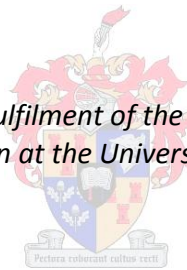


Coenzyme Q10 for Statin-Induced Myopathy: A Systematic Review

by
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*Thesis presented in partial fulfilment of the requirements for the degree
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December 2012

DECLARATION OF AUTHENTICITY

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ABSTRACT

Background

Statins are drugs of known efficacy in the treatment of hypercholesterolaemia. However, statin-induced myopathy, an adverse effect of statins in up to 15% of its users, has warranted a reduction in the prescription dose or discontinuation of the drug. The exact mechanism of statin-induced myopathy is unknown, but the potential of Coenzyme Q10 (CoQ10) as treatment has been recognized due to decreased human plasma CoQ10 levels found after statin use and the concomitant role of CoQ10 in muscle function.

Objectives

This systematic review assessed the effect of CoQ10 supplementation on: the severity of statin-induced myopathic symptoms, levels of plasma creatine kinase, intramuscular and plasma CoQ10, as well as whether any adverse effects of CoQ10 supplementation such as abdominal pain, nausea and vomiting or headaches were experienced.

Search methods

Two searches for studies were conducted in The Cochrane Central Register of Controlled Trials (inception to March 2011 and inception to November 2011), MEDLINE (inception to March 2011 and inception to November 2011), Web of Science (inception to March 2011 and inception to November 2011), Science Direct (inception to March 2011 and inception to February 2012), Wiley Online Library (inception to March 2011 and inception to February 2012), Springerlink (inception to April 2011 and inception to February 2012), EBSCOhost [Academic Search Premier and CAB abstracts (inception to March 2011 and inception to February 2012), CINAHL (inception to March 2011 and inception to November 2011)], Scopus (inception to March 2011 and inception to November 2011) and Google Scholar (inception to March 2011 and inception to February 2012). Reference lists of articles were hand searched for relevant clinical trials. Only trials with a full text were included in the review.

Selection criteria

Randomised controlled trials (RCTs) were included with adult participants (mean of 18-64.99 years) of all race/ethnic groups and gender on statin therapy with reported myopathic symptoms from an unknown cause. The intervention was in the form of a pure oral supplement of CoQ10 irrespective of dose, duration and frequency, and the control in the form of a placebo, a similar antioxidant, or no intervention. Outcomes included the severity of myopathic symptoms, levels of plasma creatine kinase (U/L), intramuscular CoQ10 ($\mu\text{mol/kg}$) and plasma CoQ10 ($\mu\text{mol/L}$), as well as adverse effects of CoQ10.

Data collection and analysis

The principle investigator and one independent reviewer selected the studies, extracted data and assessed for risk of bias using the Cochrane Collaboration's tool for assessing risk of bias. Authors of relevant clinical trials were contacted for additional information.

Results

Two RCTs were included in the review, totaling 76 participants. A meta-analysis could not be performed, thus the review is narrative. There were an insufficient number of RCTs to confirm whether routine supplementation of CoQ10 improves statin-induced myopathic symptoms.

Conclusions

More and larger RCTs are required to determine the efficacy of CoQ10 supplementation in statin-induced myopathy. Consensus needs to be reached regarding the definition and measurement instrument/s of myopathy so that results of future studies can easily be compared and synthesized.

OPSOMMING

Agtergrond

Statiene is medikasie bekend vir die effektiewe behandeling van hipercholesterolemie. Station-geïnduseerde miopatie is egter 'n nuwe-effek wat voorkom in tot 15% van gebruikers, wat 'n vermindering in die voorgeskrewe dosis of staking van die medikasie tot gevolg het. Die presiese meganisme van station-geïnduseerde miopatie is onbekend, maar die potensiaal van Koënsiem Q10 (CoQ10) is geïdentifiseer as 'n moontlike behandeling aangesien menslike plasma CoQ10 vlakke verlaag na die gebruik van statiene en as gevolg van die rol van CoQ10 in spierfunksie.

Doelwitte

Hierdie sistematiese literatuuroorsig het die effek van CoQ10 suplementasie bepaal op: die graad van station-geïnduseerde miopatiëse simptome, plasma kreatien kinase vlakke, intramuskulêre en plasma CoQ10 vlakke, asook die teenwoordigheid van enige nuwe-effekte van CoQ10 suplementasie soos abdominale pyn, naarheid en braking of hoofpyn.

Soektogstrategie

Twee soektogte vir studies is uitgevoer in *The Cochrane Central Register of Controlled Trials* (ontstaan tot Maart 2011 en ontstaan tot November 2011), *MEDLINE* (ontstaan tot Maart 2011 en ontstaan tot November 2011), *Web of Science* (ontstaan tot Maart 2011 en ontstaan tot November 2011), *Science Direct* (ontstaan tot Maart 2011 en ontstaan tot Februarie 2012), *Wiley Online Library* (ontstaan tot Maart 2011 en ontstaan tot Februarie 2012), *Springerlink* (ontstaan tot April 2011 en ontstaan tot Februarie 2012), *EBSCOhost [Academic Search Premier en CAB abstracts* (ontstaan tot Maart 2011 en ontstaan tot Februarie 2012), *CINAHL* (ontstaan tot Maart 2011 en ontstaan tot November 2011)], *Scopus* (ontstaan tot Maart 2011 en ontstaan tot November 2011) en *Google Scholar* (ontstaan tot Maart 2011 en ontstaan tot Februarie 2012). Verwysingslyste van artikels is ook met die hand nagegaan vir relevante kliniese proewe. Slegs kliniese proewe waarvan die volteks beskikbaar was, is ingesluit in die oorsig.

Seleksiekriteria

Ewekansige gekontroleerde proewe (EGP) is ingesluit met volwasse deelnemers (gemiddeld 18-64.99 jaar) van alle rasse/etniese groepe en geslag op statien-terapie met gerapporteerde miopatie simptome van onbekende oorsaak. Die intervensie was 'n suiwer orale supplement van CoQ10 ongeag die dosis, duurte en frekwensie, en die kontrole 'n plasebo, soortgelyke antioksidant, of geen intervensie. Uitkomst: die graad van miopatie simptome, vlakke van plasma kreatien kinase (U/L), intra-muskulêre CoQ10 ($\mu\text{mol/kg}$) en plasma CoQ10 ($\mu\text{mol/L}$), sowelas newe-effekte van CoQ10.

Dataversameling en -analise

Die hoof ondersoeker en een onafhanklike hersiener het die seleksie van studies en data-ekstraksie onderneem en die risiko vir sydigheid geassesseer deur gebruik te maak van die *Cochrane Collaboration's tool for assessing risk of bias*. Outeurs van relevante kliniese proewe is geraadpleeg vir addisionele inligting

Resultate

Twee EGP is ingesluit in die oorsig met 'n totaal van 76 deelnemers. 'n Meta-analise kon nie uitgevoer word nie, dus is die oorsig beskrywend. Daar was te min EGP om te bewys dat roetine suplementasie van CoQ10 statien-geïnduseerde miopatiëse simptome verbeter.

Gevolgtrekkings

Meer en groter EGP is nodig om die effektiwiteit van CoQ10 suplementasie in statien-geïnduseerde miopatie te bepaal. Konsensus moet bereik word ten opsigte van die definisie en metingsinstrument/e van miopatie sodat die resultate van toekomstige studies makliker vergelyk en verwerk kan word.

ACKNOWLEDGEMENTS

The authors would like to acknowledge healthcare librarian, Wilhelmine Poole (WP), who assisted with electronic searches of databases. Janine Kriel (JK) is the independent reviewer who assisted with data extraction and assessment of risk of bias – she has experience in systematic review methodology and data extraction.

CONTRIBUTIONS OF AUTHORS

Lauren Pietersen (LP) conceived the review question, completed the protocol, completed the review and edited the review after peer review. Marietjie Herselman (MH) and Elizma Van Zyl (EVZ) assisted with planning of the protocol and writing of the paper. Alfred Musekiwa (AM) assisted with the statistical pooling of results as well as with the typing up of the review results.

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LIST OF ABBREVIATIONS

ACC:	American College of Cardiology
ADI:	Acceptable Daily Intake
AERS:	Adverse Event Reporting System
AHA:	American Heart Association
ATP:	Adenosine Triphosphate
BPI:	Brief Pain Inventory
CI:	Confidence Interval
CK:	Creatine Kinase
CoQ9:	Coenzyme Q9
CoQ10:	Coenzyme Q10
CVD:	Cardiovascular Disease
DSHEA:	Dietary Supplement Health and Education Act
ecSOD:	Extracellular Superoxide Dismutase
FDA:	Food and Drug Administration
GI:	Gastrointestinal
HDL:	High-Density Lipoprotein
HIV:	Human Immunodeficiency Virus
HMG-CoA:	Hydroxymethylglutaryl Coenzyme A
LDL:	Low-Density Lipoprotein
NA:	Not Applicable
NHLBI:	National Heart, Lung and Blood Institute
NLA:	National Lipid Association
NOAEL:	No-Observed-Adverse-Effect Level
OSL:	Observed Safety Level

PIS:	Pain Interference Score
PRIMO:	Prediction of Muscular Risk in Observational Conditions
PSS:	Pain Severity Score
RCT:	Randomised Controlled Trial
UL:	Upper Limit
ULN:	Upper Limit of Normal
VAS:	Visual Analogue Scale
VLDL:	Very Low-Density Lipoprotein
WHO:	World Health Organisation

LIST OF DEFINITIONS

MEDICAL

Acute Renal Failure: “Renal failure of sudden onset, such as from physical trauma, infection, inflammation, or toxicity. Symptoms include uremia and usually oliguria or anuria, with hyperkalemia and pulmonary edema. Three types are distinguished: prerenal, associated with poor systemic perfusion and decreased renal blood flow, such as with hypovolemic shock or congestive heart failure; intrarenal, associated with disease of the renal parenchyma, such as tubulointerstitial nephritis, acute interstitial nephritis, or nephrotoxicity; and postrenal, resulting from obstruction of urine flow out of the kidneys.” ¹

Amyotrophic Lateral Sclerosis: “A progressive neurological disorder characterized by loss of connection and death of motor neurons in the cortex and spinal cord.” ²

Coronary Artery Disease: “An abnormal condition that may affect the heart’s arteries and produce various pathologic effects, especially the reduced flow of oxygen and nutrients to the myocardium. The most common kind of coronary artery disease is coronary atherosclerosis, now the leading cause of death in the Western world. Other coronary artery diseases include coronary arteritis and fibromuscular hyperplasia of the coronary arteries. Also called coronary heart disease.” ³

Cardiovascular Disease: “Any abnormal condition characterized by dysfunction of the heart and blood vessels. In the United States, cardiovascular disease is the leading cause of death. Some common kinds of cardiovascular disease are atherosclerosis, myocardopathy, rheumatic heart disease, syphilitic endocarditis, and systemic venous hypertension.” ⁴

Diabetes Mellitus: “A condition characterised by a raised concentration of glucose in the blood due to a deficiency in the production and/or action of INSULIN, a hormone made in special cells in the pancreas called the islet cells of Langerhans. It is one of the world's most serious health problems.” ⁵

Huntington’s disease [after George S. Huntington, American physician, 1851–1916]: “A rare abnormal hereditary condition characterized by chronic progressive chorea and mental

deterioration that results in dementia. An individual afflicted with the condition usually shows the first signs in the fourth decade of life and dies within 15 years. It is transmitted as an autosomal trait and becomes progressively worse in severity as the trinucleotide repeats grow in successive generations. There is no known effective treatment, but symptoms can be relieved with medication.”⁶

Hypertrophic Cardiomyopathy: “An abnormal condition characterized by gross hypertrophy of the interventricular septum and left ventricular free wall of the heart. Ventricular hypertrophy results in impaired diastolic filling and reduced cardiac output. Signs and symptoms, such as fatigue and syncope, are often associated with exercise when the demand for increased cardiac output cannot be met. This is commonly a genetic disease, with numerous genes implicated. Also called hypertrophic obstructive cardiomyopathy.”⁷

Hypothyroidism: “A condition characterized by decreased activity of the thyroid gland. It may be caused by surgical removal of all or part of the gland, over dosage with antithyroid medication, decreased effect of thyroid-releasing hormone secreted by the hypothalamus, decreased secretion of thyroid-stimulating hormone by the pituitary gland, atrophy of the thyroid gland itself, or peripheral resistance to thyroid hormone.”⁸

Idiopathic Infertility: “Idiopathic is a term applied to diseases to indicate that their cause is unknown. Infertility is the inability to conceive or induce conception.”^{9,10}

Lipophilic: “The ability to dissolve or attach to lipids.”¹¹

Lymphatic System: “A vast, complex network of capillaries, thin vessels, valves, ducts, nodes, and organs that helps protect and maintain the internal fluid environment of the entire body by producing, filtering, and conveying lymph and producing various blood cells.”¹²

