acute coronary syndrome. The researchers found that the diagnostic impression by physicians influenced

the timely delivery of evidence-based therapies (Bajaj, Goodman, Yan, Bagnall, Gyenes, Welsh et al., 2013:202). In this study, the predictive accuracy of the GRACE risk scores as well as the outcomes, were assessed in relation to the diagnostic impression of possible acute coronary syndrome and definite acute coronary syndrome made by the treating physician. There were a total of 16 618 patients, of whom 11 152 were diagnosed as definite acute coronary syndrome with 5 466 diagnosed as possible acute coronary syndrome by the physician. Of the 5 466 with possible acute coronary syndrome, 76% received a final diagnosis of acute coronary syndrome. The patients in the possible acute coronary syndrome group had a greater rate of myocardial infarction, heart failure and pulmonary oedema than those in the definite group (Bajaj et al., 2013:205). These patients also had a greater GRACE risk score than those in the definite acute coronary syndrome group as stratified by physician; these were the individuals who less frequently received the evidence-based therapies within 24 hours of admission (Bajaj et al., 2013:205). The researchers concluded that the GRACE risk assessment tool provided accurate risk assessment regardless of what the initial diagnostic impression of the treating physician was (Bajaj et al., 2013:206). This study proved that risk assessment using risk assessment tools delivered more accurate results than without the tools.

A study to determine prognostic value beyond the patient risk assessment by the treating physician, enrolled a total of 1 728 patients (Yan, Yan, Tan, Casanova, Labinaz, Sridhor et al., 2007:1072). The physician had to categorise patients into low-, intermediate- and high-risk categories for acute coronary syndrome as based on medical history, physical examination and laboratory findings, which included troponin levels and ECG findings (Yan et al., 2007:1073). Then a risk was calculated for each patient with the GRACE, PURSUIT and TIMI risk assessment tools. The endpoint measured was death. Physician risk categorisation was compared to that of risk scores (Yan et al., 2007:1074). The results were that the treating physician's high-risk group was three times more likely to die than the low-risk group. Those from the TIMI's high-risk group had a five-fold risk of death compared to the TIMI's low-risk group. The results for the GRACE and PURSUIT tools were even higher. Those in the high-risk groups for both tools had a 10 to 15 times higher mortality rate than those of the low-risk groups for both tools (Yan et al., 2007:1074). From this evidence, it is noted that all three risk scores provided more accurate and prognostic information than did the risk assessment by the treating physician. Both the GRACE and PURSUIT risk assessment tools were analysed as continuous variables; the risk assessment done by the physician failed to deliver any incremental prognostic value (Yan et al., 2007:1074). Therefore the researchers concluded that both these tools were more accurate in predicting outcomes and were able to deliver additional prognostic value beyond the global risk

assessment currently used by physicians. Risk assessment tools were found to refine risk stratification and assist in decision-making, thus improving acute coronary syndrome patient care (Yan et al., 2007:1078). This study also proved that the GRACE and PURSUIT tools could be safely used to deliver good results.

To evaluate whether care provided to acute coronary syndrome patients correlated with perceived and calculated risk, another study was performed to explore how well clinicians estimated risk of death, an adverse outcome, among acute coronary syndrome patients (Chew, Junbo, Parsanage, Kerkar, Sulimov, Horsfall & Mattchoss, 2013:209). Physicians were asked to estimate the risk of ischemic events for 1 542 patients to develop myocardial infarction or acute coronary syndrome or die (Chew et al., 2013:302). The GRACE tool was used to calculate a score for death in six months. The findings from the physician risk assessments were that they overestimated the risk for death at six months for the GRACE low-risk score patients, and underestimated the risk of death for the GRACE high-risk score patients (Chew et al., 2013:303). The results showed that mortality at six months was higher for the physician's low-risk group than for the physician's high-risk group. The low-risk physician's group was identified as high risk by the GRACE risk score (Chew et al., 2013:306). Therefore the GRACE risk score had significantly superior discriminatory power in comparison to physicians' risk estimates (Chew et al., 2013:303). This study also showed that estimation of risk using the GRACE risk assessment tool was superior to physician risk assessment (Chew et al., 2013:306).

Yan et al. (2007:1076) emphasise that risk scores are clinical tools that must be used as a supplement to clinical judgement, not to replace it. For example, risk scoring will score a patient with triple vessel coronary artery disease, left ventricular systolic dysfunction presenting with angina but with a normal ECG and cardiac markers as low risk, where in fact this is a high-risk patient for acute coronary syndrome (Yan et al., 2007:1076). By using risk scores and clinical judgement, a more comprehensive and accurate diagnosis can be made for a patient with acute coronary syndrome.

This review of literature showed that diagnosing of patients with acute coronary syndrome was more accurately done when physical assessment, cardiac markers and ECG (current practice in South Africa) was combined with the use of risk assessment tools (international practice). The GRACE and HEART risk assessment tools were selected for reviewing because from literature they proofed to be more superior as well having the ability to assess the entire spectrum of acute coronary syndrome.

2.6 SUMMARY

Mahmoud et al. (2010:60) comment that the outcomes for patients with acute coronary syndrome are poor, although this in an era in which there are modern advances in technologies and therapies. In this chapter, the researcher has explored possible reasons for these poor outcomes. Acute coronary syndrome is a difficult disease to diagnose. To rely only on subjective risk assessment places many patients at risk of adverse outcomes as well as risking not receiving lifesaving therapy and treatment within the first 24 hours of admission. A clinician or physician should use both subjective and objective data before diagnosing a patient with or without acute coronary syndrome, as the first 24 hours are crucial for such patients.

In Chapter Three, the researcher will provide a detailed discussion of the research design, method and quality measurement of the study.

2.7 CONCLUSION

In this chapter, the researcher explored various studies regarding acute coronary syndrome: what it is, what causes it, what is the prevalence and prognosis for someone with this syndrome. Previous literature was also reviewed and the researcher assessed the method of diagnosing acute coronary syndrome in South Africa and its limitations. Risk assessment tools used internationally were described and the benefits and limitations of using such tools were discussed. The researcher identified the gap that exists between risks assessments currently used in South Africa, and risk assessment with the use of risk scores. The conclusion made by the researcher is that both subjective and objective risk assessments are necessary to complement each other as they both have limitations.

CHAPTER THREE: RESEARCH METHODOLOGY

3.1 INTRODUCTION

In Chapter One, a synopsis of the study was presented. Chapter Three will provide the reader with a detailed discussion of the research design, method and quality measurement of the study. The steps of the research process will then be described in detail.

A research project can only be considered successful if the identification and creation of the research problem is accurate. Once the problem has been accurately identified, a definite plan and presentation of research methods can be decided upon. The research design and method describe the method used to solve the research problem.

This chapter's purpose is to provide a broad description of the research design and research method used to achieve the following objectives:

- To estimate the accuracy of GRACE and HEARTS in predicting acute coronary syndrome in adults.
- To compare the accuracy of the two tools in risk prediction of acute coronary syndrome in adults..
- To propose recommendations for a potential risk assessment tool for South Africa.

3.2 RESEARCH DESIGN

A research design is defined by Grove, Burns and Gray (2013:692) as a blueprint required to conduct a research study. The blueprint maximises the researcher's control over factors that could affect the validity of the research findings (Burns & Grove, 2011:253). In this research study, the research design followed a systematic review format of the Cochrane Collaboration handbook of diagnostic test accuracy reviews (Deeks, Wisniewski & Davenport, 2013).

3.2.1 Systematic review

A systematic review was performed in order to explore and describe existing literature related to the accuracy of acute coronary syndrome risk prediction tools. A systematic review is defined as a rigorous synthesis of research findings, using a systematic process of sampling, data collection and a formal protocol (Polit & Beck, 2012:745).

Joubert & Ehrlich (2008:69) state that a systematic review is a review where bias has been reduced through systematic identification, appraisal, and synthesis and if relevant, statistical aggregation of relevant studies based on an identified topic according to a predetermined and explicit method. Systematic reviews are conducted to create evidence from several high-quality studies which used a similar methodology. A systematic review is usually done by a team of experts who use a rigorous synthesis process. The results of a systematic review are usually used to create standardised guidelines which are then utilised in healthcare practice (Burns & Grove, 2011:24).

3.2.2 Purpose of doing a systematic review

There has been an explosion in medical and nursing publishing in the last few years and this trend is likely to continue. This explosion makes it very difficult to keep up with primary research evidence. Over the last few years, internet access to articles has grown tremendously and this creates an overwhelming number of articles one needs to explore (Hemingway & Brereton, 2009:2).

Clinicians, nurses and policymakers require access to extensive information which is of good quality, effective and appropriate. This need for information can conflict with busy workloads and often leads to a lack of necessary knowledge for the people concerned. There may also be a number of studies available concerning a specific subject, but each published article may provide only limited insight into a problem. When these different articles are synthesised into a systematic review, the resulting review can deliver a clear and concise image of a problem (Hemingway & Brereton, 2009:2).

Systematic reviews are necessary to establish the clinical and cost effectiveness of a certain intervention. They are also required to ascertain if an intervention is feasible, if it is appropriate (ethically or culturally) or if it relates to evidence of experiences. Systematic reviews are also required to propose a future research plan when the way forward may be unclear (Hemingway & Brereton, 2009:3). A systematic review provides a researcher with an overview of many different authors' articles rather than the opinion of only one author, thus decreasing the chance of bias (Hemingway & Brereton, 2009:2). For these reasons, a systematic review approach was selected to assess the accuracy of acute coronary syndrome risk prediction tools. As previously noted, these risk assessment tools are not implemented in South Africa. Recommendations will be made based on the evidence and will not reflect any bias on the part of the researcher.

3.3 RESEARCH METHOD

Systematic reviews are often referred to as secondary research (Kitchenham, 2004:1). A systematic review necessitates a method or design in gathering and analysing data.

Grove et al. (2013:711) define a systematic review as a structured synthesis of quantitative data from studies. The aim of the synthesis process is to determine the best evidence available to enhance evidence-based practice. A systematic review is therefore a structured process where a comprehensive synthesis of research literature is carried out with the aim of finding the best research evidence available on a certain healthcare question (Grove et al., 2013:472). The main steps of this process are to initially formulate a research question and then to search for evidence related to the question. This involves selecting applicable studies based on study-specific criteria. Once the researcher has identified relevant studies, he or she is required to assess the methodological quality of studies performed. The researcher can then extract data, analyse and synthesise it. The final step in this process is to interpret the findings (Wieseler & McGauran, 2010:1240).

As a result of the need for rigour in construction of a systematic review, a formal scientific process has developed, requiring the review to be directed by a systematic review protocol (Hemingway & Brereton, 2009:4).

3.3.1 Systematic review protocol

Systematic reviews begin by defining the review protocol. The protocol specifies the research question being addressed and the methods that will be used to perform the review. A pre-defined protocol is essential to reduce the possibility of researcher bias (Kitchenham, 2004:4).

The components of a systematic review protocol include a background stating the rationale for the review, which identifies the research question and the strategy used to search for primary studies. This strategy includes the identification of databases, journals and conference proceedings to be reviewed. The strategy also indicates the search terms that are used. The protocol identifies the inclusion and exclusion criteria to assist the researcher with the study selection process. The protocol also specifies the quality assessment method that will be used. It identifies the data extraction strategy and describes how the data will be synthesised. The protocol also identifies the project timetable which defines the review plan (Kitchenham, 2004:4). A systematic review protocol was developed by the researcher for this study and the review protocol was approved by the Health Research Ethics Committee at Stellenbosch University (See Appendix A).

3.3.2 Research question

A research question can be described as a clear and concise statement created to give direction to a study. The statement contains a description of variables or describes a relationship among variables (Grove et al., 2013:708). In a systematic review a well-formulated research question is required (Hemingway & Brereton, 2009:4). A review may have more than one question to answer. The question needs to be focused and clear in order to facilitate the process of finding material that addresses the specific question (Joubert & Ehrlich, 2007:69). A research question can emanate from the direct interaction of a healthcare practitioner with patients or from the observations made by a healthcare practitioner, or from a patient who asks a question (Botma, Greeff, Mulaudzi & Wright, 2010:242).

In evidence-based practice methodology, it is recommended that a systematic review question being asked, examine the population of interest, intervention needed, comparison of intervention and outcomes needed. This is known as the PICO format (Grove et al., 2013:474). In this study, the population of interest is adults with acute coronary syndrome. The intervention is the risk assessment tools, GRACE and HEART. Initially the comparison was going to be made to elevated serum cardiac markers and positive ECG, which are the reference standards for diagnosing acute coronary syndrome. However, because these elements are part of the index test, the comparison was instead made to major adverse cardiac events (MACE). The outcome of interest is the accurate risk prediction of acute coronary syndrome. The review question posed for this study is as follows:

What is the prediction ability of risk assessment tools GRACE and HEART in predicting acute coronary syndrome in adults?

3.3.3 Searching for evidence

The researcher needs to search for relevant studies and the relevance of these studies will be based on the review question (Botma et al., 2010:243). To ensure this is an unbiased assessment, the researcher must seek to cover all literature in his or her search (Hemingway & Brereton, 2009:4). Experts in systematic reviews have different opinions about inclusion of unpublished studies and grey literature. Some experts believe that the exclusion of such studies will make one's study biased. Other experts believe that only studies with positive outcomes that are published should be included (Hemingway & Brereton, 2009:4).

Pearson et al. (2007:60) believe that it is very important to create a thorough search strategy because a poorly structured strategy may affect the quality of the study. The first step in developing the search strategy is to specify the selection criteria that will be used to locate studies. The criteria are a necessity as they assist the researcher in narrowing the search (Botma et al., 2010:244). Then the researcher can decide on which databases and search terms to use. The strategy for identifying grey literature and unpublished articles should also be described (Grove et al., 2013:476). The search strategy used in this study will now be described.

3.3.3.1 Search strategy

The American Dietetic Association (2008:19-20) describes the aim of the search strategy as identifying all possible literature relevant to the research question. The strategy used should be comprehensive, thus improving the credibility of the review performed and reducing the risk of bias (Centre for reviews and dissemination, 2009:19). The Centre for Evidence-Based Conservation (2009:6) describes the search process as the identification of a “sample” and recommends the use of electronic databases, manual search of unpublished journals and the use of grey literature such as conference proceedings to identify this sample. The search process must be documented; this ensures transparency and repeatability (Magarey, 1997:378).

Two reviewers independently performed a literature review search for articles from inception to 2014 by using the following databases: Cochrane Library, MEDLINE, EMBASE and CINAHL. Search terms were “acute coronary syndrome”, “chest pain”, “NSTEMI”, “STEMI”, “unstable angina pectoris”, “angina pectoris”, “risk assessment”, “risk stratification”, “risk prediction”, “predict”, “accuracy”, “GRACE”, “HEART” and “HEARTS3”.