Mitochondria: “Specialized organelles of all eukaryotic cells that use oxygen. Often called the powerhouses of the cell, mitochondria are responsible for energy generation by the process of oxidative phosphorylation.”¹³

Mitochondrial Cytopathy: “A diverse group of disorders characterized by decreased energy production by the mitochondria; they may be acquired or secondary to another disorder such

as hyperthyroidism or result from heritable defects in the mitochondrial genome. Symptoms develop gradually and manifestations are extremely variable and often resemble those of other diseases, affecting the muscles, central and peripheral nervous systems, eyes, ears, heart, kidneys, liver, and pancreas.”¹⁴

Multiple Sclerosis: “A disorder of the central nervous system caused by damage of the myelin sheath. Symptoms include pain, weakness, numbness, tingling, paralysis, tremors, and muscle dysfunction.”¹⁵

Parkinson’s Disease [after James Parkinson]: “A slowly progressive degenerative neurologic disorder characterized by resting tremor, pill rolling of the fingers, a mask-like facies, shuffling gait, forward flexion of the trunk, loss of postural reflexes, and muscle rigidity and weakness.”¹⁶

STATISTICAL

Blinded: “Within a clinical trial, hiding the knowledge of a particular treatment. The three types of blinding are the following: observer-blind—when the researcher does not know the particular treatment that a patient undergoes; single-blind, when only the patient does not know to which group he or she belongs; and double-blind, when both the patient and the one providing the treatment do not know group identity. These types of blinding ensure—all other factors being identical—that any observed results are not the result of bias of the study participants.”¹⁷

Confidence Interval: “An interval which has a specified probability of containing a given parameter or characteristic.”¹⁸

Forest Plot: “Plot that displays effect estimates and confidence intervals for both individual studies and meta-analyses.”¹⁹

Funnel Plot: “A possible strategy to detect potential publication bias. A funnel plot is a scatterplot of sample size versus estimated effect size for all included studies in a meta-analysis. If the plot obtained does not resemble the shape of a funnel, then the possibility of a publication bias is considered highly likely.”²⁰

Heterogeneity: “Variability in the intervention effects being evaluated in the different studies is known as statistical heterogeneity, and is a consequence of clinical or methodological diversity, or both, among the studies.”²¹

Meta-Analysis: “The use of statistical methods to summarise the results of independent studies.”²²

Narrative Review: “Subjective (rather than statistical) methods for reviews where meta-analysis is either not feasible or not sensible.”²³

Randomised Controlled Trial: “A clinical trial in which the subjects are randomly distributed into groups which are either subjected to the experimental procedure (as use of a drug) or which serve as controls.”²⁴

Risk of Bias: “Bias is a systematic error or deviation in results or inferences from the truth. In studies of the effects of health care, the main types of bias arise from systematic differences in the groups that are compared (selection bias), the care that is provided, exposure to other factors apart from the intervention of interest (performance bias), withdrawals or exclusions of people entered into a study (attrition bias) or how outcomes are assessed (detection bias). Reviews of studies may also be particularly affected by reporting bias, where a biased subset of all the relevant data is available.”²⁵

Systematic Review: “A systematic review is a review that attempts to collate all empirical evidence that fits pre-specified eligibility criteria in order to answer a specific research question. It uses explicit, systematic methods that are selected with a view to minimizing bias, thus providing more reliable findings from which conclusions can be drawn and decisions made.”²²

CHAPTER 1: BACKGROUND AND MOTIVATION FOR THE REVIEW

1.1. PLAIN LANGUAGE SUMMARY

Statins are drugs of known efficacy in the treatment of high blood cholesterol and are recommended for the prevention of heart (cardiovascular) disease, the number one cause of death globally.

Although statins are effective to decrease bad (LDL) cholesterol, the prevalence of their use is low. One explanation for this is improved access to health information from the Internet or other sources, increasing fears of the side effects of statins, which results in statin discontinuation. Concern has been expressed particularly about severe muscle toxicity as a side effect of statin use, which may initially present as a condition known as myopathy, a term used to refer to any muscle complaints. The symptoms of myopathy range from mild muscle aches, weakness and elevation of the muscle enzyme, creatine kinase (CK). Severe muscle toxicity, known as rhabdomyolysis, is diagnosed as very high CK levels and is often also accompanied by kidney failure.

Symptoms of myopathy have been reported to prevent moderate exertion in daily activities, confine patients to bed and even result in cessation of employment, demonstrating a decrease in quality of life. Because high cholesterol doesn't have any symptoms, any unwanted side effect of a drug used for its management can undermine adherence to the drug, compromising treatment. This warrants research to better identify patients at risk for myopathy induced by statin use as well as to evaluate the current management strategies. The onset of myopathy may be aggravated by a higher statin dose, amongst other, but, to date, the exact cause of myopathy is unknown. One mechanism may be because statin use decreases blood levels of a nutrient called coenzyme Q10 (CoQ10), a powerful antioxidant that plays a role in muscle function. A decrease in blood and/or muscle levels of CoQ10 may thus contribute to the development of myopathy. Although the potential of the use of CoQ10, which is available as a non-prescription nutritional supplement, has been recognized, it has not been conclusively supported to form a part of medical guidelines to prevent or treat myopathy. In this review, only two small studies were identified that examined the effect of CoQ10 in statin-induced myopathy, one which is supportive of CoQ10 for statin-induced myopathy and the other not. Although CoQ10 may have numerous health benefits and is well

tolerated at high doses, its use continues to be considered only in certain patients until more clinical trials are conducted to conclude whether CoQ10 is effective and the cost of its use justified.

1.2. INTRODUCTION

Statins, also known as hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, are drugs of known efficacy in the treatment of hypercholesterolaemia and are recommended for both primary and secondary prevention of cardiovascular disease (CVD),^{26,27} which is the number one cause of death globally.²⁸ With worldwide estimated sales grossing \$19 billion annually, a figure that is consistently growing,²⁹ statins are one of the top selling prescription drug families in the world.³⁰

Statins inhibit HMG-CoA reductase, an important enzyme for the synthesis of cholesterol, reducing low-density-lipoprotein (LDL) cholesterol by up to 60%, alongside many other beneficial effects.³¹ In some patients, statins may decrease CVD morbidity and mortality by 25%.³² Six statins, namely lovastatin, pravastatin, simvastatin, fluvastatin, atorvastatin and cerivastatin, were initially approved by the United States Food and Drug Administration (FDA), and were introduced between 1987 and 1997.³³ Although they fall under the same class and share a common mechanism of action, these statins differ in chemical structure, pharmacokinetic profile and efficacy in modifying blood lipids.³⁴ Despite overall efficacy for reducing LDL-cholesterol, the number of people receiving statins for their hypercholesterolaemia is very low, even among those who are aware of their condition.³⁵ Multinational data on the treatment of hypercholesterolaemia from the World Health Organisation (WHO) multinational monitoring of trends and determinants in cardiovascular disease cohort component, also known as the MONICA Project,³⁵ reported that the prevalence of drug treatment was on average 8% in men and 6% in women. The study of Mitka (2003)³⁰ also found that more than 40% of patients eligible for statin use were not receiving treatment.

1.2.1. Barriers to Statin Use

One barrier to statin use has been affordability,³⁰ which may explain the limited use. Another is improved access to information from sources such as the Internet, increasing patient fears of statin side effects. This may result in non-adherence to statin therapy as well as the use of alternative cholesterol-lowering therapies.³² Of the various adverse effects of statins, only liver- and muscle-related toxicity are consistently reported.³⁶ Liver toxicity is recognised as subclinical aminotransferase elevations and occurs in 1 to 2 % of patients. Clinically important liver injury is, however, uncommon.³⁷ The American College of Cardiology (ACC), the American Heart Association (AHA) and the National Heart, Lung and Blood Institute (NHLBI), define myopathy as a term that refers to any disease of the muscle, including toxic disorders.³² Current management guidelines implicate that the progressive worsening of the symptoms or markers of myopathy as an adverse effect warrants a reduction in the prescription dose of statins or temporary discontinuation of the drug,³⁸ which compromises cardiovascular risk management.²⁷ In the Prediction of Muscular Risk in Observational conditions (PRIMO) study,³⁹ 4% of patients developed symptoms of myopathy from statin therapy that confined them to bed or resulted in cessation of employment, and as many as 38% had symptoms that prevented moderate exertion during daily activity. These are all factors affecting patient quality-of-life, a measurement that can be variable and that is mostly subjective in nature. Dimensions of patient quality-of-life include: the absence of distressing physical symptoms (e.g. pain and/or weakness and fatigue), emotional well-being, functional status (e.g. the ability to complete daily activities), quality of close interpersonal relationships, the ability to participate in and enjoy social interaction, satisfactory medical treatment and finances thereof, as well as intimacy, amongst other.⁴⁰ Impairment of a patient's quality of life may explain the poor compliance to statins reported in the study of Jackevicius (2002)⁴¹. In this study, 75% of the 85 020 patients using statins for the primary prevention of CVD had discontinued the drug, suggesting that they received no or limited benefit from its use. Overall, because hypercholesterolaemia is usually asymptomatic, any unwanted side effect, which may also affect quality of life, will undermine adherence to the drug used for its treatment.⁴²

1.2.2. Coenzyme Q10

Coenzyme Q10 (CoQ10), a fat-soluble nutrient, was first chemically synthesized in 1958, and was approved as a pharmaceutical drug in Japan for the treatment of congestive heart failure in 1974.⁴³ In the USA, following the Dietary Supplement Health and Education Act (DSHEA), CoQ10 has been sold as a supplement to the diet since 1994.⁴³ The efficacy of CoQ10 for the treatment of statin-induced myopathy is hypothesized due to the decreased plasma (and muscular) CoQ10 concentration observed after statin use, as well as the concomitant role of CoQ10 in muscle function.³¹ Although the use of CoQ10, which is available as a non-prescription nutritional supplement, does not form part of current management guidelines for statin-induced myopathy, its potential has been recognized. To further this, the aim of the current study is to systematically review the available evidence regarding CoQ10 supplementation for the treatment (elimination or improvement) of statin-induced myopathy. The outcomes could assist medical practitioners in determining whether CoQ10 supplementation is indeed effective in improving/treating statin-induced myopathy and thus whether it should be a recommended treatment mechanism in clinical practice.

1.3. DESCRIPTION OF THE CONDITION – STATIN-INDUCED MYOPATHY

There are various definitions available for statin-induced myopathy. The ACC, AHA, NHLBI, FDA, and the National Lipid Association (NLA) have each proposed definitions for statin-induced muscle effects (Table 1.1).^{38,44,45}

Myopathy has generally been defined as any muscle complaints or creatine kinase (CK) elevation with or without associated muscle symptoms.³⁸ Biopsy evidence suggests that some statin-induced myopathic changes may be present in the context of normal CK levels - myopathy thus does not necessarily connote symptoms or any degree of CK elevation.⁴⁷ In statin-treated patients, muscle-related symptoms range from mild, transient myalgia and myositis to rhabdomyolysis.⁴⁸ These symptoms are typically reported in the proximal limbs and trunk.⁴⁸⁻⁵⁰ In general, patients with isolated and unilateral symptoms have an alternative explanation for their complaint.⁵¹ The specific clinical characteristics associated with the different classifications of symptomatic myopathy are summarized in Table 1.2. These are namely muscle aches and weakness, but may progress to renal dysfunction in

rhabdomyolysis. The terms myalgia, myositis and rhabdomyolysis are used to describe muscle toxicity – myopathy is the general term used to refer to all of these problems.

1.3.1. Diagnosis

It is important to differentiate between the clinical and laboratory characteristics that accompany each term. However, it appears that the definitions given by the Canadian Working Group, ACC, AHA and NHLBI differ to those given by the FDA in Table 1.1, where rhabdomyolysis is accompanied by definitive evidence of organ damage.

Table 1.1: Proposed definitions for statin-induced myopathy

Clinical entity	ACC/AHA/NHLBI	NLA	FDA
Myopathy	General term referring to any disease of muscles	Symptoms of myalgia (muscle pain or soreness), weakness, or cramps, plus CK >10 x ULN	CK \geq 10 x ULN
Myalgia	Muscle ache or weakness without CK elevation	NA	NA
Myositis	Muscle symptoms with CK elevation	NA	NA
Rhabdomyolysis	Muscle symptoms with significant CK elevation (typically >10 x ULN), and CK (usually with brown urine and urinary myoglobin)	CK >10 000 IU/L or CK >10 x ULN plus an elevation in serum creatinine or medical intervention with intravenous hydration	CK >50 x ULN and evidence of organ damage, such as renal compromise

ACC/AHA/NHLBI = American College of Cardiology/American Heart Association/National Heart, Lung, and Blood Institute; FDA = U.S. Food and Drug Administration; NA = not

available; NLA = National Lipid Association; ULN = upper limit of normal; CK =Creatine Kinase

Source: Mancini et al (2011)⁴⁶

According to the definitions by the ACC, AHA and NHLBI, diagnosis can generally be eased by means of measurement of the patients' plasma CK. According to the Canadian Working Group, however, hyperCKaemia may not necessarily confirm diagnosis. Given the above differences, it comes by no surprise that, in the study of Thompson (2006)⁵², the Muscle Expert Panel recommended that the given definitions of statin-induced myopathy be standardized. They found it difficult to diagnose muscle problems in clinical practice and to compare the results of different studies with the varying definitions presented.

1.3.2. Symptoms

Rhabdomyolysis is the main life-threatening adverse effect of statin-induced myopathy due to the risk of acute renal failure. However, it continues to be a rare condition, affecting around 0.01 percent of statin users.²⁷ For all statins (excluding cerivastatin), the incidence of rhabdomyolysis (using the FDA definition) in two cohort studies was 3.4 (1.6 to 6.5) per 100 000 person-years.⁵³ Cerivastatin was withdrawn from the US market in August 2003⁵⁴ because of an apparent 15- to 80-fold increased risk of rhabdomyolysis.⁵⁵ A meta-analysis from 74 102 patients in 35 randomised clinical trials through December 2005 compared statin monotherapy versus placebo, with a follow-up period from 1 to 65 months. When patients treated with cerivastatin were excluded, there was no significant risk of myalgias, CK elevation, rhabdomyolysis, or discontinuation of the statin due to any adverse effect.⁵⁶ There was a risk difference of 4.2 [95% confidence interval (CI), 1.5– 6.9; P <0.01] for statin-induced increases in transaminases per 1000 patients. A meta-analysis of 83 858 patients treated with atorvastatin, fluvastatin, lovastatin, pravastatin, simvastatin, and only 114 with cerivastatin also revealed a low incidence of myositis (0.11%) and rhabdomyolysis (0.016%), with no significant increase in the patients using statins compared with the patients using the placebo.⁵⁷ In general, rhabdomyolysis is more common with higher statin doses (ranging from 40 mg to 80 mg daily, depending on the type of statin)^{36,39,53} and when fibrate therapy is administered simultaneously.⁵⁸

Muscle weakness, tiredness, cramps and/or increased CK activity remain the most frequently reported adverse effects of statin therapy, affecting from 0.5 to 2³¹ and up to 10-15⁵⁹ percent of statin users. Among 68 629 participants in 12 clinical trials, muscle pain, tenderness or weakness sufficient to consult a physician or to stop taking treatment occurred in 97 participants using statins and 92 participants using a placebo per 100 000 person-years of treatment.⁵³ In the Heart Protection Study, the largest trial examining statin-induced myopathy,⁶⁰ 10 269 patients received 40 mg of simvastatin and 10 267 a placebo for a median of 5 years. At least one episode of unexplained muscle pain or weakness occurred in 32.9% of the simvastatin and 33.2% of the placebo group, but only 0.5% in each group stopped treatment because of these complaints.

The prevalence of muscle complaints has thus been very similar in statin and placebo groups of controlled trials. However, the PRIMO study did report muscular complaints in 10.5% of 7924 unselected patients treated with high-dosage statin therapy (fluvastatin 80 mg, atorvastatin 40 to 80 mg, pravastatin 40 mg, or simvastatin 40 to 80 mg) for at least 3 months.³⁹ Subjects of this report were, however, not blinded and data were obtained by questionnaire. The results may also more closely represent the experiences of physicians prescribing higher statin doses.⁶¹ Given the inconsistent definitions, however, it is difficult to compare the incidence of statin-induced myopathy in research with the incidence in clinical practice. Post-marketing surveillance through the US FDA Adverse Event Reporting System (AERS) has also documented low reporting rates of statin-induced myopathy,³² meaning that incidence may indeed be much higher than those documented.

Table 1.2: Integrated Canadian Working Group consensus terminology for myopathic syndromes and hyperCKaemia*

Terms	Laboratory characteristics	Clinical characteristics
Myopathy	NA	General term referring to any disease of the muscle
Symptomatic myopathy		
Myalgia	CK \leq ULN	Muscle ache/weakness
Myositis	CK>ULN	Muscle ache/weakness
Rhabdomyolysis	CK> 10x ULN (CK>10 000 U/L)	Muscle ache/weakness; renal dysfunction may result from myoglobinuria; need for hydration therapy
HyperCKaemia		
Mild, grade 1	CK>ULN; \leq 5x ULN	May/may not have myositis
Mild, grade 2	CK>5x ULN; \leq 10x ULN	May/may not have myositis
Moderate	CK>10x ULN; \leq 50x ULN	May/may not have rhabdomyolysis with/without renal dysfunction
Severe	CK>50x ULN	May/may not have rhabdomyolysis with/without renal dysfunction

CK=creatine kinase; NA=not applicable; ULN=upper limit of normal

Source: Mancini et al (2011)⁴⁶

1.3.3. Measurement

To date, a standardized measurement tool that is specific to myopathy does not exist. Studies that have measured myopathy have merely listed the prevalence of symptoms; namely muscle weakness, tiredness, cramps and/or increased CK activity; or have adopted tools that are used to assess pain. Pain is, however, difficult to measure as it is a subjective sensation. Several features or attributes may describe pain – these include the quality, location, intensity, emotional impact and frequency, amongst others. Pain intensity is, however, one of the most relevant attributes.⁶² One of the tools to assess a patient's pain experiences is called the Brief Pain Inventory (BPI), which is considered a multidimensional pain measurement tool. It provides information about the history, intensity, location, and the quality of the patient's pain. Numeric scales from 0 to 10 are used to indicate the intensity of pain overall, at its worst, at its least, and at the present time; a percentage scale indicates pain relief from the relevant therapies; and a figure resembling the human body is given to the patient to shade the area which best positions where his/her pain is being experienced. Finally, seven questions determine the patients' pain interference with daily functioning. This tool has been validated in patients suffering from pain in a variety of conditions as well as from different geographical areas.^{63,64} Another tool used is called the Visual Analogue Scale (VAS), which is considered a one-dimensional pain measurement tool. It mostly uses a simple numeric scale of 0 to 10 or a horizontal 100-mm visual analogue scale and is often considered the ideal tool because it is continuous, is similar to a ratio scale, and is more independent from language than a verbal scale.^{65,66} However, the validity of this scale is strongly dependent on the method of administration as well as the instructions given to the participants of the study.⁶⁵ Although the BPI and VAS are well researched and their use recommended by the Expert Working Group of the European Association of Palliative Care, amongst other, most of the evidence is in cancer patients and/or palliative care. One should also note that symptoms of myopathy range from mild, transient muscle aches to muscle aches with weakness in statin-treated patients – myopathy thus does not always necessarily connote pain.⁴⁸ In the study of Thompson (2006)⁵², the Muscle Expert Panel implicated that the evaluation of statin-induced myopathy should include the evaluation of the minor symptoms of myopathy listed above, even when they occur without CK elevation. These minor symptoms may still affect the patient's quality of life as well as adherence to statin therapy, and thus CVD management.⁵²

Two of the recommendations to researchers, funding agencies and pharmaceutical companies in the study of Thompson (2006)⁵² were to 1) develop a tool to measure mild statin-induced myopathy and 2) to incorporate measurements of muscle strength into research on statin therapy, which would include handgrip, elbow flexor and knee extensor or strength.⁵² These recommendations have not yet been implemented.

1.3.4. Risk Factors

Two proposed categorisations for the risk factors to statin-induced myopathy have been identified. One is from the study of Venero (2009)⁶¹, where risk factors were categorized as conditions that increase statin serum and muscle concentration, drugs that affect statin metabolism, and factors that increase muscle susceptibility to injury (Table 1.3). The other categorisation is from the ACC/AHA/NHLBI clinical advisory board, who propose that risk factors be categorized into patient- and treatment-related factors (Table 1.4). With regards to the dose of statin: simvastatin, pravastatin and rosuvastatin at doses double those currently marketed have caused higher rates of muscle damage. In patients post-myocardial infarction, simvastatin at 80 mg/day resulted in more frequent marked increases in CK levels versus simvastatin at 40 mg/day.⁶⁷ The type of statin, as well as the extent of lipid reduction are also proposed factors that may increase risk to statin-induced myopathy. Muscle toxicity has been reported with all available statins.⁵⁷ From 2002 to 2004 however, the FDA AERS rates for myopathy were the lowest for fluvastatin (0.43 cases per 1 million prescriptions) and the highest for rosuvastatin (2.23 cases).³²

Table 1.3: Risk factors associated with statin-induced myopathy

<p>1. Factors related to an increase in statin serum level</p> <ul style="list-style-type: none">a. Statin doseb. Small body framec. Decreased statin metabolism and excretion<ul style="list-style-type: none">i. Drug–drug interactionsii. Grapefruit juice (possibly also pomegranate & star fruit)iii. Hypothyroidism and diabetes mellitusiv. Advanced agev. Liver diseasevi. Renal disease <p>2. Factors related to muscle predisposition</p> <ul style="list-style-type: none">a. Alcohol consumptionb. Drug abuse (cocaine, amphetamines, heroin)c. Heavy exercised. Baseline muscular diseasei. Multisystemic diseases: diabetes mellitus, hypothyroidismii. Inflammatory or inherited metabolic muscle defects
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Source: Venero (2009)⁶¹

Table 1.4: ACC/AHA/NHLBI risk factors to statin myopathy

1.Patient-related factors	2.Treatment-related factors
a.Advanced age	a.High-dose statin therapy
b.Female gender	b.Interactions with concomitant drugs
c.Small body size	i.Fibrates
d.Multisystem disease (esp. liver and/or kidney)	ii.Cyclosporine
e.Alcoholism	iii.Antifungals
f.Excessive grapefruit consumption	iv.Macrolide antibiotics
g.Excessive physical activity	v.Nefazodone
h.Family history of myopathy while receiving lipid-lowering therapy	vi.Amiodarone
i.History of myopathy while receiving another lipid-lowering therapy	vii.Verapamil
j.History of CK elevation	viii.Protease inhibitors (anti-HIV drugs)
k.Hypothyroidism	
l.Major surgery or the preoperative period	

Source: Joy (2009)³²

In a double-blind, randomised, cross-over study, subjects who tested positive for myalgia showed greater decreases in total and LDL-cholesterol when compared to subjects who did not develop myalgia,⁶⁸ suggesting that muscle toxicity may be an effect of lipid reduction.⁵²

1.3.5. Current Recommendations

Statins are prescribed for chronic use (for a duration of 3 months or longer) and are usually continued unless liver enzymes increase to more than three times the upper limit of normal – liver and muscle enzymes may be checked upon the initiation of therapy, and at least one set of liver enzymes will be tested between one to three months later, and annually thereafter.³⁹ Muscle enzymes need not be checked regularly unless the patient develops muscle symptoms and, if damage is suspected, statin use is usually stopped and CK measured.³¹ The study of Mancini et al (2011)⁴⁶, however, reported that the public consciousness about adverse effects and the commonness of symptoms such as myalgia suggests that it is prudent to measure CK at 6 to 12 weeks, usually at the time of a repeat lipid assessment. Although there are currently no definitive treatment mechanisms for statin-induced myopathy, there are several options that can be explored and implemented according to practicality from patient to patient. These options include the use of different statins or a lower statin dose, as well as nutrients such as vitamin D and E. In general, symptoms that are not minor/not tolerated motivates for the statin to be stopped until the patient is asymptomatic.⁴⁶ The same statin at the same dose may then be restarted. If the symptoms reoccur, it is suggestive of statin intolerance, at which stage a lower dose of statin and/or a different type of statin can be considered. Only when a well-tolerated statin does not achieve adequate lipid-lowering, the statin can be replaced or supplemented with adjunctive use of non-statin lipid-lowering therapies such as Ezetimibe, Niacin, Fibrates or Bile Acid Sequestrants, amongst other.⁴⁶ However, no controlled trials exist to implicate the use of Vitamin D to relieve statin-induced myopathy and a severe Vitamin D deficiency is associated with intrinsic muscle disease, which is not related to statin use. In one study of 38 vitamin D-deficient patients, Vitamin D was given at 50 000 IU per week for 12 weeks, where after myalgia was resolved in 92% of the patients.⁶⁹ Vitamin E was also shown to have no value for pain relief in one controlled trial.⁷⁰

1.4. DESCRIPTION OF THE INTERVENTION – COENZYME Q10

CoQ10, also known as ubiquinone (Figure 1.1), is a natural component of living cells. CoQ belongs to a homologous series of compounds that share a common benzoquinone ring

structure, but differ in the length of the isoprenoid side chain. In humans and a few other mammals, this side chain contains 10 isoprene units, and is thus called CoQ10.⁷¹

1.4.1. Measurement

Plasma/serum CoQ10 concentrations are used to assess CoQ10 status in humans, primarily because sample collection is much easier using these methods.⁷¹ Plasma CoQ10 concentration may not be a good indicator of CoQ10 concentration in the tissue,^{72,73} but it serves as a good measure of the overall CoQ10 status in the individual and also as a guide to the dose of CoQ10 the patient may require.⁷¹ Several methods for this measurement are preferred,⁷¹ and have been tested in studies from the year 1987.⁷⁴ These methods include mostly ultraviolet and electrochemical detection and/or liquid chromatography.⁷⁵⁻⁸⁰ Thus far, a single reference value/range for plasma CoQ10 has not been specified. A few studies have indicated normal plasma levels for males and females, (Table 1.5) which appear to be in the range of 0.227 to 1.9 mmol/l.