To increase the precision of the search, terms of the disease were combined with terms of the risk assessment tools during the search. The Cochrane handbook for systematic reviews of diagnostic test accuracy recommends use of more than one approach when conducting searches. In addition to the methodological filter search with terms for the index test and disease, reference lists of identified articles were searched for the identification of more studies. Authors were also contacted electronically where articles were only published in foreign languages, to enquire about English versions. Hand-searching was done to find relevant articles in medical and cardiology journals (Cardiology Journal of SA, 2002-2007; SA Heart Journal, 2007-2014; The South African Medical Journal, 2003-2014). Cardiology conference proceedings from inception to 2014 were also searched for relevant articles (American Heart Association, British Cardiovascular Society, European Society of

Cardiology, American College of Cardiology and American College of Chest Physicians). The search criteria used will now be discussed.

3.3.3.2 Selection criteria

Types of study

The type of studies considered in this review include cross-sectional studies, cohort studies and randomised controlled trials investigating the prediction ability of risk assessment tools (GRACE and HEART) to predict acute coronary syndrome. Studies investigating the prediction ability of risk assessment tools, to determine the presence of acute coronary syndrome, were included. Where studies were in foreign language, the researcher made efforts to secure an English version. The most recent or completed study was included if there was a duplicate publication of the same data.

Types of participants

Studies were included if they reported on participants aged 18 years and above and of any gender. This age group was selected because CVD affects adults from 18 years onwards in low- and middle-income countries (WHO, 2012). The target population included those at risk and those with acute coronary syndrome.

Setting

Study or research setting refers to the location of where a study is being conducted (Grove, Burns & Gray, 2013: 373). Studies conducted in any setting were included in the review.

Index test

The index test refers to the test whose performance is being evaluated; therefore the index test is referred to as the intervention in diagnostic test accuracy reviews (Centre for Reviews and Dissemination, 2009). In this review the two index tests were the GRACE and HEART risk assessment tools.

The risk assessment tools described below are commonly used to predict acute coronary syndrome. The GRACE risk assessment tool assesses the following aspects: age, systolic blood pressure, heart rate, killip class (to assess heart failure), creatinine levels, cardiac arrest on admission, elevated cardiac enzymes and ST-segment deviation (Marshall, 2011: 52). Each aspect is scored and the total is determined by adding the different scores. A total can be anything between 0 and 258. There are three categories; low risk, intermediate risk and the high-risk category (Abu-Assi, Gracia-Acuna, Pena-Gil & Gonzalez-Juanatey, 2009:642). The threshold for this index test is a GRACE score of ≤ 108 for an in-hospital

event (GRACE ACS Risk Score, 2013). Values from 0 to 108 are considered low risk; intermediate risk is 109 to 140 and all scores of more than 140 are considered high risk. The GRACE risk assessment tool is more complex to use because it requires a computer programme to calculate the total (Chin et al., 2010: 217). The HEART risk assessment tool gives a score for each aspect; this score can be 0, 1 or 2 points and the total is calculated at the end of the assessment. The aspects assessed are history, electrocardiogram, age, and risk factors. The total for the HEART ranges between 0 and 10. Scores of 0 to 3 are low risk; medium risk is 4 to 6 and high risk is 7 to 10. The HEART risk assessment tool has a threshold of ≤ 2 (Six, Cullen, Backus, Greenslade, Parsonage, Aldous, et al., 2013:124). Both the GRACE and the HEART risk assessment tools use troponin and ECG to predict acute coronary syndrome and this may have a likelihood of bias. For this reason, authors of the included articles used MACE as their reference standard.

Outcomes

We considered studies that compared the results of GRACE or HEART to those of elevated serum cardiac markers and/or positive ECG. Due to the fact that both cardiac markers and ECG findings formed part of the index test, the outcome that was reported in the studies identified was MACE. MACE are major adverse cardiac events that are an indirect result of acute coronary syndrome being present. Therefore if one has MACE, this serves as indirect proof that acute coronary syndrome is present (Backus et al. 2010:164). These results were presented as estimates of sensitivity and specificity.

Reference standards

The reference standard refers to the best test currently available to confirm the presence of a disease. It is the standard against which the index test is compared in a review of test accuracy (Centre for Reviews and Dissemination, 2009).

The reference standard for confirming the presence of acute coronary syndrome (STEMI, NSTEMI or unstable angina pectoris) in this review was the presence of MACE.

MACE

As discussed under the outcomes section of this chapter, the reference standard ECG and cardiac markers are what is used to confirm the presence of acute coronary syndrome, but due to these forming part of the index test, the results might be biased and not allow a true reflection of the index tests ability to predict or refute the presence of acute coronary syndrome. MACE was used as reference standard in the selected studies. MACE refers to major adverse cardiac events that occur due to the presence of acute coronary syndrome. The four of interest in this study were percutaneous coronary intervention (PCI), coronary

bypass graft (CABG), acute myocardial infarction (AMI) and death. PCI is described as a process of mechanical reperfusion of a thrombotic coronary occlusion. It serves as an alternative therapy to surgical intervention (Lewis et al., 2004:821). Lewis et al. (2004:822) refers to a CABG as myocardial reperfusion which is the surgical treatment for coronary artery disease. CABG is a surgical procedure where there is construction of new blood vessels between the aorta and the other major arteries in the myocardium to bypass the obstructed coronary artery. Therefore with the new blood flow pathway, oxygenated blood is provided to the myocardium beyond the area that has stenosis (Lewis et al., 2004:822). Acute myocardial infarction or myocardial infarction refers to irreversible cell death of the myocardium due to sustained ischemia caused by thrombotic coronary occlusion. Cell death occurs approximately after 20 minutes of sustained ischemia, and the cell death is known as necrosis and is irreversible (Lewis et al., 2004:810). The other adverse event is death resulting from cardiac causes.

3.3.3.3 Study selection

The selection of studies can be seen as a sampling technique (Polit & Beck, 2012:657). Burns and Grove (2005:357) stress that the selection must be explicit and sensitive to ensure that only studies which are relevant and unbiased are included in the review. Once all possible studies had been identified, each study needs to be assessed for eligibility against the inclusion criteria. Only then, full text articles of those which meet the inclusion criteria are retrieved (Hemingway & Brereton, 2009:4). The study selection in this review was done following a three-step study selection process. The inclusion criteria have been described under item 3.3.3.2.

Two reviewers selected studies that were eligible. The first step was the selection of studies based on their titles and abstracts. Each reviewer selected eligible studies for review of the full text articles, making use of the selection criteria described above. The second step was each reviewer retrieving the full text articles of the selected studies and assessing them for inclusion based on the selection criteria. Full text articles were also obtained where eligibility was unclear from reading the title and abstract only. In the final step, reviewers consulted each other regarding the selected articles and a decision was made on which of these articles was to be included. Authors of articles were contacted for missing data.

Disagreements were resolved by discussion. The process of selection of studies is illustrated in Chapter Four with the use of the Preferred Reporting Items for Systematic Reviews And Meta-Analyses flow diagram (Moher, Liberati, Tetzlaff & Altman, 2009).

3.3.4 Critical appraisal

A critical appraisal is done to assess the methodological quality of an article. It is suggested that two or more experts perform the critical appraisal independently of each article and make judgement about the article's quality (Grove et al., 2013:477). A critical appraisal is also referred to as the critiquing of literature. This refers to an approach that is organised and systematic where research studies are evaluated using a set of established critical appraisal criteria. The purpose of this approach is to objectively determine the strength, quality and consistency of the study to establish if it is applicable to research (LoBiondo-wood & Haber, 2010:57). The evidence from primary studies needs to be evaluated to determine how much confidence to place in the study's findings. Studies that are methodologically sound are given more weight than weaker methodology studies in coming to a conclusion regarding the body of evidence (Polit & Beck, 2012:658). The evaluation of study quality might involve the use of quantitative ratings. There are many quality assessment scales that have been developed (Polit & Beck, 2012:658). The researcher is required to select the most appropriate one for the type of study being conducted. The critical appraisal in this study was conducted as detailed below.

Quality assessment was performed by using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool (see Appendix B). The tool rates the bias and applicability of diagnostic accuracy studies (Whiting, Rutjes, Westwood, Mallet, Deeks, Reitsma, et al., 2011:529). The QUADAS-2 tool consists of four domains, namely patient selection, index test, reference standard, and flow and timing. Each domain assesses the risk of bias. The first three domains assess concerns regarding the applicability of the study as well. The tool is applied in four phases: summarise the review question, tailor the tool to review and produce review-specific guidance, construct a flow diagram for the primary study and assess risk of bias and concerns regarding applicability (Whiting et al., 2011:529).

The chosen studies were subjected to independent assessment of methodological quality by the two reviewers. Once the methodological quality was determined, a discussion was held between the two reviewers to determine which articles were of sufficiently good quality for inclusion. Differences of opinion between the two reviewers were resolved by discussion. If no consensus was reached, a third reviewer was available. In the following chapter, the results of the methodological quality are illustrated in a table and the results are described.

3.3.5 Data extraction

Data extraction refers to the extraction of relevant data about study characteristics, methods as well as findings. The data extraction process requires the researcher to develop a data

extraction form and a coding manual to guide those who are extracting the data (Polit & Beck, 2012:659). The data extraction process ideally is done by two independent reviewers (Hemingway & Brereton, 2009:4). The data extraction process for this review is discussed below.

Data was extracted by each of the reviewers independently. An adapted data extraction tool (see Appendix C), which is available from the Cochrane website, was used (The Cochrane Consumers and Communication Review Group, 2011:3–7). A pilot study comprising of three selected trials, was conducted to determine the feasibility of the study, search range, assessment and extraction tools to minimise errors and to ensure reliability and validity of the extraction tool. Minor changes were made to the original data extraction tool. In the method section consumer involvement was removed as it was not applicable to this systematic review. In the participant section the geographic location, gender and ethnicity was removed as this information was not necessary in this review. The pilot test articles were included in the review. Baseline characteristics of included studies were documented in tabular format, including participant characteristics, methodology, population and sample size, setting and the country where the study was conducted. These results will be discussed in Chapter Four. Data was entered into Review Manager 5.2 software and checked for accuracy. Graphs and tables were created from the results and are presented in the next chapter. The excluded articles were tabulated as well as reasons for exclusion documented (see Tables 5 and 6).

3.3.6 Data analysis and synthesis

Data analysis refers to the technique used to reduce information, organise it and provide meaning to the retrieved data (Burns & Grove, 201:535). Data synthesis provides an overall summary of the findings and it includes the documentation of differences as well as consistencies between similar studies (Joubert & Ehrlich, 2008:72). The data can be reported narratively and as a meta-analysis. A meta-analysis is described by Grove et al. (2013:699) as the pooling of statistical results from several studies into a single quantitative analysis. This provides the researcher with the highest level of evidence for an intervention's accuracy study. Meta-analyses are usually used when studies address the same question, uses similar population; administer the same intervention and measures similar outcomes (Botma et al., 2010:245).

The study results were presented separately. The statistical software Review Manager 5.2 was used. The researchers calculated the test performance for predicting acute coronary syndrome of each index test compared with MACE as primary outcome. The results were

categorised into true positives value (TP), false positives value (FP), true negatives value (TN) and false negatives value (FN) for each study. The TP refers to the number of individuals who have the disease, whereas the TN refers to the number of individuals who do not have the disease. The FP represents those who tested positive for the disease but did not actually have it. The FN represents those who tested negative for the disease but actually had the disease (Centre for Reviews and Dissemination, 2009). These values were taken directly from the source papers, and if this was not possible, values were calculated from the data that was provided. The data retrieved was inserted into contingency 2 x 2 tables. A 2 x 2 table provides a visual illustration of the relationship between the results of the index test and the reference standard at a given threshold. The threshold selected for the HEART risk score was a score of 0 to 6 = no MACE present, and a score of 7 to 10 = MACE present (Backus et al., 2013:4). The GRACE risk score threshold was as follows: 1 to 206,5 = No MACE present, and a score of 206,5-330 = MACE present (Lee et al., 2011:66); 1 to 13 = No MACE present and 14 to 20 = MACE present (Lyon et al., 2007:92); 0 to 30 = No MACE present, while a score of more than 30 = MACE present respectively (Ramsay et al., 2007:13). These results were presented as estimates of sensitivity and specificity in a table format and illustrated using a forest plot. Sensitivity of a diagnostic test refers to the accuracy of the test (Grove et al., 2013:709). Polit and Beck (2012:742) define sensitivity as the ability of a screening instrument to correctly identify an individual with a condition. Grove et al. (2013:701) on the other hand, define specificity of a diagnostic test as the accuracy of a screening test. LoBiondo-Wood and Harber (2010:586) describe it as the measurement of how well a test rules out a disease when the disease is really absent. Forest plots in diagnostic test accuracy studies report the number of TP, TN, FN and FP for each study, and then estimate the sensitivity and specificity with the confidence interval (CI) (Macaskill et al., 2010:16). Macaskill et al. (2010:16) further explains that the forest plot is known as a coupled forest plot as it contains two graphs, one depicting sensitivity and another specificity.

The results from the forest plot were illustrated in a graph format using the summary receiver operating characteristics curve (SROC). The SROC curve represents the performance of a diagnostic test (Walter, 2002:1237). Walter describes the SROC curve as a curve that illustrates the relationship between true positive rates and the false positive rates across different studies. The SROC curve estimates the expected values of sensitivity and specificity for a test across many thresholds (Macaskill et al., 2010:18). The SROC curve thus illustrates the trade-off between sensitivity and specificity of the diagnostic test due to varying diagnostic thresholds (Centre for Reviews and Dissemination, 2009). The SROC curve has two axes, the horizontal axis representing the false positive rate (1-specificity) and

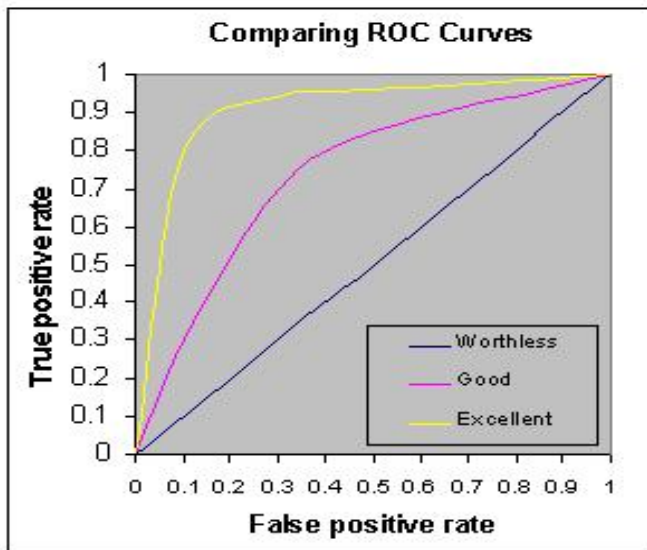
the vertical axis representing the true positive rate (sensitivity) (Rosman & Korsten, 2007:77). The SROC is similar to the receiver operating characteristics curve, but each plotted point indicates a different study result (Jones & Athanasiou, 2005:18). The SROC curve is shaped by the results across studies. Not all the points will lie on the SROC curve, because the curve is positioned as close as possible to the overall data set (Jones & Athanasiou, 2005:18). There is a diagonal line running through the middle of the SROC graph and this line represents a line of no-discrimination (Jones & Athanasiou, 2005:18). This implies that any study result plotted on this line shows that the test is uninformative; a random guess could just as well be taken to predict whether a patient has the disease or not. Jones and Athanasiou (2005:18) explain that this is where sensitivity and specificity is 50%. The top left-hand corner is where sensitivity and specificity is 100% and this is known as the perfect classification (Zhu, Zeng & Wang, 2005:3). Any study result plotted to the left above the no-discrimination line indicates that a test has value and is able to discriminate between disease and no-disease (Eng, 2005:910). The closer the plot is to the left-hand border and to the top of the border, the more accurate the test will be (Thomas, 2003). Therefore the overall accuracy of a test is measured by the closeness of the graph to the left-hand corner. The closer the graph is, the higher the sensitivity and specificity of the test (Jones & Athanasiou, 2005:18). The closer the plot is to the 45-degree diagonal line the less accurate the test will be (Thomas, 2003). Any study result plotted below the no-discrimination line to the right indicates that the test has no value and is unable discriminate between disease and no disease (Eng, 2005:910). Zhu et al. (2005:4) contend that in order to measure the accuracy of a diagnostic test, the researcher must calculate the area under the curve (AUC). The larger the AUC and the closer the value approaches 1, the more accurate the test will be. An AUC of 0,5 indicates that a test is worthless (Jones & Athanasiou, 2005:18). The researcher will not calculate the AUC as part of the data synthesis process. The researcher will use a rough guide proposed by Thomas (2003) to estimate and then classify the AUC with a traditional academic point system based on the curve of the SROC. The point system is as follows:

- ,90 to 1 = excellent
- ,80 to ,90 = good
- ,70 to ,80 = fair
- ,60 to ,70 = poor
- ,50 to ,60 = fail

Thomas (2003) uses a ROC curve diagram (Figure 3.1) to indicate excellent, good, and worthless tests plotted on the same graph with the use of the point system. He uses the

values above and categorizes them into three main classes. An excellent test ranging between 0,8 and 0,9, a good test ranging between 0,7 and 0,8 and a worthless test ranging between 0,5 and 0,6. He states that the accuracy of a diagnostic test will depend on how well that test is able to identify those with disease and those without the disease.

Figure 3.1: ROC curve diagram



3.4 SUMMARY

In Chapter One, the researcher discussed very briefly the research design and methods used. In Chapter Two the researcher provided a discussion on the existing body of knowledge regarding risk assessment tools and acute coronary syndrome. A research design and research method is of great importance in the planning and implementation of a research study. In this chapter the researcher discussed these elements in great depth as well as how each was implemented in this study. In Chapter Four, the results of the search strategy, critical appraisal, data extraction and data synthesis are described.

CHAPTER FOUR: RESULTS

In the previous chapters, the research methods and the background literature relevant to the research topic was described. In this chapter, the researcher describes the results of the search, the quality assessment and the data synthesis. The results are also summarised in tables and graphs in this chapter.

4.1 INTRODUCTION

Data was collected in the empirical phase of a study must be summarised, analysed and interpreted. A researcher discusses the process and the findings in the result section of a study. This phase is known as the interpretative phase (Brink et al., 2012:56). The results of the data analysis set the stage for interpretation, discussion and limitations section of a study (LoBiondo-Wood et al., 2010:336). The researcher will discuss the findings of the sampling procedure (identified relevant studies for inclusion), the findings of the quality assessment (examining for completeness and accuracy of included studies) and then summarise the evidence from data that was extracted.

4.2 SEARCH RESULTS

The search was conducted with the aim of locating and including all studies relevant to the research question. The first step of the search was to perform a broad search, thereby ensuring that all possible studies were included. Then filtering of studies was done to ensure all included studies were relevant.

4.2.1 Sources

The researcher ensured that the search was unbiased by including multiple sources, thereby identifying all potentially relevant studies as illustrated in Table 4.1 below.

Table 4.1: Sources used in search strategy

Electronic database		Type of literature included
International	1. Cochrane Library 2. MEDLINE 3. Embase 4. CINAHL	Systematic reviews of studies Journal articles Journal articles Journal articles
National	1. SUNScholar	Theses and dissertations
Other studies		
Manual		<ul style="list-style-type: none"> • Grey literature searched such as conference proceedings, unpublished research theses • Manual search used to obtain articles from the internet identified from reference lists

Four electronic databases were searched using search strings (Cochrane Library, MEDLINE, Embase and CINAHL) to identify potential journal articles. Databases were searched for articles from inception to 2014 and there were no language restrictions on the search. SUNScholar was also searched for relevant theses or dissertations on the topic. A manual search was conducted to search for grey literature such as conference proceedings (American Heart Association, British cardiovascular society, European Society of Cardiology, American College of Cardiology and American College of Chest Physicians) and other relevant articles identified from reference lists using the internet.

4.2.2 Search terms

A combination of keywords was used to search for literature. The following keyword combinations were used as displayed in Tables 4.2 and 4.3.

Table 4.2: Search strings for Cochrane Library, MEDLINE & CINAHL

Database	Search string
Cochrane Library	A: "ACS AND Risk assessment AND GRACE OR HEART OR HEARTS3"
MEDLINE	B: "ACS AND Risk prediction AND GRACE OR HEART OR HEARTS3"
CINAHL	C: "ACS AND Risk stratification AND GRACE OR HEART OR HEARTS3"

	<p>D: “NSTEMI OR STEMI OR Unstable angina pectoris AND Risk assessment AND GRACE OR HEART OR HEARTS3”</p> <p>E: “NSTEMI OR STEMI OR Unstable angina pectoris AND Risk prediction AND GRACE OR HEART OR HEARTS3”</p> <p>F: “NSTEMI OR STEMI OR Unstable angina pectoris AND Risk stratification AND GRACE OR HEART OR HEARTS3”</p> <p>G: “Chest pain AND Risk assessment AND GRACE OR HEART OR HEARTS3”</p> <p>H: “Chest pain AND Risk prediction AND GRACE OR HEART OR HEARTS3”</p> <p>I: “Chest pain AND Risk stratification AND GRACE OR HEART OR HEARTS3”</p>
--	--

Table 4.3: Search strings for Embase

Embase	<p>A 1: “ACS AND Risk assessment AND GRACE”</p> <p>A 2: “ACS AND Risk assessment AND HEART OR HEARTS3”</p> <p>B & C 1: “ACS AND Risk prediction OR Risk stratification AND GRACE”</p> <p>B & C 2: “ACS AND Risk prediction OR Risk stratification AND HEART OR HEARTS3”</p> <p>D 1: “NSTEMI OR STEMI OR Unstable angina pectoris AND Risk assessment AND GRACE”</p> <p>D 2: “NSTEMI OR STEMI OR Unstable angina pectoris AND Risk assessment AND HEART OR HEARTS3”</p> <p>E 1: “NSTEMI OR STEMI OR Unstable angina pectoris AND Risk prediction AND GRACE”</p> <p>E 2: “NSTEMI OR STEMI OR Unstable angina pectoris AND Risk prediction AND HEART OR HEARTS3”</p> <p>F 1: “NSTEMI OR STEMI OR Unstable angina pectoris AND Risk stratification AND GRACE”</p> <p>F 2: “NSTEMI OR STEMI OR Unstable angina pectoris AND Risk stratification AND HEART OR HEARTS3”</p> <p>G 1: “Chest pain AND Risk assessment AND GRACE”</p> <p>G 2: “Chest pain AND Risk assessment AND HEART OR HEARTS3”</p> <p>H 1: “Chest pain AND Risk prediction AND GRACE”</p> <p>H 2: “Chest pain AND Risk prediction AND HEART OR HEARTS3”</p>
--------	---

	I 1: "Chest pain AND Risk stratification AND GRACE" I 2: "Chest pain AND Risk stratification AND HEART OR HEARTS3"
--	---

To ensure that relevant data was not missed, the search strings were searched in the categories of All or Title or Abstract. There was a lack of relevant results from Embase database when the full combination of search string was used. The researcher therefore selected keyword combinations to obtain relevant results as displayed in Table 4.3.

4.2.3 Documentation of search

The search was documented and Table 4.4 provides a summary of the results of the search.

Table 4.4: Summary of search

Summary of search	Database	Search results
Electronic database: International	1. Cochrane Library	0
	2. MEDLINE	146
	3. Embase	52
	4. CINAHL	71
National	1. SUNScholar	0
Internet & references		11
Total:		280

The search yielded a total of 280 articles from the different search sources. In the initial search using the search strings in the different databases, titles and abstracts of articles were examined and a total of 269 articles were identified. A total of 11 additional articles were identified from reference list of articles. There were 117 duplicate articles from various database sources and they were excluded, leaving 163 abstracts to be extracted and reviewed for possibility of inclusion.

From the 163, a further 126 articles were excluded as the abstracts revealed studies not to meet the inclusion criteria, and five of the 126 articles were unobtainable due to various reasons (Table 4.5). A total of 37 articles were selected for review of full text articles. The obtained full text articles were read by the two reviewers independently and a decision was made on whether to include articles for critical appraisal as based on the review question. A total of 13 full text articles did not meet the inclusion criteria and were excluded (Table 4.5). A total of 24 articles remained for critical appraisal. A total of 19 articles were excluded after

critical appraisal, for various reasons (Table 4.6). A total of five articles remained for data extraction. The results of electronic database and hand searching are outlined in Figure 4.2 below.

Figure 4.2: Flow of studies identified in literature search for systematic review

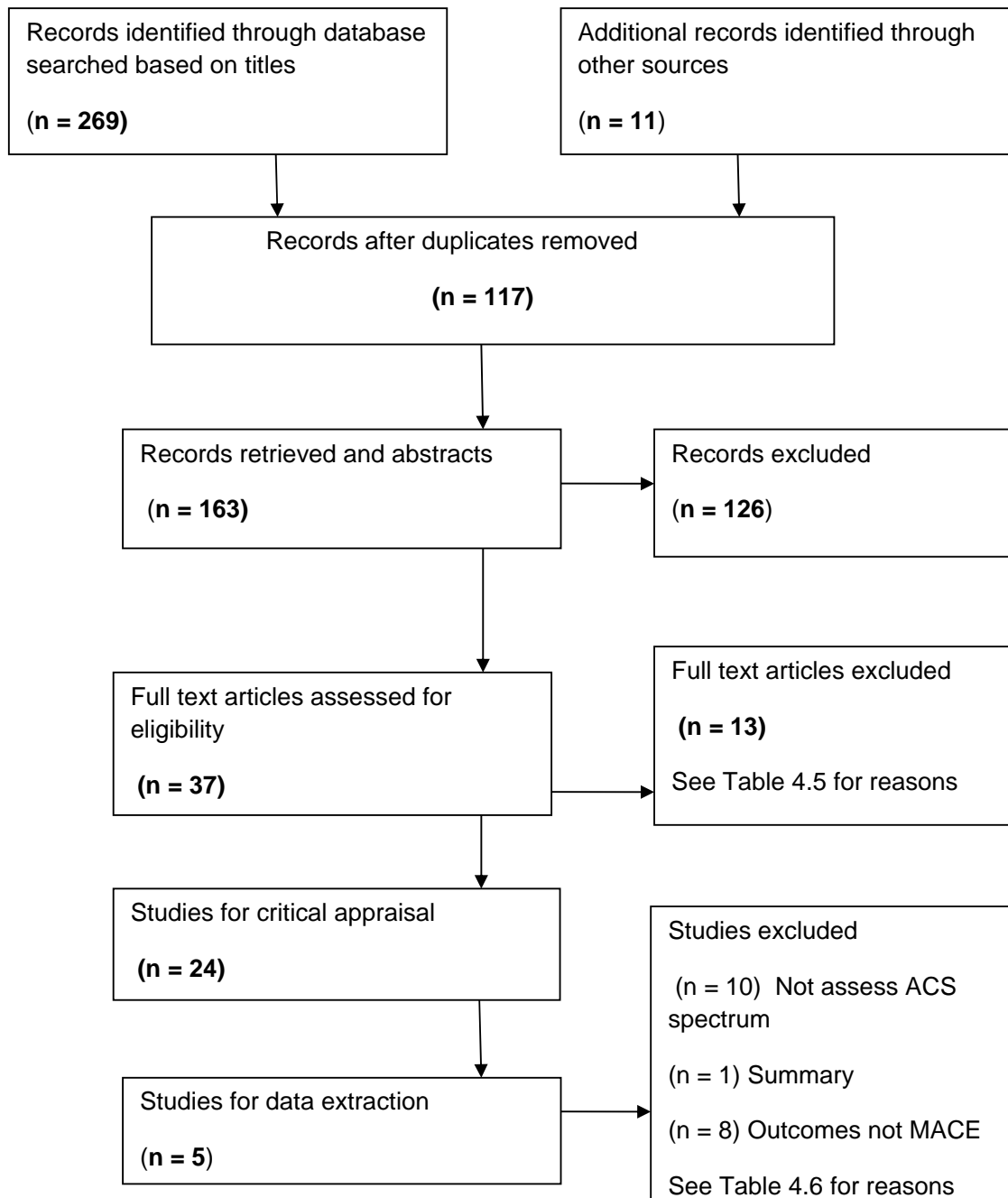


Table 4.5: Excluded full text articles

Article Identification	Reason for exclusion
1. Graham et al., 2014	Not available for free
2. Graham et al., 2014	Not available for free
3. Backus et al., 2009	Powerpoint summary of articles done on HEART risk score
4. Barba et al., 2013	Only in Italian, no English version
5. Martin et al., 2013	No English version
6. Abelin et al., 2013	Only assesses one spectrum: STEMI
7. Barbosa et al., 2012	Only assesses one spectrum: NSTEMI-ACS
8. D'Ascenzo et al., 2012	Systematic review
9. Fesmire et al., 2012	Only assesses one spectrum: NSTEMI-ACS
10. Filipiak et al., 2011	Validate another tool by comparing to GRACE
11. Fox et al., 2010	SUMMARY
12. Gale et al., 2008	Validate another tool by comparing to GRACE
13. Gonçalves et al., 2005	Only assesses one spectrum: NSTEMI-ACS
14. Khalil et al., 2009	Only assesses one spectrum: NSTEMI-ACS
15. Scruth et al., 2013	Only assesses one spectrum: STEMI
16. Backus et al., 2008	Only assesses one spectrum: NSTEMI-ACS
17. GRACE Investigators, 2001	Not a diagnostic study
18. Yan et al., 2007	Only assesses one spectrum: NSTEMI-ACS

4.3 QUALITY ASSESSMENT

A total of 24 studies remained for critical appraisal. Critical appraisal is the last step of the sampling procedure where the researcher evaluates the methodological quality of selected articles. The QUADAS 2 tool (see Appendix B) was found to be applicable for critical appraisal and is recommended by the Cochrane group for systematic reviews of diagnostic test accuracy studies.