1.4.2. Functions

CoQ10 has many functions: it is a powerful antioxidant,³³ membrane stabilizer,³³ and may have an effect on gene expression.⁸⁴ The major physiological role of CoQ10 is that it functions as an irreplaceable component of the mitochondrial energy electron transduction chain and adenosine triphosphate (ATP) production.⁸⁵ These high-energy phosphates are necessary for many cellular functions, including muscle contractions.⁸⁶ Statins block the conversion of HMG-CoA to mevalonate by inhibiting HMG-CoA reductase, decreasing cholesterol production but also suppressing formation of isoprenoids (Figure 1.3).⁵⁷ It is well documented that serum CoQ10 levels decrease with statin treatment (Table 1.6).⁸⁷ Statins are known to reduce CoQ10 levels in the plasma, where supplementation with CoQ10 will increase these levels without affecting the efficacy of the statin therapy.^{31,88-108} The highest decreases in CoQ10 in these studies appear to be related to a higher dose of statin as well as longer duration of statin use.^{88,94,95} Because plasma and intramuscular CoQ10 levels do not correlate, different regulatory mechanisms have been suggested.¹⁰⁹ However, the effect of statins on intramuscular CoQ10 may also be drug and dose-dependent. Very few studies have investigated skeletal muscle CoQ10 levels after statin therapy. However, data from

these representative human studies show that low dose statin treatment (<40 mg daily) does not significantly reduce intramuscular CoQ10,^{32,94,95} even when used for longer durations of up to 6 months. Hence its function in the electron transport chain, a CoQ10 deficiency resulting from statin therapy may impair muscle energy metabolism and therefore may contribute to the development of statin-induced myopathy.⁸⁷

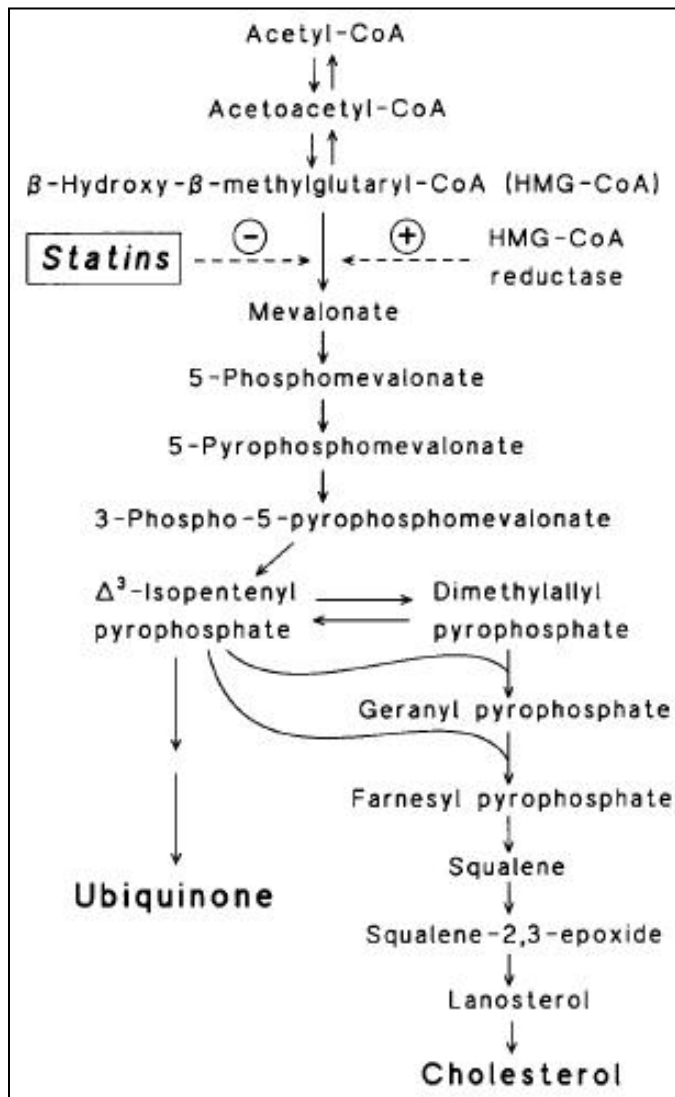
Table 1.5: Serum/plasma CoQ10 reference values

Serum/plasma CoQ10 (mmol/l) - Females	Serum/plasma CoQ10 (mmol/l)- Males	Reference
0.43 to 1.47	0.40 to 1.72	Kaikkonen (2002) ⁸¹
0.50–1.9		Miles et al (2003) ⁸²
0.227 to 1.432 (mean of 0.675)		Duncan (2005) ⁸³

The plasma depletion of CoQ10 due to statin use in humans was also associated with an elevation in lactate to pyruvate ratio in the study of De Pinieux et al (1996)⁹⁷, suggesting a shift toward anaerobic metabolism and possible impairment in mitochondrial bioenergetics. This may also contribute to muscle injury and myopathy during statin use due to the importance of the mitochondria in muscle function.

CoQ10 is a fat-soluble nutrient (a quinone) but not considered a vitamin as it is synthesized in all cells in healthy human subjects from tyrosine (or phenylalanine) and mevalonate (Figure 1.1).⁷¹ Because CoQ10 is lipophilic, its absorption follows the same process as that of lipids in the gastrointestinal (GI) tract.⁷¹ It is transported to the small intestine where secretions from

the pancreas and bile facilitate emulsification and micelle formation. Thereafter it passes into the lymphatic system and finally to the blood and tissues. Almost all of the CoQ10 in the human circulation exists in its reduced form, ubiquinol (Figure 1.2).^{82,111}



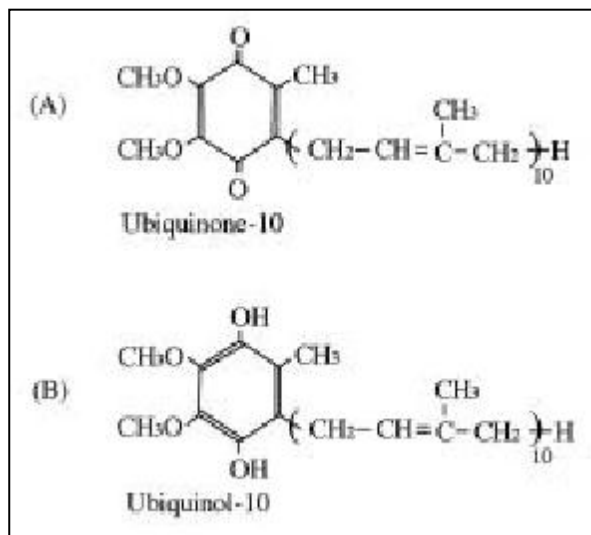
Formation of mevalonate is the rate limiting step in synthesis.⁵⁷

Figure 1.1: Endogenous synthesis of ubiquinone and cholesterol

Source: Palomaki (1998)¹¹⁰

1.4.3. Digestion

After absorption, ubiquinol initially forms a part of lipoproteins. These particles are converted to chylomicron remnants in the circulation by lipoprotein lipase and are then taken up rapidly by the liver. Here CoQ10 forms a part of very-low-density-lipoprotein (VLDL) and/or LDL particles, which are rereleased into the circulation.¹¹² High-density-lipoprotein (HDL) particles also contain a small amount of CoQ10.



About 95% of CoQ10 in human circulation exists in its reduced form, Ubiquinol.

Figure 1.2: Molecular structures of ubiquinone (A) and ubiquinol (B)

Source: Mabuchi et al (2005)¹⁰⁷

CoQ10 is mainly found in active organs, such as the heart, kidney and liver.¹¹⁴ Only up to 10% of total CoQ10 is located in cytosol and about 50% in mitochondria, making it vulnerable to free radicals that may form during oxidative phosphorylation.¹¹⁵ The total amount of CoQ10 in an adult human body must be replaced daily by endogenous synthesis and dietary intake.¹¹⁶ It is thought that 50% of CoQ10 is obtained through exogenous sources and the other 50% through endogenous synthesis,¹¹⁷ with an average turnover rate in the body being around 4 days.¹¹⁸ Exogenous sources of CoQ10 need to be increased if endogenous synthesis is impaired. Low levels of CoQ10 are typically found in disease or ageing.¹¹⁹⁻¹²² Table 1.6 presents genetic mutation, aging, cancer and statin type drugs as causes for a

serum or tissue decrease in CoQ10 and the relative tissue analyses to determine whether there is a deficiency.⁴²

1.4.4. Sources

Exogenous sources of CoQ10 include various food items and nutritional supplements. The content in food is, however, generally low - the average dietary intake is between 3 and 6 mg daily.¹²⁵ Although studies regarding the CoQ10 content of different foods are limited, it appears that meat and fish have the highest contents due to their relatively high levels of fat and mitochondria.¹²⁶ An overview of CoQ10 contents in some common foods can be seen in Table 1.7. A more comprehensive list can be sourced from the study of Pravst (2010)¹²⁷. CoQ10 as a dietary supplement, however, has been extensively researched in healthy subjects and patients (mostly chronic heart failure) and results in a definitive increase in plasma CoQ10 concentrations after routine supplementation of 2 weeks or longer.⁷¹ A 1.470¹³⁰ to 4.074¹³¹ fold increase in CoQ10 concentration from baseline to after the intervention was seen in studies with chronic low/moderate doses (30 to 300 mg) of CoQ10. Up to 7.5 fold increases were seen with chronic high (300 to 3000 mg) doses.¹³² It is currently available in different supplemental preparations, including crystalline CoQ10 powder in hard gelatin capsules, oily dispersions and as solubilizates in soft-gel capsules,¹³³ all which can be bought over the counter. The efficacy of absorption of orally administered preparations may, however, be poor because they are mostly lipophilic and have a relatively large molecular weight.^{71,134} Studies also cite slow absorption of CoQ10 from the GI tract (Tmax = ≥ 6 hours).^{135,136} The extent of the increase in the serum level of CoQ10 will depend on factors such as the dosage, duration and also the type of formulation. Large single doses of CoQ10 either as a powder or as an oil-suspension has little or no effect in human subjects,^{81,137,138} whereas, after two weeks of supplementation, concentrations of plasma CoQ10 was seen to stabilize in the study of Tomono (1986)¹³⁶ and more recently in the study of Hosoe (2007)¹³⁹. In this study, CoQ10 concentrations were above reference values in the study participants and increased according to the CoQ10 dose given. The increases were, however, not linear.

Table 1.6: CoQ10 deficiency in humans

Basis	Tissue analysis	Decrease from control (%)	Reference
Genetic	Lymphocytes	-	Rotig et al (2000) ¹²³
Genetic	Skin fibroblasts	90	Rotig et al (2000) ¹²³
Age ^{***}	Myocardium	72	Rosenfeldt et al (1999) ¹²⁰
Age [*]	Heart	58	Kalen (1989) ¹¹⁶
Age	Pancreas	83	Kalen (1989) ¹¹⁶
Age	Adrenal	50	Kalen (1989) ¹¹⁶
Age	Liver	17	Kalen (1989) ¹¹⁶
Age	Kidney	45	Kalen (1989) ¹¹⁶
Age	Skin epidermis	75	Hoppe et al (1999) ¹¹⁹
Pravastatin ⁰	Serum	20	Mortensen et al (1997) ⁹⁴
Lovastatin ⁰	Serum	29	Mortensen et al (1997) ⁹⁴
Simvastatin ⁰	Serum	26	Bargossi et al (1994) ⁸⁹
Cancer (pancreas)	Serum	30	Folkers et al (1997) ¹²⁴

* Change from age 19–21 to age 77–81.

** Change from age 30 to age 80.

*** Change from avg. age 58 ± 1.7 to 76 ± 6.8.

⁰HMG CoA reductase inhibitors of isoprene synthesis.