The internal validity of the study was ensured because the critical appraisal tool fitted the design. The QUADAS 2 tool is a structured and objective instrument used to assess quality of articles, reducing the risk of researcher's bias. Twenty-four full text articles were critically appraised using the QUADAS 2 tool. Of the 24, a total of 19 articles were excluded for various reasons as stated above (Table 4.6).

Table 4.6: Excluded studies after critical appraisal

Article Identification	Reason for exclusion
1. Conti et al., 2012	Excludes STEMI & NSTEMI
2. Correia et al., 2009	Only assesses one spectrum: NSTEMI-ACS
3. Cullena et al., 2013	Excludes STEMI
4. Goodacre et al., 2012	Excludes STEMI
5. Halpern et al., 2013	Excludes STEMI

6. Mahler et al., 2011	Excludes STEMI
7. Marcoon et al. 2013	Excludes STEMI
8. Melki et al., 2013	Excludes STEMI
9. Poldervaart et al., 2013	Excludes STEMI
10. Six et al., 2013	Excludes STEMI
11. Aragam et al., 2009	Outcome: Mortality Not MACE
12. Backus et al., 2013	Summary
13. Bajaj et al., 2012	Outcome: Death and Re-MI, not MACE
14. Elbarouni et al., 2009	Outcome: In hospital mortality not MACE
15. Meune et al., 2011	Outcome: Death & AMI, not MACE
16. Mahmoud 2009	Outcome: Mortality, not MACE
17. Prabhudesai et al., 2012	Outcome: Mortality & MI, not MACE
18. Stracke et al., 2010	Outcome: Mortality not MACE
19. Soderholm et al., 2011	Outcome: Low-risk complications, not MACE

Five articles were included in the review. The methodological quality of the included studies is illustrated in Table 4.7.

Table 4.7: QUADAS 2 risk of bias

Study	RISK OF BIAS				APPLICABILITY CONCERNS		
	PATIENT SELECTION	INDEX TEST	REFERENCE STANDARD	FLOW AND TIMING	PATIENT SELECTION	INDEX TEST	REFERENCE STANDARD
Backus 2010	😊	😊	😊	😊	😊	😊	😊
Backus 2013	😊	?	😊	😊	😊	😊	😊
Lee 2011	😊	😊	😊	😊	😊	😊	😊
Lyon 2007	?	☹️	😊	😊	😊	😊	😊
Ramsay 2007	😊	😊	😊	😊	😊	😊	😊

😊 Low Risk ☹️ High Risk ? Unclear Risk

The two reviewers independently assessed the 24 articles included for risk of bias. The risk of bias for the included studies varied. One article of the final five studies had incomplete data under the patient selection Domain 1 (Lyon 2007), where 21 patients were missing from the initial sample, and the reason for this was not stipulated in the study. The remaining four studies had low risk of bias for Domain 1. Two of the studies had been identified as potentially biased due to poor reporting on the index test (Domain 2). In the Backus et al. 2013 article, the threshold was not pre-specified but reference was made to a previous study

performed. Thus the domain was marked as unclear. The other study (Lyon et al. 2007) had been identified as high risk of bias in Domain 2 (the index test) as there was no pre-specified threshold given. All articles had low risk of bias in Domain 3 reference standards and Domain 4 (flow and timing). All five articles were applicable in all four domains to this study. A total of five articles of good methodology quality remained for data extraction.

4.4 DATA EXTRACTION

The researchers independently extracted data from eligible studies. Data was extracted from the final five studies using an adapted standard data extraction form from the Cochrane website (see Appendix C). The data extraction characteristics of these studies are displayed in Table 4.8.

Table 4.8: Characteristics of articles for inclusion

Study Identification	Methods	Size	Intervention	Outcome
1. Backus et al., 2010	Retrospective multicentre analysis – cohort study	n=880	Duration: 1 January – 31 March 2006 Index-test: HEART	MACE in 6 weeks (AMI, PCI, CABG & death) Reference standard: -PCI: hospital charts (therapeutic catheter intervention in coronary arteries) -CABG: hospital charts (cardiac surgery on coronary arteries) -AMI (typical chest pain, ECG changes, rise troponin levels & creatinine phosphokinase -Death
2. Backus et al., 2013	Prospective study – cohort study	n=2388	Duration: October 2008 – November 2009 Index test: HEART	MACE in 6 weeks (AMI, PCI, CABG, death) Reference standard: - PCI: patient records (therapeutic catheter intervention in coronary arteries) -CABG: hospital charts (cardiac surgery on coronary arteries) - AMI (rise and fall troponin level above 99 percentile with evidence of myocardial ischemia, distinction made STEMI/NSTEMI see article) -Death
3. Lee et al., 2011	Secondary analysis prospective cohort study	n=4743	Duration: Not specified Index test: GRACE	MACE in 30 days (AMI, death, revascularisation (PCI & CABG)

				Reference standard: - Death: record review, family member or social security death index - Revascularisation: record review, PCI or CABG - AMI (as per European society of cardiology & American college of cardiology guidelines: rise or fall troponin level above 99 percentile of upper ref limit with one of flw: symptoms of ischemia; new significant ST or T changes or new LBBB; Pathological Q wave on ECG)
4. Lyon et al., 2007	Retrospective descriptive study – cohort study	n=734	Duration: 2-month period Index test: GRACE	MACE in 30 days (STEMI, positive troponin ACS, PCI, death) Reference standard: - Mortality: hospital recorded, telephone calls - PCI - ST elevation MI or Troponin positive ACS
5. Ramsay et al., 2007	Prospective observational study – cohort study	n=347	Duration: November 2005 – February 2006 Index test: GRACE	MACE in hospital and at 3 months (mortality, MI, revascularisation) Reference standard: - Mortality: electronic patient database - Revascularisation: electronic patient database - MI: (ST deviation, troponin elevation)

Data that was extracted from the five included articles was the study design used, participant characteristics (setting, size, age, signs and symptoms), intervention (duration of study, index test used) and primary outcomes, including the reference standard used. Of the five articles, two assessed the HEART risk assessment tool and its ability to diagnose patients with acute coronary syndrome. The remaining three articles assessed the GRACE risk assessment tool and also the ability to confirm the presence of acute coronary syndrome. The HEART studies used different study designs – one a retrospective design and the other a prospective design. The research designs used by the GRACE studies were a retrospective study (one article) and a prospective design (the other two articles). All five articles identified chest pain as the main sign and symptom with which a patient presented. The outcomes of the two HEART studies assessed the occurrence of major adverse cardiac events (MACE) within six weeks. MACE was used in all the studies as the outcome as it describes adverse events of acute coronary syndrome, and thus serves as indirect proof of

diagnosis of acute coronary syndrome (Backus, 2010:164). The main four adverse events are percutaneous coronary intervention (PCI), coronary artery bypass graft (CABG), acute myocardial infarction (AMI) – which is described as chest pain with ECG changes and/or elevated troponin levels – and finally, death. The three GRACE studies outcomes were also MACE. Two articles assessed the outcome of MACE within a 30-day period follow up. The other article assessed the outcome of MACE occurring while patient was in hospital and occurring at three months follow-up period. The outcomes were similarly described as for the HEART studies but PCI and CABG were classified as revascularisation. Data extracted included the sample size and the main findings, as illustrated in Table 4.9.

Table 4.9: Summary of study

Article Identification	Participants	Outcomes measured	Summary of main findings
1. Backus et al., 2010	<p>Setting: Four separate hospitals in the Netherlands. Three sites were community-based hospitals: Emergency department</p> <p>Age: No restrictions (Mean age of participants 61 with standard deviation of 15,7)</p> <p>Signs & symptoms: Chest pain</p>	- MACE in 6 weeks (AMI, PCI, CABG & death)	<p>- 58/880 had MACE in 6 weeks.</p> <p>- HEART score has a great discriminatory ability.</p>
2. Backus et al., 2013	<p>Setting: Ten hospitals in the Netherlands: Emergency department</p> <p>Age: No restrictions (Mean age was 60 with standard deviation of 15,4)</p> <p>Signs & symptoms: Chest pain</p>	- MACE in 6 weeks (AMI, PCI, CABG, death)	<p>-407/2388 had MACE in 6 weeks.</p> <p>-HEART score is a reliable predictor of MACE.</p>
3. Lee et al., 2011	<p>Setting: Hospital of the University of Pennsylvania: Emergency department</p> <p>Age: >30 years</p> <p>Signs & symptoms: Chest pain or equivalent that is concerning for ACS</p>	- MACE in 30 days (AMI, death, revascularisation (PCI & CABG))	<p>- 319/4743 had MACE in 30 days.</p> <p>- GRACE identified participants for MACE correctly, there was increasing MACE with increased risk score.</p>
4. Lyon et al., 2007	<p>Setting: Edinburgh Royal Infirmary,</p>	- MACE in 30 days (STEMI, positive	- 123/760 had one MACE at 30 days.

	Scotland: Emergency department Age: >20 years Signs &Symptoms: Chest pain	troponin ACS, PCI, death)	- 28/760 had multiple MACE at 30 days. -GRACE has potential to risk stratify patients with chest pain.
5. Ramsay et al., 2007	Setting: - Royal Infirmary of Edinburgh: accident and emergency department, the combined assessment area, coronary care unit or direct to a cardiology ward Age:> 18 years Signs & symptoms: Chest pain	- MACE in hospital and at 3 months (mortality, MI, revascularisation	-140/347 was diagnosed with ACS on discharge & 8/347 had MACE. -24/347 had MACE at 3 months -GRACE found to be predictive of these MACE

In the study of the HEART risk score, the sample size was n=880; 158 of this sample had MACE within 6 weeks. It was found that the HEART score had great discriminative ability. The other study on the HEART risk score had a sample size of n=2388 of which 407 had MACE within 6 weeks. It was found that the HEART score was a reliable predictor of MACE. The specifics of the sample size with MACE versus those without MACE, and in which risk score group the events occurred, have been illustrated in Table 4.10.

Table 4.10: Summary of findings for HEART risk score

HEART Studies	Score levels	No. patients with MACE	No. patients without MACE
Backus et al., 2010 n=880	Low 0-3	3	300
	Medium 4-6	48	365
	High 7-10	107	57
Total:		158	722

HEART Studies	Score levels	No. patients with MACE	No. patients without MACE
Backus et al., 2013 n=2388	Low 0-3	15	855
	Medium 4-6	183	918
	High 7-10	209	208
Total:		407	1981

In the study of GRACE risk score the sample size was n=4743, of which 319 had MACE in 30 days; the GRACE score was found to have correctly identified patients for MACE. The next study had a sample size of 760 of which 123 had MACE and 28 had multiple MACE. The originators of the GRACE score stated that the GRACE risk score had the potential to accurately risk-stratify patients. The last study of the GRACE risk score had a sample size of n=347. Of these, 140 had a discharge diagnosis of ACS, 8 had MACE in hospital and 24 had MACE at 3 months after hospitalisation. The GRACE score was found to be predictive of these outcomes. The specifics regarding the amount of sample size that had MACE versus those without MACE and in what risk score group the events occurred has been illustrated in Table 4.11.

Table 4.11: Summary of findings for GRACE risk score

GRACE studies	Score levels	No. patients with MACE	No. patients without MACE
Lee et al., 2011 n=4743	1-41.25	1	214
	41.25-82.5	59	2252
	82.5-123.75	134	1411
	123.75-165	83	449
	165-206.25	33	81
	206.25-247.5	8	16
	247.5-288.75	1	1
	288.75-330	0	0
Total:		319	4424

GRACE studies	Score levels	No. patients with MACE	No. patients without MACE
Lyon et al., 2006 n=734	1-5	12	287
	6-9	37	223
	10-13	49	80
	14-16	15	17
	17-20	10	4
Total:		123	611

GRACE studies	Score levels	No. patients with MACE	No. patients without MACE
Ramsay et al., 2007 n=347 (140 were ACS)	Low <15	1	136
	Medium 16-30	4	115
	High >30	19	72
Total:		24	323

The number of patients who had MACE in the specific period as described by each study are further classified into secondary outcomes namely PCI, CABG, AMI and death and these are illustrated in Tables 4.12 and 4.13.

Table 4.12: MACE findings of HEART risk score

Study identification	No. of patients with MACE	Secondary outcomes (AMI, PCI, CABG, death)
1. Backus et al., 2010	n=158	AMI: 92 PCI: 82 CABG: 36 PCI & CABG: 1 Death: 13
2. Backus et al., 2013	n= 407	AMI:155 PCI: 251 CABG: 67 Death: 13

Table 4.13: MACE findings of GRACE risk score

Study identification	No. of patients with MACE	Secondary outcomes (AMI, PCI, CABG, death)
3. Lee et al., 2011	n= 319	AMI: 163 in hospital : 172 at 30 days Revascularisation: 155 in hospital : 175 at 30 days Death: 28 in hospital : 59 at 30 days
4. Lyon et al., 2007	n= 123	AMI (STEMI & Troponin positive ACS & readmit with AMI): 40; 65; 1 Revascularisation: 29 Death: 16
5. Ramsay et al., 2007	n= 8 in hospital n=24 in 3 months	AMI: 3 in hospital : 7 at 3 months Revascularisation: 0 in hospital : 1 at 3 months Death: 5 in hospital : 16 at 3 months In addition to MACE findings: Re-admission for ischemic chest pain 17

4.5 DATA SYNTHESIS

Data synthesis was performed using Review Manager 5.2 software. Study results were collected from the five inclusion articles. The results of each study were entered into a 2x2

contingency table (see Tables 4.14 to 4.18). A 2x2 contingency table categorises study subjects for several purposes. The variables of each study are assigned to a class (TP,TN,FP,FN) and then the information in the table is used to measure associations between them, for example to determine the sensitivity and specificity of a diagnostic tool (University of Michigan, 2010).

Table 4.14: Backus et al., 2010 2x2 contingency table

		REFERENCE Standard MACE in 6 weeks		Total:
		Positive MACE	Negative No MACE	
INDEX Test HEART	Positive 7-10 risk score group	TP 107	FP 57	164
	Negative 0-6 risk score group	FN 51	TN 665	716
Total:		158	722	n=880

Table 4.15: Backus et al., 2013 2x2 contingency table

		REFERENCE Standard MACE in 6 weeks		Total:
		Positive MACE	Negative No MACE	
INDEX Test HEART	Positive 7-10 risk score group	TP 209	FP 208	417
	Negative 0-6 risk score group	FN 198	TN 1773	1971
Total:		407	1981	n=2388

Table 4.16: Lee et al., 2011 2x2 contingency table

		REFERENCE Standard MACE in 30 days		Total:
		Positive MACE	Negative No MACE	
INDEX Test GRACE	Positive 206,25-330	TP 9	FP 17	26
	Negative 0-206,25	FN 310	TN 4407	4717
Total:		319	4424	n=4743

Table 4.17: Lyon et al., 2007 2x2 contingency table

		REFERENCE Standard MACE in 30 days		Total:
		Positive MACE	Negative No MACE	
INDEX Test GRACE	Positive 14-20	TP 25	FP 21	46
	Negative 1-13	FN 98	TN 590	688
Total:		123	611	n=734

Table 4.18: Ramsay et al., 2007 2x2 contingency table

		REFERENCE Standard MACE in 3 months		Total:
		Positive MACE	Negative No MACE	
INDEX Test GRACE	Positive > 30	TP 19	FP 72	91
	Negative 0-30	FN 5	TN 251	256
Total:		24	323	n=347

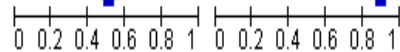
The data from the 2x2 contingency tables was grouped together for the HEART risk score to create a coupled forest plot depicting sensitivity and specificity (see Figure 4.3).

Figure 4.3: Forest plot for HEART risk score

Study ID	TP	FP	FN	TN
Backus 2010	107	57	51	665
Backus 2013	209	208	198	1773

HEART

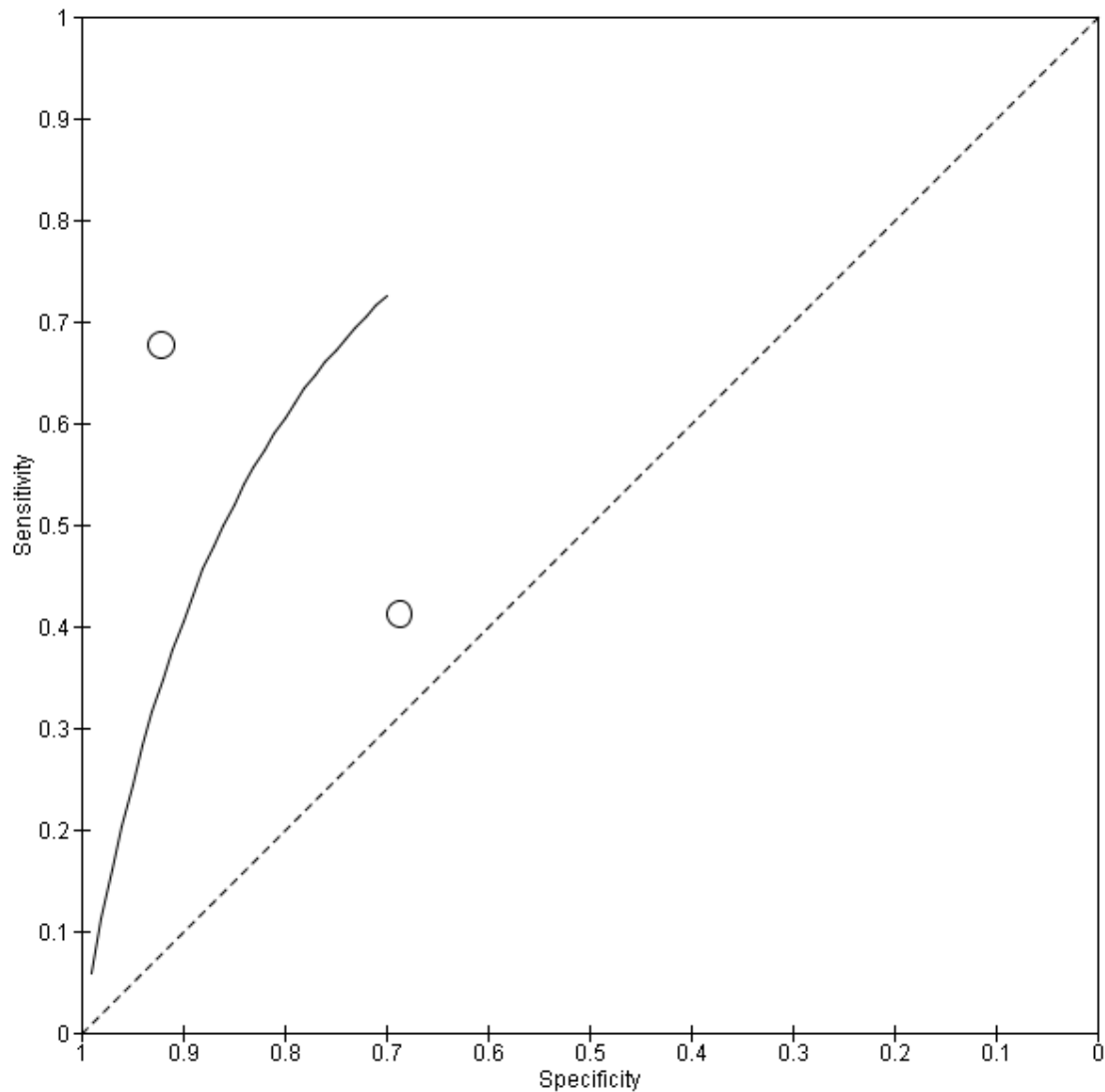
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Backus 2010	107	57	51	665	0.68 [0.60, 0.75]	0.92 [0.90, 0.94]		
Backus 2013	209	208	198	1773	0.51 [0.46, 0.56]	0.90 [0.88, 0.91]		



Two studies on the HEART risk score provided data from 3268 individuals. Values of sensitivity were low in both studies whereas the specificity was high. The sensitivity of the HEART risk score varied from 0,51 (95% CI 0,46 to 0,56) (Backus 2013)) to 0,68 (95% CI 0,60 to 0,75) (Backus 2010)) respectively. The specificity varied from 0,90 (95% CI 0,88 to 0,91) (Backus 2013)) to 0,92 (95% CI 0,90 to 0,94) (Backus 2010)) respectively.

The data from the forest plot was used to create an SROC curve for the HEART risk score as illustrated in Figure 4.4. The SROC curve has two axes, the horizontal axis representing the false positive rate (1-specificity) and the vertical axis representing the true positive rate (sensitivity). There is a straight line running through the middle of the graph. This line represents the area of no-discrimination. The test is thus uninformative if plotted anywhere on this line.

Figure 4.4 follows on page 58.

Figure 4.4: SROC curve for HEART risk score

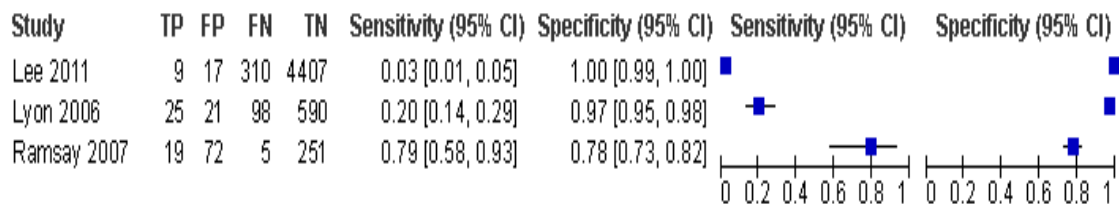
The sensitivity and specificity of the two HEART studies has been plotted with a clear circle in the ROC space. The SROC curve is placed as close as possible to both data sets. The SROC curve lies on the left side of the diagonal line, signifying that the HEART risk score has value in its prediction ability of acute coronary syndrome. This means that the tool is better than a random guess for predicting whether a patient has the disease or not. The AUC is estimated to be between 0.7 and 0.8 when using the traditional academic point system which indicates that the tool has a fair ability to accurately predict the presences of acute coronary syndrome in adults. The HEART risk score has a 70% to 80% probability of correctly classifying a patient as diseased or not.

The data from the 2x2 contingency tables was grouped together for the GRACE risk score to create a coupled forest plot depicting sensitivity and specificity (see Figure 4.5).

Figure 4.5: Forest plot for GRACE risk score

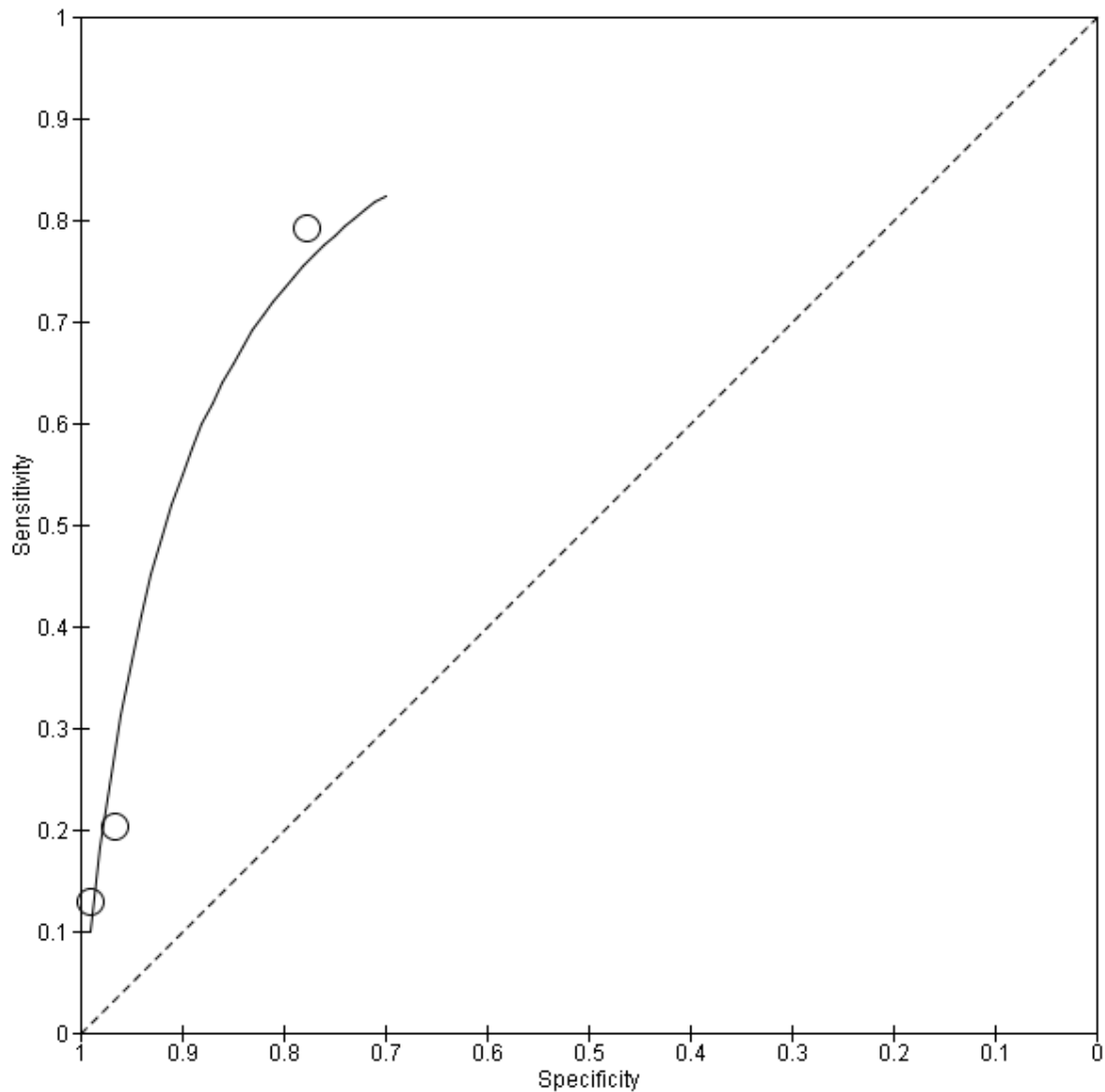
Study ID	TP	FP	FN	TN
Lee 2011	9	17	310	4407
Lyon 2006	25	21	98	590
Ramsay 2007	19	72	5	251

GRACE



Three studies on the GRACE risk score provided data from 5824 individuals. Values of sensitivity varied between low and high whereas the specificity in all three studies was high. The sensitivity of the GRACE risk score varied, in the first study the sensitivity was 0,03 (95% CI 0,01 to 0,05) (Lee 2011)). The sensitivity in the second study was 0,20 (95% CI 0,14 to 0,29) (Lyon 2006)) and in the third study it was 0,79 (95% CI 0,58 to 0,93) (Ramsay 2007)). The specificity varied among the three studies. In the first study the specificity was 1,00 (95% CI 0,99 to 1,00) (Lee 2011)). In the second study the specificity was 0,97 (95% CI 0,95 to 0,98) (Lyon 2006)) and in the third study the specificity was 0,78 (95% CI 0,73 to 0,82) (Ramsay 2007)).

The data from the forest plot was used to create an SROC curve for the GRACE risk score as illustrated in Figure 4.8 on page 60.

Figure 4.6: SROC curve for GRACE risk score

The sensitivity and specificity of the three GRACE studies has been plotted with a clear circle in the ROC space. The SROC curve is placed as close as possible to all three data sets. The SROC curve lies on the left side of the diagonal line, signifying that the GRACE risks score has value in its prediction ability of acute coronary syndrome. This means that the tool is better than a random guess for predicting whether a patient has the disease or not. The AUC is estimated to be between 0.8 and 0.9 when using the traditional academic point system, which indicates that the tool has a good ability to accurately predict the presence of acute coronary syndrome in adults. The GRACE risks score has an 80% to 90% probability of correctly classifying a patient as diseased or not.

The two forest plots shown in Figure 4.7 were combined with the two SROC curves into one ROC space (Figure 4.8), to allow the researcher to make a comparison between the HEART and GRACE risk scores. The purpose was to determine which of the two tools has a greater ability to accurately predict the presence of acute coronary syndrome in adults.