Source: Crane (2001)⁴²

Better absorption is mostly achieved with oil-based forms of CoQ10 as a soft-gel capsule.^{125,140} Absorption may also be enhanced if the nutritional supplement of CoQ10 is ingested in the presence of fat due to its lipophilic nature, which is the rationale for oil-based preparations. The importance of CoQ10 formulation for bioavailability has been suggested by the continuous search for formulations with increased absorption.^{71,142,143} Table 1.8, adapted from Bhagavan (2006)⁷¹, presents data on the dose, duration and net plasma increase in CoQ10 concentration from representative human studies. Plasma CoQ10 increases range from 0.5 $\mu\text{mol/L}$ (300 mg CoQ10 emulsion) to 3.255 $\mu\text{mol/L}$ (120 mg solubilized CoQ10). Despite the higher CoQ10 dose, the limited bioavailability of the formulation appears to result in smaller changes in the CoQ10 plasma value. Bhagavan (2006)⁷¹ reported that individual variability in plasma response to ingested CoQ10 was observed in the studies in Table 1.8 as was indicated by large standard deviations.⁷¹

Table 1.7: An overview of the CoQ10 content in some commonly eaten foods

	Food	CoQ10 µg/g	Daily portion g/day	CoQ10 intake mg/day
Meat	Pork heart	203	120	24
	Chicken leg	17	120	2
	Beef heart	41	120	4.8
	Beef liver	19	120	2.3
	Lamb leg	2.9	120	3.5
Fish	Herring	27	26	0.7
	Trout	11	100	1.1
Vegetable	Cauliflower	0.6	200	0.12
	Spinach	2.3	200	0.46
Fruit	Orange	2.2	200	0.44
Starch	Potato	0.24	200	0.05

Source: Crane (2001)⁴²

Data from: Lester (1959)¹²⁸ and Weber (1997)¹²⁹

More studies are needed to determine whether patient age, gender, lipoprotein status and diet, amongst other factors, may affect the bioavailability of CoQ10 with chronic dosing.¹⁴⁵

1.4.5. Recommendations for Intake

The suggested daily intake of CoQ10 from exogenous sources varies from 30 to 100 mg for healthy subjects and 60 to 1200 mg when used in combination with other therapies in some medical conditions.¹⁴⁶⁻¹⁴⁸ The acceptable daily intake (ADI) is 12 mg/kg/day, calculated from the no-observed-adverse-effect level (NOAEL) of 1200 mg/kg/day derived from a 52 week

chronic toxicity study in rats.^{149,150} CoQ9 is, however, the major CoQ homologue in rats, so they may not be the appropriate animal model for studying CoQ10 intake and metabolism.⁷¹

Table 1.8: Data from representative human studies on the dose, duration and net plasma increase in CoQ10 concentration of different formulations

CoQ10 Formulation	Daily Dose (mg)	Duration of intervention with CoQ10	Plasma CoQ10 increase (micromol/l)	Reference
Oil based	90	9 months	1.214*	Folkers (1994) ¹⁴³
Oil based	90	2 weeks	1.200 ^a	Weber (1994) ¹³⁵
Oil based	100	2 weeks	0.524 ^b	Lonrot et al (1996) ¹⁴⁴
Powder based	90	2 months	1.810	Kaikkonen et al (1997) ¹³⁸
Oil based	90	2 months	1.900	Kaikkonen et al (1997) ¹³⁸
Powder based	120	3 weeks	1.310	Chopra (1998) ¹³³
Oil based	120	3 weeks	1.008	Chopra (1998) ¹³³
Solubilized	120	3 weeks	3.255	Chopra (1998) ¹³³
Oil based	300	1 week	0.530	Lyon (2001) ¹⁴⁰
Emulsion	300	1 week	0.500	Lyon (2001) ¹⁴⁰

Plasma CoQ10 values corrected for baseline.

*Whole blood; CoQ10 in divided doses,^aExtrapolated from figure,^bWith 500 mg Vitamin C.

Source: Bhagavan (2006)⁷¹

Thus far, no adverse effect directly related to CoQ10 consumption by humans exists, meaning that there is no reference NOAEL and that an upper limit (UL) cannot be derived.¹⁵¹

The dosages of CoQ10 used in clinical trials are thus evaluated according to the presence of

adverse effect/s at the level of CoQ10 supplemented – this is also known as the observed safety level (OSL).¹⁵¹ Risk assessment for CoQ10 based on various clinical trial data indicate that the OSL for CoQ10 is 1200 mg/day/person,¹⁴⁹ In the study of Shults et al (2002)¹⁵², up to 1200 mg CoQ10 per day was given to patients with Parkinson's disease for 16 months, and in the Huntington Study Group (2001)¹⁵³, 600 mg CoQ10 per day was given to patients with Huntington's disease for 30 months. In these studies, the frequency of side effects were almost equal to that in the relative control groups, which indicated that the doses of CoQ10 given were within tolerable limits. It is notable, however, that the studies mentioned are on patients and not healthy individuals. No safety data of CoQ10 in healthy individuals have been reported, however typical doses of CoQ10 supplementation in most conditions is 60 to 200 mg daily in divided doses.¹⁰⁷ Up to 15 mg/kg/day are being given for mitochondrial cytopathy.¹⁵⁴ More recent data document the safety and tolerability of CoQ10 at doses as high as 3000 mg a day in patients with Parkinson's disease and amyotrophic lateral sclerosis.^{132,155}

1.4.6. Benefits of Supplementation

There are numerous health benefits with CoQ10 supplementation. A large number of these studies demonstrating benefits relate to CVD where CoQ10 has been used in combination with standard medical therapy.¹⁵⁶ Cardiovascular benefits of CoQ10 may be due to its bioenergetic role, its capability of antagonizing oxidation of plasma LDL, and its ability to improve endothelial function.¹⁵⁷ Thus far, cardiovascular benefits reported include improved endothelium-bound extracellular superoxide dismutase (ecSOD)¹⁵⁸ in patients affected by coronary artery disease; decreases of up to 17 mmHg in systolic and 10 mmHg in diastolic blood pressures;¹⁵⁹ and improved diastolic dysfunction in hypertrophic cardiomyopathy. Some other claims for the use of CoQ10 includes an anticancer effect through immune stimulation, decreased insulin requirements in patients with diabetes,¹⁶⁰⁻¹⁶⁴ slowed progression of Parkinson's disease, improved semen quality in men with idiopathic infertility,¹⁶⁵ reduced risk of pre-eclampsia and protection against anthracycline cardiotoxicity.^{107,166} Although studies suggest that CoQ10 may be useful in treating these disorders, amongst others (e.g. Multiple Sclerosis and Huntington's disease), results are unclear mostly due to the design of the

available trials and thus the quality of the evidence - more trials are needed for conclusive results.

1.4.7. Adverse Effects of Supplementation

Overall, CoQ10 is deemed safe as a dietary supplement. High doses of oral CoQ10 given over longer periods of time is well documented in humans,¹⁶⁷ but GI symptoms such as loss of appetite, abdominal pain, nausea and vomiting; and central nervous system changes such as dizziness, photophobia, irritability and headaches may occur.¹⁶⁸ Other adverse effects include itching, rash, fatigue and flu-like symptoms.¹⁶⁸ Symptoms were found in 24 cases in a randomised, controlled trial (RCT)¹⁶⁹ and were said to be caused by the oil content of the CoQ10 test capsules. Since commercial capsules use oil as a base due to the lipophilic nature of CoQ10, GI symptoms should be monitored, especially when high doses are taken over a short period of time.¹⁶⁹

Currently there are no known contra-indications for CoQ10 supplementation other than being undertaken with the chemotherapeutic agent, adriamycin, as CoQ10 affects its metabolism.¹⁷⁰ CoQ10 may also decrease a patient's response to Warfarin.¹⁶⁸

1.5. HOW THE INTERVENTION MIGHT WORK

The exact pathophysiology of statin-induced myopathy is unknown. There are many possible mechanisms, one which is believed to be because statins inhibit mevalonate production, which results in a decrease in the formation of products of the mevalonate pathway (Figure 1.3) – one of these products is CoQ10.³¹ A CoQ10 deficiency has merely been hypothesized to be a cause of statin-induced myopathy as CoQ10 is involved in mitochondrial electron transfer and serves as an important intermediary in the oxidative phosphorylation pathway.¹⁷¹

Not many intervention studies on the efficacy of CoQ10 in statin-induced myopathy exist to confirm the etiological role of CoQ10 in statin-induced myopathy. In the study of Caso (2007)⁷⁰, oral CoQ10 was given to patients at 100 mg per day for 30 days to evaluate the effect on symptoms of myopathy. The Pain Severity Score (PSS) and pain interference with daily activities (PIS) for the CoQ10 group decreased significantly. Sixteen of the 18 participants

receiving CoQ10 reported pain relief, which included a decrease in pain, ache, burning sensation and overall muscle fatigue. These findings suggested that CoQ10 may be beneficial for patients using statins by decreasing myopathic symptoms and improving subject's quality of life. However, in the study of Young et al (2007)²⁷, where oral CoQ10 was given to patients at 200 mg per day for 12 weeks to also evaluate the effect on symptoms of myopathy, there was no difference in the change in pain scales between the CoQ10 and the control group. No significant beneficial effect of oral CoQ10 supplementation on simvastatin tolerability and myalgic symptoms in patients could thus be demonstrated. Although both of these studies were comparative, they included only a small number of participants given the statistics of CVD. A conclusion cannot be drawn from the data as one study was positive and the other not, the efficacy of CoQ10 is thus inconclusive. The study of Langsjoen (2005)¹⁷² is a prospective analysis in which cardiology clinic patients on statin therapy were evaluated for possible adverse effects, including myalgia and fatigue, amongst other. All patients discontinued statin therapy due to side effects and began supplemental CoQ10 at an average of 240 mg/day upon the initial visit. The prevalence of patient symptoms on initial visit and on most recent follow-up demonstrated a decrease in fatigue and myalgia, and it was concluded that statin-related side effects were reversible with the combination of statin discontinuation and supplemental CoQ10. Although positive, the study was not a RCT and statin therapy was discontinued when CoQ10 supplementation commenced, which is seen as two simultaneous interventions.

1.6. MOTIVATION FOR THE REVIEW

Statins are drugs of known efficacy in the treatment of hypercholesterolaemia. However, statin-induced myopathy, an adverse effect of statins in up to 15% of its users, has warranted a reduction in the prescription dose or temporary discontinuation of the drug. Statin-induced side effects are far more common than previously published,^{172,173} so statin-induced myopathy will probably increase, especially with greater numbers of people starting high-dose statin therapy. This warrants research to better identify patients at risk for statin-induced myopathy as well as to evaluate the current management strategies.^{32,172} The exact mechanism of statin-induced myopathy remains unknown, but the potential of CoQ10, available as a non-

prescription nutritional supplement, has been recognized due to decreased human CoQ10 levels found after statin use, and the concomitant role of CoQ10 in muscle function.

Healthcare providers have immense amounts of information, including healthcare research, to process. They thus have limited time and/or resources to search for information, interpret it, as well as incorporate it into healthcare decisions. The purpose of this systematic review is thus to identify, appraise and synthesize the research-based evidence on CoQ10 for statin-induced myopathy for this purpose.²² A meta-analysis was planned to provide more precise estimates of the effect of CoQ10 for statin-induced myopathy than what can be determined in individual studies. It may also facilitate investigation of the consistency of evidence across the studies found as well as explore the differences across these studies.²² A previous systematic review on the role of CoQ10 in statin-induced myopathy was completed in 2007. In this review by Marcoff (2007)¹⁷³, the search for English-language studies, completed in August 2006, used PubMed as the only database and a meta-analysis was not attempted as only the abstracts of relevant studies could be obtained. The review concluded that there was not enough evidence to confirm the etiological role of CoQ10 in statin-induced myopathy and that large, well-designed, clinical trials were required to address the issue.¹⁷³ The current review aimed to improve on the methodology adopted in the study of Marcoff (2007)¹⁷³ by completing a more comprehensive search of available databases. Searching merely one database may not have been sufficient to identify all relevant studies for inclusion in the review. The identification of more RCTs may also allow for meta-analyses of results.

CHAPTER 2: METHODOLOGY

2.1. RESEARCH QUESTION

In adults with symptoms of statin-induced myopathy, does CoQ10 supplementation act as an effective treatment by improving symptoms compared to a placebo/similar antioxidant/no intervention?

2.2. OBJECTIVES

2.2.1. Primary Objectives

The primary objectives of the review were as follow:

- 2.2.1.1. To determine the effect of CoQ10 supplementation on the severity of statin-induced myopathic symptoms as compared to controls (placebo/similar antioxidant/no intervention).
- 2.2.1.2. To determine the effect of CoQ10 supplementation on plasma CK levels compared to a placebo/similar antioxidant/no intervention.
- 2.2.1.3. To determine the effect of CoQ10 supplementation on intramuscular and plasma CoQ10 levels compared a placebo/similar antioxidant/no intervention.
- 2.2.1.4. To determine whether any adverse effects of CoQ10 supplementation; such as abdominal pain, nausea and vomiting or headaches; are experienced as compared to a placebo/similar antioxidant/no intervention.

2.2.2. Secondary Objectives

The secondary objectives of the review were as follow:

- 2.2.2.1. To determine the average duration of CoQ10 supplementation to elicit a positive response.
- 2.2.2.2. To determine the average dose of CoQ10 supplementation required to elicit a positive response.