Figure 4.7: Comparison of GRACE and HEART forest plots

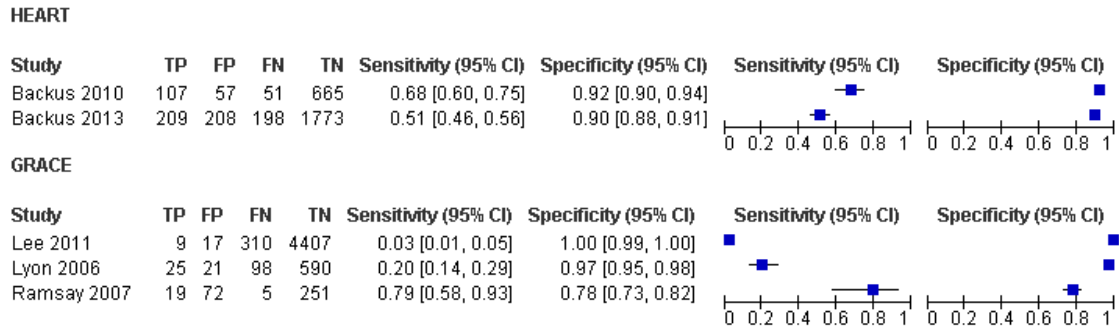
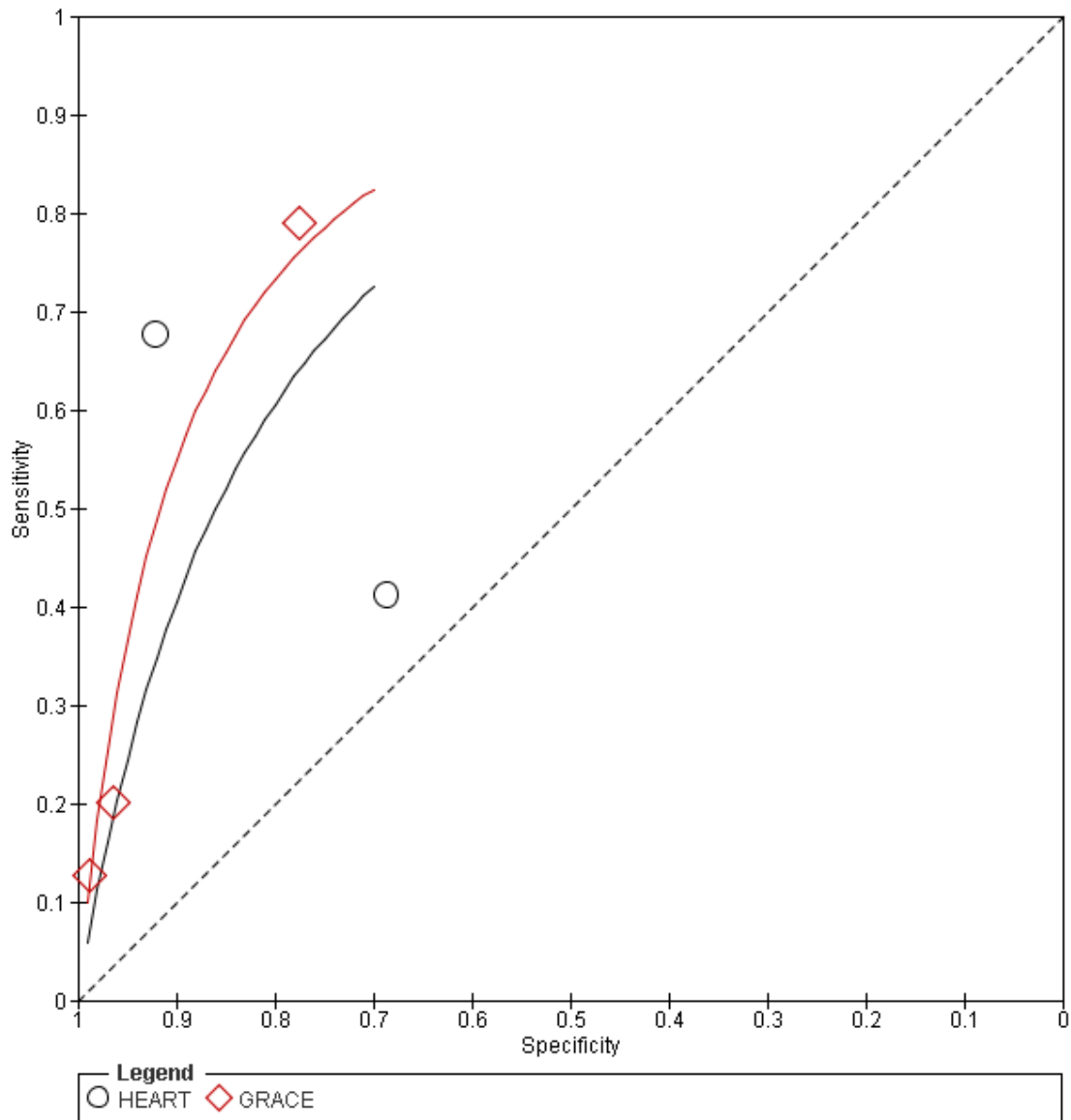


Figure 4.8 follows on page 61.

Figure 4.8: Comparison of GRACE and HEART SROC

Each risk tool was allocated its own shape and colour in the ROC space to make differentiation between the two tools easier. The HEART risk score is illustrated with a clear black round circle and a black curve, whereas the GRACE risk score is illustrated with a red diamond shape and a red curve. As mentioned above, both the SROC curves are situated on the left side of the diagonal line, which indicates that both tools are valuable. The AUC for both tools is greater than 0,5 which indicates that neither of the two risk tools is worthless. When assessing the AUC according to the traditional academic point system, it is evident that the GRACE risk score range (0,8 to 0,9) is higher than the HEART risk score range (0,7 to 0,8). This shows that the GRACE risk score has a probability of 80% to 90% of correctly

classifying a random positive-negative case pair. The HEART risk score has a probability of 70% to 80% of correctly classifying a random positive-negative case pair.

4.6 SUMMARY

In this chapter, the researcher described the results of the search and the quality assessment that was performed which represented the sampling procedure of the thesis. The researcher also described the findings of the data extraction and synthesis process. In the next chapter, the researcher discusses the results and draws conclusions from the findings. A discussion of the limitations of the study will also be presented and the researcher will then make recommendations for research and nursing practice.

CHAPTER FIVE: DISCUSSION, CONCLUSIONS AND RECOMMENDATIONS

In the previous chapter, the results of the search, quality assessment, data analysis and synthesis were described. In this chapter the researcher discusses the results, draws conclusions and makes recommendations.

5.1 INTRODUCTION

The researcher discusses each objective described in the first chapter and discusses whether these objectives were attained. Limitations that were encountered are described and the researcher will conclude by posing recommendations for future research.

5.2 DISCUSSION

The following research question was stated in Chapter One: What is the prediction ability of risk assessment tools in predicting acute coronary syndrome in adults?

The aim of the study was to systematically appraise evidence on the accuracy of risk prediction tools for acute coronary syndrome in adults. The study therefore investigated whether the HEART and GRACE risk assessment tools could accurately predict the presence of acute coronary syndrome in adults. To be able to answer the research question the researcher created objectives to guide the study. The objectives were as follows:

- To estimate the accuracy of GRACE and HEART in predicting acute coronary syndrome in adults.
- To compare the accuracy of the two tools in risk prediction of acute coronary syndrome in adults.
- To propose recommendations for a potential risk assessment tool for South Africa.

WHO (2012) state that there is a need to increase government investment in prevention and early detection of CVD as the death rates for this disease are increasing.

Acute coronary syndrome is diagnosed with the use of a physical examination, history taking and reference standards (ECG and cardiac markers) (Dalby, 2001:88). This author explains that there are limitations and drawbacks with ECG and cardiac markers and these can lead to a false negative result, resulting in a missed diagnosis and subsequent advance disease

and death. Ramsay et al., (206:12) advise that one cannot rely on ECG and clinical symptoms only as they have low diagnostic accuracy. They therefore suggest adding troponin I to aid the diagnosis process. Symptoms experienced by patients may not always indicate myocardial ischemia, and elevated troponin levels may not always indicate that the disease is present as both are not specific or isolated to acute coronary syndrome only. In addition, Troponin I and T take at least six to twelve hours before increasing, thus still leaving room for error when diagnosing a patient (Kumar & Cannon, 2009:921).

A study performed by Yan et al. (2007:1074) compared risk categorisation by physicians to risk categorisation by risk scores. The high risk group risk stratified by the physician were three times more likely to die due to acute coronary syndrome whereas the high-risk group stratified by the risk score were five times more likely to die. The results proved that risk scores had more accurately risk-stratified a patient than the treating physician. Yan et al. (2007:1076) emphasise that risk scores are clinical tools and should not replace clinical judgement, the reason being that the tool will not be able to correctly risk-stratify a patient with a more complex history. Another study was performed by Yan et al. (2009:379) to examine the risk assessment done by physicians and compare it to an objective risk score evaluation. The study proved that certain patients risk-stratified by a physician as low risk had actually been incorrectly categorised. When compared to the risk stratification of the risk score, the risk score correctly stratified these same patients as intermediate or high risk patients. Yan et al. (2009:379) concluded that risk scores were found to be superior to physician risk assessment and that a risk score was a necessity for accurate and comprehensive diagnoses. Yan et al. (2009:376) once again explained that risk score was not to replace clinical judgement but rather should form part of clinical judgement.

Bajaj et al. (2013:202) conducted a similar study to compare physicians' initial diagnostic impression – of possible acute coronary syndrome to definite acute coronary syndrome – with the GRACE risk scoring. The study results proved that individuals in the possible group had a greater rate of having myocardial infarction than those in the definite group. This result compared to the GRACE risk scoring showed that individuals in the possible group had higher GRACE risk scores than those in the definite group as stratified by the physician. The conclusion drawn was that the GRACE tool provided a more accurate risk assessment than the physician not using the GRACE risk assessment tool.

In total, only five studies describing these two tools, that fulfilled the criteria for a test of screening intervention, were identified. The overall methodological quality of the five studies was variable. One of the five studies on the HEART risk assessment tool (Backus et al. 2013) had an overall judgement of unclear risk of bias because the index test threshold was

not pre-specified but reference was made to a previous study done. Another study on the GRACE risk assessment tool (Lyon et al. 2007) had an overall judgement of high risk of bias because details of 21 patients from the initial sample size were missing from the initial sample size and the authors did not document this. The other reason for the high risk of bias was that no threshold for the index test was pre-specified. The methodological quality of the other three studies (Backus et al. 2010; Lee et al. 2011; Ramsay et al. 2007) had an overall low risk of bias. There were overall low concerns regarding the applicability of the five studies. Two of the five studies would potentially not be replicable due to poor methodological reporting. The other three studies would be replicable as they had good methodological reporting.

Three of the five studies used a prospective research method and two of the studies used a retrospective research method. All five studies were cohort studies. In total 9 092 individuals were included in the study. The HEART studies included a total of 3 268 individuals and the GRACE studies included a total of 5 824 individuals. The main outcome assessed by all five studies was MACE within six weeks up to three months. MACE refers to major adverse cardiac events occurring due to acute coronary syndrome being present, which therefore serves as indirect proof of the prescience of the disease (Backus et al., 2010:164). The four major cardiac events of interest for this review were PCI, AMI, CABG and death.

In total, the two HEART studies identified 565 individuals with MACE; while a total of 2 703 individuals were identified without MACE. The two studies on the HEART risk assessment tool concluded that the HEART risk score had great discriminatory power and was found to be a reliable predictor of MACE. The three studies on the GRACE risk score identified a total of 466 individuals with MACE and 5 358 were identified without MACE. The three studies on the GRACE risk assessment concluded that the GRACE risk score was able to correctly identify a patient with MACE; therefore the GRACE risk score was found to be predictive of MACE (Lyon et al., 2007; Lee et al., 2011; Ramsay et al., 2007).

The results of the five studies were reported separately. A coupled forest plot was used to illustrate the sensitivity and specificity of each tool. The HEART risk assessment tool proved to have a low sensitivity, in that it was only able to accurately predict the prescience of acute coronary syndrome in 51% to 68% of patients admitted to the emergency department with chest pain. The HEART risk assessment tool, on the other hand, had a high specificity, indicating the ability of the tool to accurately predict an adult without acute coronary syndrome in 90% to 92% of cases. This confirmed the findings from the two HEART studies (Backus et al., 2010; Backus et al., 2013) which showed that the tool was able to correctly identify 565 patients with MACE and able to correctly identify 2 703 patients without MACE.

The GRACE risk assessment tool also had a low sensitivity, only being able to predict the presence of acute coronary syndrome in 3% to 79% of patients admitted to the emergency department with chest pain. The tool, on the other hand, has a high specificity indicating the ability to accurately identify a patient without the disease in 78% to 100% of cases. This confirmed the findings of the three GRACE studies (Lee et al., 2011; Lyon et al., 2006; Ramsay et al., 2007) which showed that the tool was able to correctly identify 466 patients with MACE and 5 358 patients without MACE. The HEART risk assessment tool shows a higher sensitivity than the GRACE risk assessment tool, but both are still low.

From the sensitivity and specificity findings, it is clear that both tools are unable to accurately predict the presence of acute coronary syndrome in a patient with chest pain due to the low sensitivity of each diagnostic tool. The strength of the tools is that they both have high specificity and therefore rather accurately diagnose a patient admitted to the emergency department without acute coronary syndrome. Both diagnostic tools might have low sensitivity and may not be able to accurately predict the presence of acute coronary syndrome 100%, but individuals identified as positive for the presence of acute coronary syndrome have a high probability of having acute coronary syndrome. This allows the treating physician or practitioner to safely discharge patients with low risk scores. This confirms the findings from Six et al., (2008:196) that a patient with a low risk score has a 2,5% risk of developing MACE and can therefore be safely discharged. The researcher can conclude from the findings that both tools can accurately identify truly negative individuals with a minimal number of identifications being falsely negative. The findings also show that both tools can minimize the number of 'missed' diagnosed patients through identifying individuals with a high probability for acute coronary syndrome requiring further investigation. This confirmed the findings by Six et al. (2008:196) that a patient with a high score has a 72,7% risk of developing MACE and these patients should be admitted and requires aggressive treatment.

The results from the forest plot were used and plotted in a ROC space and an SROC curve was created. The SROC curve was used to allow the researcher to perform a comparison between the two risk assessment tools to determine which has greater predictor ability. Both tools proved to be informative when making a diagnosis as both SROC curves were plotted above the non-discriminatory line. Both the risk assessment tools showed that they had a predictive value greater than a random guess. This reinforces the findings from the studies by Yan et al. (2007), Yan et al. (2009) and Bajaj et al. (2013) which indicated that the risk scores were more accurate and superior to physician risk stratification. The GRACE SROC curve was closer than the HEART SROC curve to the upper left corner, the point known as "perfect" classification. This indicated that the GRACE risk score has better prediction ability,

therefore making the GRACE tool more accurate. The AUC was estimated using the traditional academic point system. The HEART risk score showed it had a probability of 70% to 80% of correctly classifying a patient with acute coronary syndrome. The GRACE showed it had a probability of 80% to 90% of correctly classifying a patient with acute coronary syndrome. When these findings were compared, the GRACE risk assessment tool proved to have a greater predictive ability than the HEART risk assessment tool. This finding was different from the finding reported by Fesmire et al., (2012:1830) which was that the GRACE risk score was outperformed by the HEART risk score.