(A positive response is defined as a decrease in myopathic pain intensity/frequency, plasma CK levels and symptoms from the adverse effects of CoQ10, if any.)

2.3. CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

2.3.1. Types of Studies

Randomised controlled trials (RCTs).

2.3.2. Types of Participants

Adults (mean of 18-64.99 years) of all race/ethnic groups and gender on statin therapy with reported myopathic symptoms from no other known cause. Elderly patients were excluded as their CoQ10 levels are depleted at baseline irrespective of disease status (see Table 1.6).

2.3.3. Types of Interventions

2.3.3.1. Intervention

Pure oral supplement of CoQ10 irrespective of dose, duration and frequency.

2.3.3.2. Control

Placebo, a similar antioxidant, or no intervention.

2.4. TYPES OF OUTCOME MEASURES

2.4.1. Primary Outcomes

- The severity of myopathic symptoms

2.4.2. Secondary Outcomes

- Plasma creatine kinase (CK) (U/L)
- Intramuscular CoQ10 ($\mu\text{mol/kg}$)
- Plasma CoQ10 ($\mu\text{mol/L}$)

- Adverse effects of CoQ10 such as gastrointestinal symptoms (loss of appetite, abdominal pain, nausea and vomiting) and central nervous system changes (dizziness, photophobia, irritability and headaches). Other adverse effects include itching, rash, fatigue and flu-like symptoms.

2.5. SEARCH METHODS FOR IDENTIFICATION OF STUDIES

2.5.1. Electronic Searches

An electronic search for studies was performed by the principle investigator (LP) with the assistance of a qualified librarian (WP) in March 2011 and again in November 2011. All of the electronic searches were restricted to English-language only. The following electronic databases were searched:

- Science Direct (Elsevier) (inception to February 2012),
- PubMed – MEDLINE (inception to November 2011),
- The Cochrane Central Register of Controlled Trials (CENTRAL) (inception to November 2011),
- Web of Science (ISI) (inception to November 2011),
- EBSCOhost
 - Academic Search Premier and CAB abstracts (inception to February 2012),
 - CINAHL (inception to November 2011),
- Scopus (inception to November 2011),
- Wiley Online Library (inception to February 2012),
- SpringerLink (inception to February 2012), and
- Google Scholar (inception to February 2012)

2.5.2. Keywords for the Searches (Search String):

- Term to search for the health condition: ['statin' OR 'HMG CoA Reductase Inhibitor' OR 'atorvastatin' OR 'fluvastatin' OR 'lovastatin' OR 'pravastatin' OR 'rosuvastatin' OR 'simvastatin'] AND ['myopathy' OR 'myalgia' OR 'rhabdomyolysis' OR muscle* OR muscular*]

- Term to search for the intervention: 'Coenzyme Q10' OR 'CoQ10' OR 'Q10' OR 'Ubiquinone' OR 'Ubidecarenone'
- Term to search for the study design (not applicable to CENTRAL): random* AND control*

2.5.3. Searching Other Resources

Hand searches of reference lists of included RCTs were performed. Unpublished trials were requested from various CoQ10 manufacturers. However, none were provided.

2.6. DATA COLLECTION AND ANALYSIS

2.6.1. Selection of Studies

WP conducted the initial search for studies using the relevant electronic databases and search strings. LP assisted with conducting the second search and tabulated the citation list of titles and abstracts retrieved. An independent reviewer (JK) assisted LP to examine study titles and abstracts to remove studies that were irrelevant according to the predetermined selection/eligibility criteria (Table 2.1). JK was trained in systematic review methodology and the background of the current review; including the application of phase 1 and 2 criteria in order to determine which studies were relevant for inclusion in the review. After possibly eligible studies had been listed in phase 1 of the selection process, the full texts were retrieved by LP.

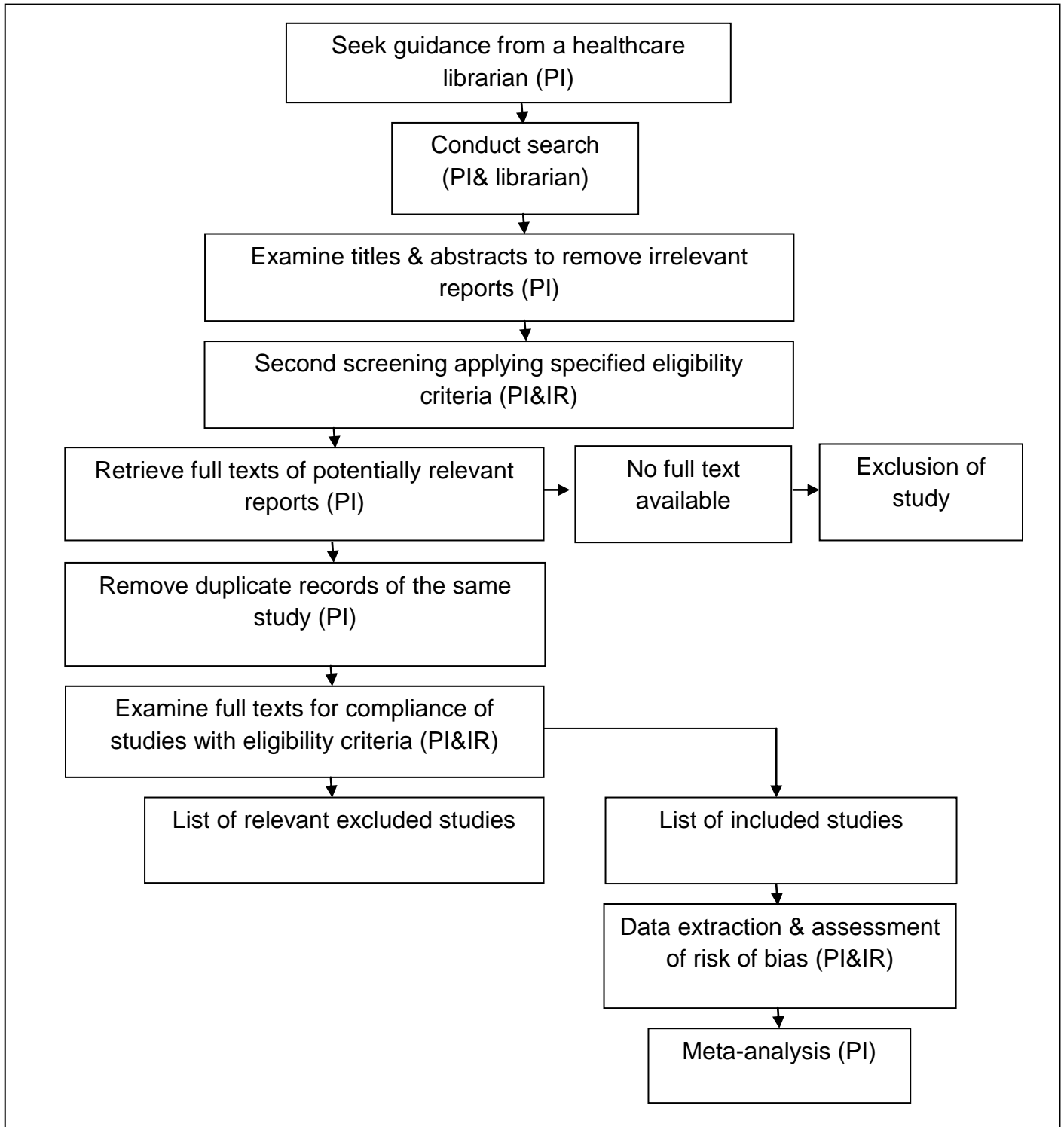
Multiple reports of the same study were linked together and duplicate records were removed by LP. These were identified by looking for the same authors in different order, similar inclusion and exclusion criteria, reports of studies done with the same name or acronym, in the same place, at the same time, as well as via results tables that look familiar. The full text reports were then scrutinized by LP and JK to assess which studies complied with the eligibility criteria (Table 2.1) in phase 2 of the selection process. If not, they were listed together with reason/s for exclusion (Table 3.5). Disagreements on inclusion/exclusion in phase 1 and 2 selection were resolved through discussion and consensus data. Arbitration by a third person was not required.

Table 2.1: Phase 1 and phase 2 eligibility criteria

Phase 1 Criteria: Liberal screening of titles and abstracts	Phase 2 Additional Criteria: Application to full texts
Inclusion Criteria	
<ul style="list-style-type: none"> • Human subjects on CoQ10 supplementation as well as statin therapy, which includes all registered oral HMG CoA reductase inhibitors (i.e. atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin and simvastatin) • There was a control group • English language studies 	<ul style="list-style-type: none"> • Participants were experiencing symptoms of myopathy identified by muscular weakness, pain and/or cramps that are caused by statin therapy • The statin therapy was taken in any prescribed dosage for any duration • The control was a placebo, similar antioxidant or no intervention • The efficacy of CoQ10 supplementation in statin-induced myopathy was measured by improvement in symptoms of myopathy and/or plasma CK levels • The participants were human adults (mean of 18-64.99 years)¹⁷⁴ • Patients used CoQ10 supplementation and the control in addition to their usual medication • Randomised controlled trials (RCTs)
Exclusion Criteria	
<ul style="list-style-type: none"> • The combination of CoQ10 as an intervention with other supplements or medication • Animal studies • No control group 	<ul style="list-style-type: none"> • Non-randomised controlled trials • Unavailable full text of the report • Participants with clinical evidence of other serious medical conditions such as hepatic, renal or endocrine disease

2.6.2. Data Extraction and Management

Data extraction forms (Addendum A) were developed following the Cochrane Collaboration's checklist of items for selecting studies and collecting data detailing the study source, eligibility, methods, participants, interventions, outcomes, results and other miscellaneous points such as references to other relevant studies.¹⁷⁵ The forms were piloted by JK using a representative sample of the studies to be reviewed – two RCTs were randomly selected from the list of included studies for this purpose. JK was trained in using the data extraction form.



PI: Principal Investigator, IR: Independent Reviewer

Figure 2.1: Flow diagram detailing the process of selection of studies

Data was extracted by LP and JK from the full text of published reports and, where possible by contacting the original researchers via electronic mail for missing data or additional information regarding methodology used. LP and JK extracted the data in a blinded fashion. Disagreement was resolved through discussion and consensus data. Arbitration by a third person was not required.

2.6.3. Assessment of Risk of Bias in Included Studies

The assessment of risk of bias form (Table 2.2) was adapted from the Cochrane Collaboration's tool for assessing risk of bias in included studies.¹⁷⁶ This was a two-part tool addressing the following six domains of methodological design: sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting and 'other sources of bias'. The first part of the tool involved a description of what was reported to have happened for each domain. Where appropriate, the description of methodology was quoted by LP and JK from the published full text report and/or from e-mail correspondence with the original researcher. The second part of the tool assigned a judgment given by LP and JK relating to the risk of bias for that domain. A question regarding the methodology of each included study for each domain was indicated on the risk of bias form to ease the judgment of LP and JK respectively. A judgment of 'yes' (low risk of bias), 'no' (high risk of bias) or 'unclear' (insufficient detail is reported to make a judgment) was given for each domain.

LP and JK piloted the tool prior to assessment for the risk of bias to ensure that criteria were applied consistently and that consensus could be reached. Representative samples of studies were reviewed - two RCTs were randomly selected from the list of included studies for this purpose. The risk of bias form adapted by LP and JK can be seen in Addendum B.

The risk of bias was assessed by LP and JK in a blinded fashion. Disagreements in risk assessment were resolved through discussion and consensus. Arbitration by a third person was not required.