It is clear from the evidence of the sensitivity, specificity, SROC curve and the AUC that risk assessment tools are better than just random guessing. The diagnostic power of a test requires both high sensitivity and specificity to make it a good test; therefore one is not necessarily better than the other. The ideal with acute coronary syndrome is to have a test that has a high sensitivity to avoid missed diagnoses. On the other hand a test with a high specificity does indicate that a positive result can be useful if one needs to rule whether a disease is present. The benefit of both tools are that they are very useful in emergency departments or general practitioner rooms when one needs to decide quickly on whether to admit for further investigation or to discharge a patient. Especially when research has shown that NSTEMI-ACS is more prevalent than STEMI-ACS. NSTEMI-ACS causes a lack of ECG changes and a lack of increased cardiac marker levels. Therefore if the HEART or GRACE risk score (which are both high in specificity) return with positive results, then there is a high probability of the presence of acute coronary syndrome. The HEART and GRACE risk tools, being more specific than sensitive, indicate that fewer non-diseased patients will go for further testing, thus reducing the waste of time and cost which is another great benefit. This will reduce the occurrence of the risk-treatment paradox described by Yan et al., (2009:376). The index tool will not replace current practice but will only improve current practice.

The researcher recommends that current practice (which can be described as “random guessing”) should be supplemented with a risk assessment tool to improve the delivery of healthcare. The GRACE risk tool appears to be more effective and accurate in its prediction ability than the other tool, and it appears to be better suited, but in South Africa the GRACE risk assessment tool may not be feasible as it requires internet access due to difficult calculation of scores. Many of our rural countries do not have access to internet. Therefore the researcher recommends that the HEART risk score should be trialled in South Africa. The HEART risk score is a basic tool, easy to use and requires no calculator or internet access, this risk score can be used additionally to current practice. This risk score can assist especially in cases of NSTEMI and unstable angina pectoris when there is a lack of ECG

changes and lack of increased cardiac marker levels, but patient exhibits suspicious symptoms of acute coronary syndrome.

5.3 LIMITATIONS OF THE STUDY

Limitations are defined by Grove et al. (2013:669) as the restrictions, both theoretical and methodological, in a study that may decrease the ability to generalise the results.

There were a few limitations identified during the study; these are detailed below.

- Although the researchers performed a rigorous and broad search for articles, some articles could not be obtained for various reasons including restricted access or no publication available in an English version. All studies that could not be obtained, even with the assistance of a librarian, were documented and reported on in the results section including the reasons.
- The quality of published data in two of the five included articles constitutes a limitation to the study. There was data missing regarding excluded participants who were not identified and no reason for exclusion was given. The researcher attempted to contact the authors per e-mail, but received no response. There was no pre-specified index test threshold identified which also affected the quality of the published data.
- Although the following is not a limitation as it did not affect the outcome, the researcher is required to report on software. In the initial protocol it was proposed that STATA software should be used for meta-analysis, as well as certain data analysis and synthesis techniques. During data analysis and synthesis however, Review Manager 5.2 software was used for the creation of forest plots and SROC curves and was found to be more applicable to the study results.
- Both the described outcome and the reference standard identified in the protocol to be used in this study were adapted during the study. Because cardiac markers and ECG form part of both HEART and GRACE risk tools, authors of the identified articles used MACE as an outcome. This serves as indirect proof of presence of acute coronary syndrome. The researchers decided to use MACE as an outcome and reference standard for the study.
- The HEART risk score was not researched and validated to the same extent as the GRACE risk score.
- Only international studies were available, and the researcher had to interpret the findings and make these relevant to the South African context.

5.4 RECOMMENDATIONS

An attribute of a systematic review is that it can help to provide recommendations for future research. The recommendations for this study are made for future research and nursing.

The data analysis showed that there is currently no risk assessment tools used in South Africa. The evidence provided can now inform any decision on whether to implement the risk assessment tool in South Africa to form part of the diagnosing of acute coronary syndrome in adults. It is therefore recommended that, based on the systematic review done in this study, a risk assessment tool be developed or the GRACE or HEART risk assessment tool be modified and then implemented into daily practice. Developing or modifying the existing risk assessment tools and implementing them will improve the quality of care rendered to a patient with acute coronary syndrome. The researcher recommends a prospective protocol for hypothesis-testing study should first be performed before change in clinical practice can be justified.

5.5 SUMMARY

In this chapter the researcher discussed the results presented in Chapter Four and whether each set objective had been attained. The researcher answered the research question as stated in the first chapter. Limitations experienced during the study were identified and described. Finally, recommendations for future research were provided.

Reference list

Aaronson, P.I. & Vard, J.P.T. & Conolly, M.J. 2013. *The Cardiovascular System at a Glance*. 4th Ed. UK: Wiley-Blackwell.

Abu-Assi, E. & Gracia-Acuna, J. M. & Pena-Gil, C. & Gonzalez-Juanatey, J. R. 2009. Validation of the GRACE risk score for predicting Death within 6 months of follow-up in a contemporary cohort of patients with acute coronary syndrome. *Revista Española de Cardiología*, 63(6): 640-648.

American Dietetic Association. 2008. *Evidence analysis manual: Steps in the ADA evidence analysis process*. Chicago: Scientific Affairs and Research, American Dietetic Association.

American Heart Association. 2012. *About Arrhythmia*. [Online]. Available: http://www.heart.org/HEARTORG/Conditions/Arrhythmia/AboutArrhythmia/About-Arrhythmia_UCM_002010_Article.jsp [2014, January 2014].

Ashley, E.A & Niebauer, J. 2004. *Cardiology Explained*. London: Remedica.

Backus, B.E. & Six, A.J. & Kelder, J.C. & Mast, T.P. & van den Akker, F. & Mast, E.G. Monnik, S.H. & van Tooren, R.M. Doevendans, P.A.F.M. 2010. Chest Pain in the Emergency Room A Multicentre Validation of the HEART Score. *Critical Pathways in Cardiology*, 9:164-169.

Bajaj, R.R. & Goodman, S.G. & Yan, R.T. & Bagnall, A.J. & Gyenes, G. & Welsh, R.C. & Eagle, K.A. & Brieger, D. & Ramanathan, K. & Grondin, F.R. & Yan, A.T. 2013. Treatment and Outcomes of Patients with Suspected Acute Coronary Syndrome in Relation to Initial Diagnostic Impressions (Insight from the Canadian Global Registry of Acute Coronary Events [GRACE] and Canadian Registry of Acute Coronary Events [CANRACE]). *American Journal Cardiology*. Jan 15;111(2):202-7.

Boersma, E. & Pieper, K.S. & Steyerberg, E.W. & Wilcox, R.G. & Chang, W. & Lee, K.L. & Akkerhuis, K.M. & Harrington, R.A. & Deckers, J.W. & Armstrong, P.W. & Lincoff, A.M. & Califf, R.M. & Topol, E.J. & Simoons, M.L. 2000. Predictors of Outcomes in Patients with Acute Coronary Syndrome Without Persistent ST-Segment Elevation: Results from an International Trial of 9462 Patients. *Circulation*, 101: 2557-2567.

- Botma, Y. & Greeff, M. & Mulaudzi, F.M. & Wright, S.C.D. 2010. *Research in Health Sciences*. Cape Town: Heinemann.
- Brink, H. & van der Walt, C & van Rensburg, G. 2012. *Fundamentals of Research Methodology for Healthcare Professionals*. 3rd Ed. Cape Town: Juta.
- Burns, N. & Grove, S.K. 2005. *The practice of nursing research: Conduct, critique and utilization*. Fifth edition. St Louis: Elsevier Saunders.
- Burns, N. & Grove, S.K. 2011. *Understanding Nursing Research*. 5th Ed. USA: Elsevier Saunders.
- Carmo, P. & Ferreira, J. & Aguiar, C. & Ferreira, A. & Raposo, L. & Gonçalves, P. & Brito, J. & Silva, A. 2011. Does Continuous ST-Segment Monitoring Add Prognostic Information to the TIMI, PURSUIT, and GRACE Risk Scores? *Annals Noninvasive Electrocardiology*, 16(3): 239-249.
- Centre for Evidence-Based Conservation. 2009. *Guidelines for systematic review in conservation and environmental management*. Bangor, Gwyneth: Bangor University.
- Centre for Reviews and Dissemination. 2009. *Systematic reviews: CRD's guidance for undertaking reviews in health care*. [Online]. Available: http://www.york.ac.uk/inst/crd/SysRev/!SSL!/WebHelp/2_2_DIAGNOSTIC_TESTS.htm [2014, July 22].
- Chew, D.P. & Junbo, G, Parsonage, W. & Kerkar, P. & Sulimov, V.A. & Hosfall, M. & Mattchoss, S. 2013. Perceived Risk of Ischemic and Bleeding Events in Acute Coronary Syndromes. *Circ Cardiacvasc Qual Outcomes*, 6: 299-308.
- Chin, C.T. & Chua, T.S. & Lim, S.T. 2010. Risk assessment models in acute coronary syndromes and their applicability in Singapore. *Annals Academy of Medicine Singapore*, 39: 216-220.
- Dalby, J. 2001. Management of Acute Coronary Syndromes Clinical Guideline. *SAMJ*, 91 (10): 879-895.
- D'Ascenzo, F. & Biondi-Zoccai, G. & Moretti, C. & Bollati, M. & Omede, P. & Sciuto, F. & Presutti, D. & Modena, M. G. & Gasparini, M. & Reed, M. J. & Sheiban, I. & Gaita, F. 2012. TIMI, GRACE and alternative risk scores in Acute Coronary Syndromes: A meta-analysis of

40 derivation studies on 216,552 patients and of 42 validation studies on 31,625 patients. *Contemporary Clinical Trials*, 33: 507-514.

Deeks JJ. & Wisniewski S. & Davenport C. 2013. *Chapter 4: Guide to the contents of a Cochrane Diagnostic Test Accuracy Protocol, Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy Version 1.0.0. The Cochrane Collaboration.* [Online]. Available: <http://srdata.cochrane.org/> [2013, July 20].

De Lemos, J.A. 2008. *Biomarker in Heart Disease*. USA: Blackwell.

Eng, J. 2005. Receiver Operating Characteristics Analysis. *Academic Radiology*, 12(7): 909-916).

Fesmire, F.M. & Martin, E.J. & Cao, Y. & Heath, G.W. 2012. Improving risk stratification in patients with chest pain: the Erlanger HEARTS3 score. *American Journal of Emergency Medicine*, 30: 1829-1837.

Fox, K.A.A. & Dabbous, O.H. & Goldberg, R.J. & Pieper, K.S. & Eagle, K.A. & van de Werf, F. & Avezum, A. & Goodman, S.G. & Flather, M.D. & Anderson, F.A. & Granger, C.B. 2006. Prediction of risk of death and myocardial infarction in the six months after presentation with acute coronary syndrome: prospective multinational observational study (GRACE). *BMJ*, 333: 1091.

Fox, K.A.A. & Eagle, K.A. & Gore, J.M. & Steg, P.G. & Anderson, F.A. 2010. The GLOBAL Registry of Acute Coronary Events, 1999-2009-GRACE. *Heart*, 96:1095 – 1101.

Grace ACS Risk Score. 2013. [Online]. Available: <http://www.gracescore.co.uk/risk-stratification> [2014, July 22].

Grove, S.K. & Burns, N. & Gray, J.R. 2013. *The practice of Nursing Research Appraisal, Synthesis, and Generation of Evidence*. Missouri: Elsevier Saunders.

Hamm, C.W. & Bassand, J. & Agewall, S. & Bax, J. & Boersma, E. & Bueno, H. & Caso, P. & Dudek, D. & Gielen, S. & Huber, K. & Ohman, M. & Petrie, M.C. & Sonntag, F. & Uva, M.S. & Storey, R.F. & Wijns, W. & Zahger, D. 2011. ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *European Heart Journal*, 32: 2999-3054.

Hamm, C. W. & Heeschen, C. & Falk, E. & Fox, K. A. A. 2006. *Acute Coronary Syndromes: Pathophysiology, Diagnosis and Risk Stratification*. [Online]. Available: https://www.mst.nl/opleidingcardiologie/boeken/esc/1405126957_chapter_12.pdf. [2013, March 07].

Heart and Stroke Foundation of South Africa .2007. *Heart Disease in South Africa*. [Online]. Available: <http://www.bizcommunity.com/Article/196/154/17763.html> [2013, April 04].

Hemingway, P. & Brereton, N. 2009. *What is a systematic review?* 2nd Ed. UK: Hayward Medical Communications.

Houghton, A. R. and Gray, D. 2003. *Making sense of the ECG a Hands-on guide*. Great Britain: Edward Arnold.

Jones, C.M. & Athanasiou, T. 2005. Summary Receiver Operating Characteristics Curve Analysis Techniques in the Evaluation of Diagnostic Tests. *Ann Thorac Surg*, 79:16-20.

Joubert, G. & Ehrlich, R. 2008. *Epidemiology A Research Manual for South Africa*. 2nd Ed. Cape Town: Oxford.

Kellett, J. & Hirschl, M.M. & Derhaschnig, U. & Collinson, P.O. & Gaze, D. & Haass, K. & Katus, H.A. & Chwallek, F. & Mueller–Bardorff, M. & Ordoñez–Llanos, J. & Merce´–Muntan˜ola, J. & Santalo´–Bel, M. & Sylve´n, C. & Schulz, I. & Zerback, R. 2004. Bedside Testing of Cardiac Troponin T and Myoglobin for the Detection of Acute Myocardial Infarction in Patients with a Nondiagnostic Electrocardiogram in the Emergency Department. *Point of Care*, 3(4): 159-161.

Ker, J.A. 2003. Acute Coronary Syndrome: Risk stratification and management. *SA Fam Pract*, 45 (8): 26-30.

Kitchenham, B. 2004. *Procedures for performing systematic review*. [Online]. Available : <http://www.idi.ntnu.no/emnee/empsc/papers/kitchenham> [2014, July 22].

Kohli, S. G. & Parajulu, M. & Maskey, A. & Acharya, C. P. 2010. An unusual presentation of acute coronary syndrome. *Journal of Nepal Health Research Council*, 8(2): 124-125.

Kumar, A. & Cannon, C. P. 2009. Acute Coronary Syndromes: Diagnosis and Management, Part I. *Mayo Clinic Proceedings*, 84 (10): 917-928.

- Lewis, S.M. & Heitkemper, M.M. & Dirksen, S.R. 2004. *Medical and Surgical Nursing: Assessment and Management of Clinical Problems*. 6th Ed. Canada: Mosby.
- Lincoff, M. 2014. Managing acute coronary syndromes: Decades of progress. *Cleveland clinic Journal of Medicine*, 81 (4): 233-242.
- LoBiondo-Wood, G & Haber, J. 2010. *Nursing Research Methods and Critical Appraisal for Evidence-Based Practice*. 7th Ed. USA: Mosby.
- Macaskill, P. & Gatsonis, C, & Deeks, J.J. & Harbord, R.M. & Takwoingi, Y. 2010. *Chapter 10: Analysing and Presenting Results In: Deeks, J.J, Bossuyt, P.M, Gatsons, C, Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy Version 1.0. The Cochrane Collaboration*. [Online]. Available: <http://srdta.cochrane.org/>. [2013, August 21].
- Magarey, J.M. 2001. Elements of a systematic review. *International Journal of Nursing Practice*, 7:376–382.
- Mahmoud, W.E.A. & Hassanein, M.M. & Elbeltagy, S.M. & ElDin, M.M.N. & Sadaka, M.A. 2010. Validation of TIMI and GRACE Acute Coronary Risk Scores in Alexandria Governorate and their Role in the Comparison of Quality of Care between Hospitals. *J Egypt Public Health Assoc*, 85 (1&2): 1-28.
- Marshall, K. 2011. Acute coronary syndrome: diagnosis, risk assessment and management. *Nursing Standard*, 25(23): 47-57.
- Manacci, C. 2013. *Critical Care Nursing made Incredibly Easy*. 3rd Ed. China: Lippincott.
- Mangla, A. 2012. *Troponins*. [Online]. Available: <http://emedicine.medscape.com/article/2073935-overview> [2014, August 08].
- Medterms*. 2012. [Online]. Available: <http://www.medterms.com/script/main/art.asp?articlekey=17534> [2013, March 26].
- Moher, D. & Liberati, A. & Tetzlaff, J. & Altman, D.G. The PRISMA Group. 2009. *Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement*. [Online]. Available: <http://www.prisma-statement.org/statement.htm> [2013, September 05].
- Mortality & Causes of death in South Africa. 2010. *Findings from death notification*. Pretoria: Statistic South Africa.
- Nowak, T.J. & Handford, A.G. 2004. *Pathophysiology Concepts and Applications for Health Care Professionals*. 3rd Ed. New York: McGraw-Hill.

Pearson, A., Field, J. and Jordan, Z. 2007. *Evidence-based clinical practice in health care: Assimilating research, experience and expertise*. Oxford: Blackwell Publishing Ltd.

Polit, D.F. & Beck, C. T. 2012. *Nursing Research Generating and Assessing Evidence for Nursing Practice*. 9th Ed. China: Lippincott Williams & Wilkins.

Prins, C. & Botes, L. & Smit, F.E. & Wheatley, D.J. & Neetling, W.M.L. 2008. *Acute Coronary Syndrome; Pathophysiology and Management Implications for South African Population*. [Online]. Available:
http://reference.sabinet.co.za/sa_epublication_article/interim_v7_n2_a12 [2014, July 22].

Ramsay, G. & Podogrodzka, M. & McClure, C. & Fox, K.A.A. 2006. Risk prediction in patients presenting with suspected cardiac pain: the GRACE and TIMI risk scores versus clinical evaluation. *Q J Med*, 100: 11-18.

Risk assessment. 2013. [Online]. Available:
<http://dictionary.reference.com/browse/risk+assessment> [2013, March 26].

Rosano, G.M. & Fini, M. & Caminiti, G. & Barbaro, G. 2008. Cardiac metabolism in myocardial ischemia. *Current Pharmaceutical Design*, 14(25): 2551-62.

Rosman, A.S. & Korsten, M.A. 2007. Application of summary receiver operating characteristics (sROC) analysis to diagnostic clinical testing. *Advances on Medical Science*, 52: 76-82.

Six, A. J. & Cullen, L. & Backus, B. E. & Greenslade, J. & Parsonage, W. & Aldous, S. & Doevendans, P. A. & Than, M. 2013. The HEART Score for the Assessment of Patients With Chest Pain in the Emergency Department A Multinational Validation Study. *Critical Pathways in Cardiology September*, 12(3): 121-126.

Six, A.J. & Backus, B.E. & Kelder, J.C. 2008. Chest pain in the emergency room: value of the Heart score. *Netherland Heart Journal*, 16 (6): 191-196.

Standard. 2014. [Online]. Available:
<http://www.oxforddictionaries.com/definition/english/standard> [2014, August 08].

- The Cochrane Public Health Group. 2011. *Guide for developing a Cochrane protocol*. [Online]. Available: http://ph.cochrane.org/sites/ph.cochrane.org/files/uploads/Guide%20for%20PH%20protocol_Nov%202011_final%20for%20website.pdf [2013, March 23].
- Thomas, G. 2003. *Plotting and Interpreting an ROC Curve*. [Online]. Available: <http://gim.unmc.edu/dxtests/Default.htm> [2014, November 05].
- Thygesen, K. & Alpert, J.S. & White H.D. 2007. Universal definition of myocardial infarction. *European Heart Journal*, 28: 2525-2538.
- University of Michigan. 2010. *2 x 2 Table/ Contingency Table*. [Online]. Available: <http://practice.sph.umich.edu/micphp/epicentral/2X2.php> [2014, October 10].
- Walter, S.D. 2002. Properties of the summary receiver operating characteristics curve for diagnostic test data. *Statistics in Medicine*, 21:1237-1256.
- Weller, S. 1997. *Bailliere's Nurses' Dictionary*. 22nd Ed. Great Britain: Bailliere Tindall.
- Whiting, P.F. & Rutjes, A.W. & Westwood, M.E. & Mallet, S. & Deeks, J.J. & Reitsma, J.B. & Leeflang, M.M. & Sterne, J.A. & Bossuyt, P.M. & QUADAS-2 Group. 2011. QUADAS-2: A Revised Tool for the Quality Assessment of Diagnostic Accuracy Studies. *Annals Internal Medicine*, 155(8): 529-536.
- Wieseler, B and McGauran, N. 2010. *Reporting a Systematic Review*. *Chest*, 137(5):1240-1246.
- World Health Organisation. 2011. *Global Atlas on cardiovascular disease prevention and control*. [Online]. Available: http://whqlibdoc.who.int/publications/2011/9789241564373_eng.pdf [2013, April 04].
- World Health Organisation. 2012. *Cardiovascular Diseases*. [Online]. Available: <http://www.who.int/mediacentre/factsheets/fs317/en/index.html> [2013, February 12].
- Yan, A.T. & Yan, R.T. & Huynh, T. & Casanova, A. & Raimondo, F.E. & Fitchett, D.H. & Langer, A. & Goodman, S.G. 2009. Understanding Physicians Risk Stratification of Acute Coronary Syndrome. *Arch Intern Med*, 169 (4): 372-378.

Yan, A.T. & Yan, R.T. & Tan, M. & Casanova, A. & Sridhar, K. & Fitchett, D.H. & Langer, A. & Goodman, S.G. 2007. Risk scores for risk stratification in acute coronary syndromes: useful but simpler is not necessarily better. *European Heart Journal*, 28: 1072-1078.

Yusufali, A. & Zubaid, M. & Alsheikh-Ali, A. A. & Suwaidi, J. A. & Rashed, W. & Sulaiman, K. & Amin, H. 2011. Validation of the GRACE Risk Score for Hospital Mortality in Patients With Acute Coronary Syndrome in the Arab Middle East. *Angiology*, 62(5): 390-396.

Zhu, W. & Zeng, W. & Wang, N. 2010. *Sensitivity, Specificity, Accuracy, Associated Confidence Interval and ROC Analysis with Practical SAS Implementations*. [Online]. Available: <http://www.lexjansen.com/nesug/nesug10/hl/hl07.pdf> [2014, November 05].

Appendix A: Ethics approval letter

Ethics Letter

15-May-2014

Ethics Reference #: X14/05/007

Clinical Trial Reference #:

Title: Accuracy of acute coronary syndrome risk prediction tools: A systematic review

Dear Mrs Johet Van Zyl,

Thank you for your application to our Health Research Ethics Committee (HREC). This application is for a systematic review.

The Health Research Ethics Committee considers this proposal to be exempt from ethical review.

This letter confirms that this research is now registered and you can proceed with study related activities.

If you have any queries or need further assistance, please contact the HREC Office 0219389657.

Sincerely,

REC Coordinator

Franklin Weber

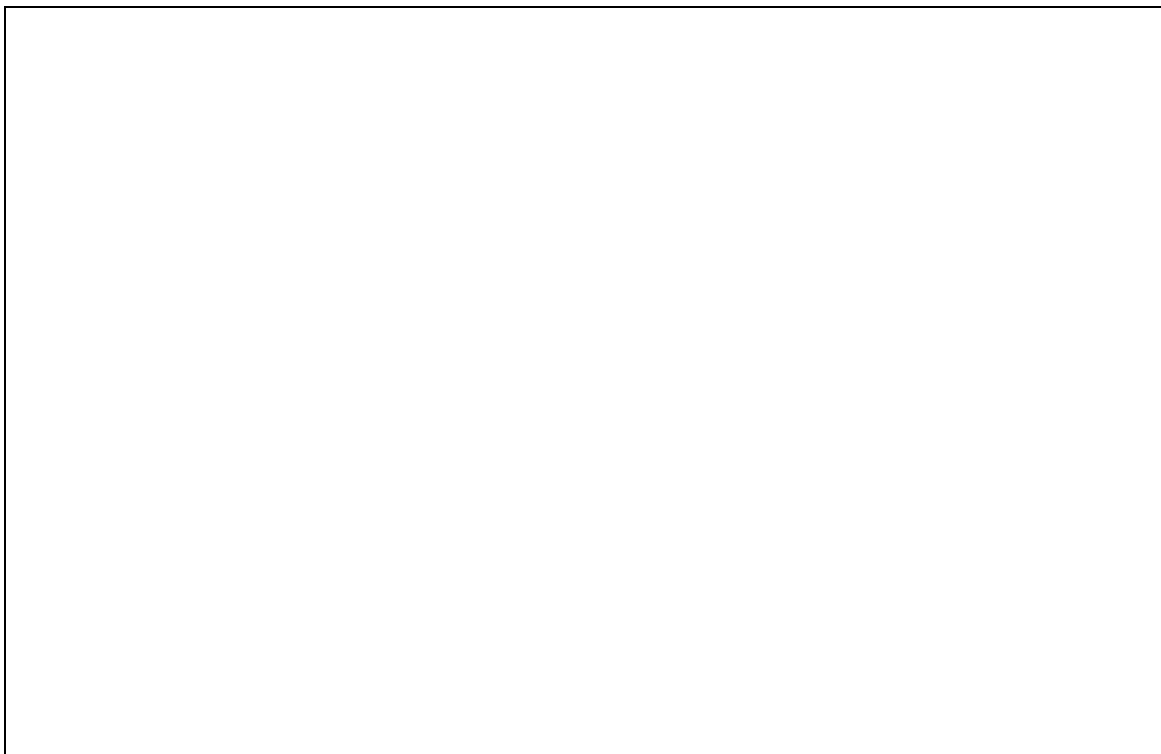
Health Research Ethics Committee 1

Appendix B: QUADAS 2 Tool

Phase 1: State the review question:

<i>Patients (setting, intended use of index test, presentation, prior testing):</i>
<i>Index test(s):</i>
<i>Reference standard and target condition:</i>

Phase 2: Draw a flow diagram for the primary study



Phase 3: Risk of bias and applicability judgments

QUADAS-2 is structured so that 4 key domains are each rated in terms of the risk of bias and the concern regarding applicability to the research question (as defined above). Each key domain has a set of signalling questions to help reach the judgments regarding bias and applicability.

DOMAIN 1: PATIENT SELECTION A. Risk of Bias

Describe methods of patient selection:

Was a consecutive or sample of patients enrolled? Yes/No/Unclear

Was a case-control design avoided? Yes/No/Unclear

Did the study avoid inappropriate exclusions? Yes/No/Unclear

Could the selection of patients have introduced bias? RISK: LOW/HIGH/UNCLEAR

B. Concerns regarding applicability

Describe included patients (prior testing, presentation, intended use of index test and setting):

Is there concern that the included patients do not match the review question? CONCERNS:LOW/HIGH/UNCLEAR

DOMAIN 2: INDEX TEST(S)

If more than one index test was used, please complete for each test.

A. Risk of Bias

Describe the index test and how it was conducted and interpreted:

Were the index test results interpreted without knowledge of the results of the reference standard? Yes/No/Unclear

If a threshold was used, was it pre-specified? Yes/No/Unclear

Could the conduct or interpretation of the index test have introduced bias? RISK: LOW /HIGH/UNCLEAR

B. Concerns regarding applicability

Is there concern that the index test, its conduct, or interpretation differ from the review question? CONCERN: LOW /HIGH/UNCLEAR

DOMAIN 3: REFERENCE STANDARD A. Risk of Bias

Describe the reference standard and how it was conducted and interpreted:

Is the reference standard likely to correctly classify the target condition? Yes/No/Unclear

Were the reference standard results interpreted without knowledge of the results of the index test? Yes/No/Unclear

Could the reference standard, its conduct, or its interpretation have introduced bias? RISK: LOW /HIGH/UNCLEAR

B. Concerns regarding applicability

Is there concern that the target condition as defined by the reference standard does not match the review question? CONCERN: LOW /HIGH/UNCLEAR

DOMAIN 4: FLOW AND TIMING A. Risk of Bias

Describe any patients who did not receive the index test(s) and/or reference standard or who were excluded from the 2x2 table (refer to flow diagram):

Describe the time interval and any interventions between index test(s) and reference standard:

Was there an appropriate interval between index test(s) and reference standard? Yes/No/Unclear

Did all patients receive a reference standard? Yes/No/Unclear

Did patients receive the same reference standard? Yes/No/Unclear

Were all patients included in the analysis? Yes/No/Unclear

Could the patient flow have introduced bias? RISK: LOW /HIGH/UNCLEAR

Appendix C: Cochrane data extraction tool (adapted)

General:

REF ID:

Reviewer:

Date:

Checked by:

Review Title:

Author:

Year:

Country of Origin:

Journal/Source of study:

Publication Type: ABSTRACT / FULL TEXT / OTHER (specify):

Fate: 1. PENDING / CHECK REFERENCE LIST / DISCUSSION

2. EXCLUDE STUDY / INCLUDE STUDY / DUPLICATION STUDY

Notes:

Methods:

Study design:

Aim of study:

Study Objectives:

Methods of recruitment of participants:

Inclusion/exclusion criteria for participation in study:

Informed consent obtained? Yes / No / Unclear

Ethical approval: Yes / No / Unclear

Funding:

Statistical methods and their appropriateness (if relevant):

Participants:

Description:

Setting:

Sample size:

Age:

Principal health problem or diagnosis:

Time period of Study:

Interventions:

Details of intervention: (*Tool used & Reference standard used*):

Details of control/usual or routine care:

Delivery of intervention: (*eg. stages, timing, frequency, duration*):

Details of providers: (*Who delivers the intervention?; number of providers; training of providers in delivery of intervention*):

Intervention quality (if relevant): (*Record any information on the quality of the intervention - assessed by study authors, others, or by*):

Fidelity/integrity: (*Was the intervention delivered as intended? Record any assessment of this*):

Outcomes:

Principal and secondary outcome measures: (*as identified by the study authors*):

Methods of assessing outcome measures: (*eg, phone survey, questionnaire, physical measurements*)