Table 2.2: Example of the Cochrane Collaboration's tool for assessing risk of bias

Domain	Description	Review Author's Judgment
Sequence generation	The methods used for sequence generation	<p>Was the allocation sequence adequately generated?</p> <p>Unclear (unclear or unknown risk of bias):</p> <ul style="list-style-type: none"> • Insufficient information <p>No (high risk of bias):</p> <ul style="list-style-type: none"> • Odd or even date of birth • Date/day of admission • Hospital or clinic record number • Allocation by judgment of physician • Allocation by preference of participant • Allocation based on the result of a laboratory test • Allocation by availability of intervention <p>Yes (low risk of bias):</p> <ul style="list-style-type: none"> • Random number table • Coin tossing • Computer random number generator • Shuffling cards or envelopes • Throwing dice • Drawing of lots • Minimization

Domain	Description	Review Author's Judgment
Allocation concealment	The allocation sequence method used	<p>Was the allocation sequence method used sufficient to conceal the intervention allocations?</p> <p>Unclear (unclear or unknown risk of bias):</p> <ul style="list-style-type: none"> • Insufficient information (method not described) <p>No (high risk of bias):</p> <ul style="list-style-type: none"> • Using an open random allocation schedule (e.g. a list of random numbers) • Assignment envelopes were used without appropriate safeguarding (e.g. unsealed, non-opaque, non-sequentially numbered) • Alternation or rotation • Date of birth • Case record number • Any other unconcealed method <p>Yes (low risk of bias):</p> <ul style="list-style-type: none"> • Central allocation (telephone, web-based and pharmacy-controlled randomization) • Sequentially numbered drug containers of identical appearance • Sequentially numbered, opaque, sealed envelopes
Blinding of participants, personnel and outcome assessors	Describe all measures used	<p>Was knowledge of the allocated intervention adequately prevented during the study?</p> <p>Unclear (unclear or unknown risk of bias):</p> <ul style="list-style-type: none"> • Insufficient information <p>No (high risk of bias):</p> <ul style="list-style-type: none"> • No/incomplete blinding, and the outcome or outcome measurement is likely to be influenced by lack of blinding • Blinding attempted but may have been broken • Participants/key study personnel were not blinded, and the non-blinding of others likely to introduce bias <p>Yes (low risk of bias):</p> <ul style="list-style-type: none"> • No blinding - but the outcome and the outcome measurement are not likely to be influenced by lack of binding • Blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken • Either participants or some key study personnel were not blinded, but outcome assessment was blinded and the non-blinding of others unlikely to introduce bias

Domain	Description	Review Author's Judgment
Selective outcome reporting	Describe how selective outcome reporting was examined and findings?	<p>Are reports of the study free of suggestion of selective outcome reporting?</p> <p>Unclear (unclear or unknown risk of bias):</p> <ul style="list-style-type: none"> • Insufficient information • Study did not address the outcome <p>No (high risk of bias):</p> <ul style="list-style-type: none"> • Not all pre-specified primary outcomes have been reported • One or more primary outcome is reported using measurements, analysis methods or subsets of data that were not pre-specified • One or more reported primary outcomes were not pre-specified (unless justification is provided) • One or more outcomes of interest are reported incompletely • Study fails to include results for a key outcome that would be expected to have been reported <p>Yes (low risk of bias):</p> <ul style="list-style-type: none"> • Study protocol is available, primary and secondary outcomes are reported in the pre-specified way • Study protocol is not available, but it is clear that the published reports include all expected outcomes, including those that were pre-specified
Other sources of bias	Other sources of bias not addressed by other domains	<p>Was the study free of other sources of bias?</p> <p>Unclear (unclear or unknown risk of bias):</p> <ul style="list-style-type: none"> • Insufficient information • Insufficient rationale or evidence that the identified problem will introduce bias <p>No (high risk of bias):</p> <ul style="list-style-type: none"> • Potential source of bias related to the study design • Study stopped early due to some data-dependent process • Extreme baseline imbalance • Study is claimed to be fraudulent • Any other problem <p>Yes (low risk of bias):</p> <ul style="list-style-type: none"> • Free of other sources of bias

Source: Cochrane Handbook for Systematic Reviews of Interventions (2008)¹⁷⁷

2.6.4. Data Analysis and Undertaking Meta-Analyses

A meta-analysis was anticipated using the Cochrane review writing software (RevMan 5) to collate results of studies reporting on the efficacy of CoQ10 versus a comparator during statin therapy.

The meta-analysis was planned to determine the direction and size of the effect and whether the effect is consistent across the studies. In consultation with the statistician it was, however, decided that a meta-analysis was not feasible as results from one of the included studies were expressed as means with standard deviations (SDs), and results from the other RCT were expressed as medians with interquartile ranges (IQRs). The results from each study were therefore reported separately and no data synthesis was performed.

2.6.5. Measures of Treatment Effect

Where possible, risk ratios (RR) would have been calculated for the dichotomous outcomes, namely the adverse effects of CoQ10 supplementation. Mean differences (MD) would have been calculated for the continuous outcomes, namely plasma CK levels, intramuscular and plasma CoQ10 levels as well as myopathic pain. Results were to be presented with corresponding 95% confidence intervals. Continuous outcomes reported as medians and interquartile ranges (IQR) were presented in tables.

2.6.6. Unit of Analysis Issues

No cluster randomised trials, cross-over trials, or trials with multiple treatment arms were found in the process of selection of studies, therefore no unit of analysis issues were encountered.

2.6.7. Dealing with Missing Data

The study authors were contacted via electronic mail to request relevant missing or unclear data. Joanna Young was contacted in October 2011 to request information regarding one missing participant in the results of her study. She responded that one patient did not return his/her diary containing visual analogue scales that documented symptoms of myalgia, which

resulted in his/her exclusion from the study. An intention to treat (ITT) analysis was planned for any data that may have been missing.

2.6.8. Assessment of Heterogeneity

Since a meta-analysis was not performed, no assessment of heterogeneity was done. The following procedure was, however, initially planned:

A Chi-squared statistical test for heterogeneity and the I^2 test would have been used across all included studies to quantify inconsistency (significance level $P < 0.1$). The importance of the I^2 value is related to the magnitude and direction of the effects as well as the strength of evidence for heterogeneity, determined by the confidence interval. If heterogeneity is identified, the cause/s must be established and if it cannot be explained, a random-effects meta-analysis must be used.

The following guidelines would have been used for the interpretation of the I^2 values:¹⁷⁸

- 0% to 40%: may not be important
- 30% to 60%: may represent moderate heterogeneity
- 50% to 90%: may represent substantial heterogeneity
- 75% to 100%: considerable heterogeneity

Possible sources of heterogeneity would have been explored further through the following sub-groups in data-analysis:

- Different measurement tool/s for myopathy between studies
- Different statin use in participants (simvastatin, atorvastatin, pravastatin, fluvastatin or lovastatin)
- Varying statin dosages in participants (low dose vs. high dose)
- Different duration of intervention between studies
- Varying CoQ10 supplementation dosages (low dose vs. high dose) in participants

2.6.9. Assessment of Reporting Biases

Reporting bias include publication, time lag, multiple publication, location, citation, language and outcome reporting biases. Detecting reporting biases can be done by means of funnel plots. These can, however, only be used if there are more than 10 studies included in the meta-analysis.¹⁷⁹ Since there were only two included studies and a meta-analysis was not performed as planned, no assessment of reporting biases was done.

2.6.10. Data Synthesis

A meta-analysis was planned to summarize the effectiveness of the experimental intervention by using Cochrane review writing software (RevMan 5). The random-effects method of meta-analysis would have been used on the assumption that the different studies estimated different, yet related, intervention effects.

2.6.11. Subgroup Analysis and Investigation of Heterogeneity

A subgroup analysis on the dose or duration of CoQ10 supplementation and/or statin therapy was planned using RevMan but was not feasible as a meta-analysis was not performed. A subgroup analysis could have been conducted on participant gender and/or statin dose, although statin dose may have been more relevant as a higher dose may increase patient risk to symptoms of myopathy.

2.6.12. Sensitivity Analysis

No sensitivity analysis was done because a meta-analysis was not performed as planned.

2.7. ETHICS/LEGAL ASPECTS/REGISTRATION INFORMATION

Ethics approval was obtained in March 2011, ethical review was not required as the study is a systematic review. Ethics Reference number: N11/03/087 (Addendum C).

CHAPTER 3: RESULTS

3.1. RESULTS OF THE SEARCHES

Two searches for studies were conducted as a considerable period of time passed between the initial search and the commencement of the review. The initial searches took place between March and April 2011 (Table 3.1), and the second searches took place between November 2011 and February 2012 (Table 3.2). The initial and second searches were completed independent of each other, and were each dated from inception. Both searches used the same databases and search strings. The aim of the second searches, however, was to identify any new records additional to those found in the initial searches. Thus, if the same records were found after the removal of duplicates and as well as after the screening of titles and abstracts, they were excluded. Duplicates of studies were defined as the repetition of a record across the 11 databases searched in the initial and second searches respectively.

3.1.1. Initial Searches

From 11 databases (section 3.3.1), 474 records were cited. The abstracts of the studies of Kelly et al (2005)¹⁹⁰ and Fedako (2009)¹⁸¹ were identified by means of hand-searching. After the removal of duplicate records, 353 records remained. After screening of the 353 titles and abstracts (phase 1, Table 2.1), only 5 records remained. Five full texts were retrieved for further evaluation according to eligibility criteria (phase 2, Table 3.1), however only 2 studies met the inclusion criteria and were included in the qualitative and quantitative synthesis.

3.1.2. Second Searches

From 11 databases, 951 records were retrieved. After the removal of duplicate records, 864 records remained. After screening of the 864 titles and abstracts (phase 1, Table 2.1), no records, additional to initial search outcome, were identified. The second search for studies thus did not identify any new studies for inclusion in the review.

Adaptations to the search string were done specifically to ensure that the maximum numbers of studies were found in the respective databases. The original search string was adapted in the March 2011 search in Scopus, as well as the March/April 2011 and February 2012 searches in the Wiley Online Library as well as SpringerLink (as shown in Tables 3.1 and 3.2).

Table 3.1: Citation list of titles and abstracts retrieved from database searches between March and April 2011

Database	Date searched	Search string	Total number retrieved to be screened
PubMed	Inception to 29/03/2011	(Statin OR HMG CoA Reductase Inhibitor OR Atorvastatin OR Fluvastatin OR Lovastatin OR Pravastatin OR Rosuvastatin) and (Myopathy OR Myalgia OR rhabdomyolysis OR muscle* OR muscular) and (coenzyme Q10 OR CoQ10 or Q10 OR Ubiquinone OR Ubicarenone)	36
Web of Knowledge			78
Cochrane Library			12
CINAHL			7
Academic Search Premier			10
CAB Abstracts			2
Google Scholar			148
ScienceDirect			59
Scopus			(coenzyme* Q10) AND supplement* AND (treat* OR therap* OR manage*) AND (statin-induced myopathy) AND (clinical trial* OR randomised control* trial*)
Wiley Online Library	Inception to 05/04/2011	(coenzyme Q10) in All Fields AND supplement* in All Fields AND treatment in All Fields AND (statin-induced myopathy) in All Fields	32
SpringerLink			18

Table 3.2: Citation list of titles and abstracts retrieved from database searches between November 2011 and February 2012

Database	Date searched	Search string	Total number retrieved to be screened
PubMed	Inception to 14/11/2011	(statin OR HMG CoA reductase inhibitor OR atorvastatin OR fluvastatin OR lovastatin OR pravastatin OR rosuvastatin) AND (myopathy OR myalgia OR rhabdomyolysis OR muscle* OR muscular) AND (coenzyme Q10 OR CoQ10 OR Q10 OR ubiquinone OR ubidecarenone)	19
Web of Knowledge			44
Cochrane Library			3
CINAHL			8
Academic Search Premier	Inception to 15/02/2012		10
CAB Abstracts			12
Google Scholar			665
ScienceDirect			33
Scopus	Inception to 14/11/2011		102
Wiley Online Library	Inception to 15/02/2012		(coenzyme Q10) in All Fields AND supplement* in All Fields AND treatment in All Fields AND (statin-induced myopathy) in All Fields
SpringerLink		18	

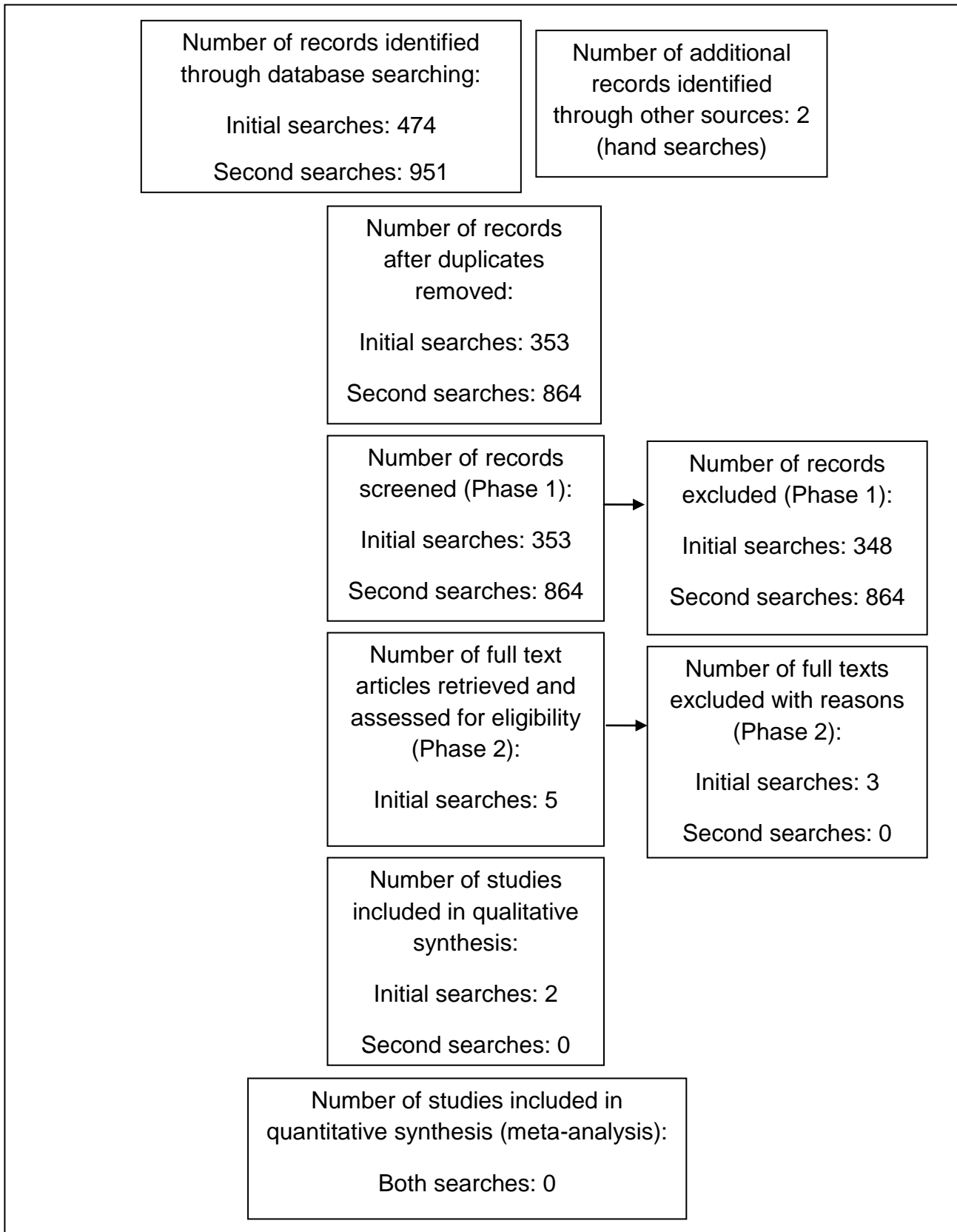


Figure 3.1: Flow diagram detailing the searches for studies

3.2. DESCRIPTION OF STUDIES

3.2.1. Included Studies

Two RCTs [Caso (2007)⁷⁰ and Young et al (2007)²⁷] met all of the inclusion criteria. The characteristics of these two studies are summarized in Table 3.6.

3.2.1.1. Study Types

Caso (2007)⁷⁰ conducted a double-blind, randomised, controlled trial and Young et al (2007)²⁷ a double-blind, placebo-controlled pilot study.

3.2.1.2. Participants

Participants were aged 59 \pm 2 years in the intervention and control groups in the study of Young et al (2007)²⁷, and 58 \pm 2 years and 64 \pm 2 years in the control and intervention groups respectively in the study of Caso (2007)⁷⁰. Participants in both included studies were of male and female gender. Race/ethnic groups were not indicated in either of the studies.

The participants in the study of Caso (2007)⁷⁰ were treated for hyperlipidemia with different types of statins (Table 3.3) at varying doses (Table 3.4) and were under the Adult Treatment Panel III/National Cholesterol Education Program. All participants reported myopathic symptoms. Patients were enrolled only if no other identifiable cause of myopathy could be determined and any patients with clinical evidence of hepatic, vascular, renal, or endocrine disease; coagulopathy; or other serious medical conditions were excluded. None of the patients enrolled in this study had been using CoQ10, vitamin E or anticoagulants before starting the study. The participants in the study of Young et al (2007)²⁷ had self-reported myalgia and were unable to continue taking adequate doses of statin therapy. Participants were using only simvastatin titrated from 10 mg/day to 40 mg/day in 4-weekly intervals. Patients were not enrolled if an acute myocardial infarction or cerebral vascular accident had been experienced within the previous 3 months, if alanine aminotransferase or aspartate aminotransferase were >3 times the upper level of normal, if calculated glomerular filtration

rate was <45 ml/min, if the patient had decompensated heart failure, was treated with warfarin, and if the patient was using antioxidant vitamin supplementation.

Table 3.3: Statin types used in the study of Caso (2007)⁷⁰

Type of statin used	No. patients in the CoQ10 group (n=18)	No. patients in the control (Vitamin E) group (n=14)
Atorvastatin	4	3
Lovastatin	1	0
Pravastatin	2	0
Simvastatin	11	11

Table 3.4: Statin doses used in the study of Caso (2007)⁷⁰

Statin dose (mg/day)	No. patients in the CoQ10 group (n=18)	No. patients in the control (Vitamin E) group (n=14)
10 to 20	9	9
≥40	9	5

3.2.1.3. Interventions

CoQ10 was the intervention used in both included studies. The CoQ10 supplements were taken once daily, however, neither of the studies indicated the method of administration of CoQ10, so it is unknown at what time of the day (and relation to meal times) the supplements were taken, whether they were in capsule or powder form, or whether they were mixed or swallowed with a particular beverage (e.g. water or fruit juice).

3.2.1.4. Controls

The control used in the study of Caso (2007)⁷⁰ was in the form of Vitamin E, which served to control for the antioxidant properties of CoQ10, and was also similar in appearance. The control in the study of Young et al (2007)²⁷ is in the form of a placebo.

3.2.1.5. Funding

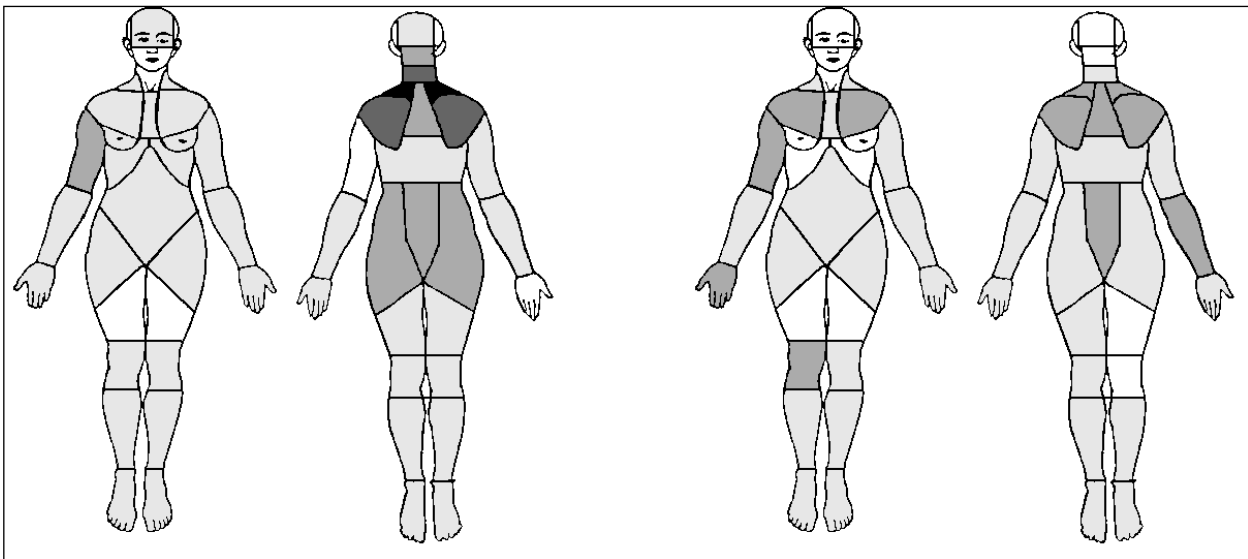
The study of Caso (2007)⁷⁰ was supported in part by a grant from the National Institutes of Health, Bethesda, Maryland, and the New York State Empire Clinical Research Investigator Program, Albany, New York. Joanna Young was contacted via electronic mail to obtain information regarding the funding of the study; however a response was not received.

3.2.1.6. Measurement Tools for Myopathy

In the study of Caso (2007)⁷⁰, symptoms of myopathy were defined as the presence of muscle pain alone or accompanied by other symptoms such as muscle weakness and fatigue. Symptoms of myopathy and their interference with patients' daily activities were evaluated before and after the intervention using the BPI questionnaire (Table 3.5). It includes a body diagram for localization of pain, 4 items to measure pain intensity in the previous 24 hours ("pain worst," "pain least," "pain average," and "pain now") rated on a numeric scale of 0 to 10 (i.e., 0 = "no pain" and 10 = "pain as bad as you can imagine"), and 7 items measuring pain interference with daily life in the previous 24 hours (i.e., general activity, mood, walking, working, relations with others, sleeping, and enjoyment of life), also rated on a 0 to 10 scale (i.e., 0 = "does not interfere" and 10 = "completely interferes"). Pain intensity was assessed by calculating a PSS, computed by averaging scores of the 4 pain intensity items. Similarly, the impact of pain on daily living activities and well-being was assessed by calculating a PIS, obtained by averaging ratings of the 7 interference items.

In the study of Young et al (2007)²⁷, severe myalgia was defined as the inability to tolerate a statin dose of 20 to 40 mg/day within 1 month of commencement, and moderate myalgia was defined as the development of myalgic symptoms at doses ≥ 20 mg/day after more than 1 month. The VAS (Table 3.5), which was used to measure myopathy, was adapted from

Landstad (2001)¹⁸², which is a descriptive study of the occurrence of pain in hospital cleaners and home-help personnel. The questionnaire used in Landstad (2001)¹⁸² contained questions about the frequency of pain and rating of perceived intensity of pain [VAS for “worst”, “least” and “present” pain were used]. The subjects indicated the location of their pain on diagrams (Figure 3.2), and categorization was based on the number of subjects (percentage) who had made a pain mark in each area of the body. These frequency intervals were evenly divided into 1–18%, 19–36%, 37–54% and 55–72%, plus a zero category. Twenty-three areas were combined to constitute the neck–shoulder–upper extremity region, nine areas constituted the lumbosacral spine–thigh region and 12 areas constituted the knee–lower leg–foot region. The intensity of pain was measured using a pain scale from 0mm (no pain) to 100mm (worst pain).



Twenty-three areas were combined - categorisation was based on the number of subjects who made a mark in each area.

Figure 3.2: Example of a diagram for self-administered location of pain

Source: Landstad (2001)¹⁸²

Table 3.5: Measurement tools for myopathy in the study of Caso (2007)⁷⁰ and Young et al (2007)²⁷

	Brief Pain Inventory Caso (2007)⁷⁰	Visual Analogue Scale Young et al (2007)²⁷
Frequency of assessment	At baseline and after the intervention	Daily
Method of administration	Self-administered	Self-administered
Scales used	<ul style="list-style-type: none"> • Pain intensity (0="no pain" to 10="pain as bad as you can imagine") • Pain interference with daily activities (0="no interference" to 10="completely interferes") 	Pain Intensity (0-100mm)
Particulars measured	<ul style="list-style-type: none"> • Localization of pain (a body diagram is given for indication) • Pain interference with daily activities (e.g. mood, walking and sleeping) (PIS) • Pain severity (PSS) 	<ul style="list-style-type: none"> • Number of sites on the body that are affected • Pain intensity (mm)

Table 3.6: Particulars of studies included in the review

Study	Intervention	Control	Participants	Methods	Evaluation of myopathy	Outcomes
Caso (2007) ⁷⁰	CoQ10 (Q-Sorb softgel), 100mg once daily	Vitamin E (softgel), 400IU once daily	32 male and female adult (59 \pm 2 years in intervention and control group) outpatients (ethnicity not indicated), Stony Brook University, New York	RCT, 30 days	Brief Pain Inventory questionnaire. Pain intensity assessed by calculating a Pain Severity Score (PSS)	To determine whether CoQ10 supplementation would reduce the degree of muscle pain associated with statin treatment. Pain severity and interference with daily activities were reported
Young et al (2007) ²⁷	CoQ10 (Q-Gel), 200mg once daily	Placebo	44 male and female adult (58 \pm 3 years in intervention group; 64 \pm 2 years in control group) outpatients (ethnicity not indicated), New Zealand	RCT, 12 weeks	Visual analogue scale adapted from Landstad et al., intensity of pain rated 0 (no pain) to 100 (worst pain) measured daily, no. of sites affected	No. of patients who tolerated simvastatin 40mg/day at 12 weeks, no. of patients remaining on simvastatin therapy and change in myalgia scores

3.2.2. Excluded Studies

Abstracts of two RCTs^{180,181} complied with phase 1 eligibility criteria. Unfortunately the full text reports of these two studies could not be sourced, which excluded them from the review. The summary of these two abstracts in Table 3.7 shows that they may have been relevant for inclusion in this review. Three studies were excluded from the review due to reasons relating to study design and outcomes measured (Table 3.8).^{172,183,184}

Table 3.7: Particulars of studies with no available full text

Study	Intervention	Control	Participants	Methods	Evaluation of myopathy	Outcomes
Kelly et al (2005) ¹⁸⁰	CoQ10, 100mg daily	Vitamin E, 400IU once daily	41 patients, University of Wisconsin	RCT, 30 days	Pain score	Mean pain scores are reported
Fedako (2009) ¹⁸¹	CoQ10 (dose not indicated) vs. placebo	Selenium vs. placebo	60 patients, single centre, Kosice (Slovakia)	Double-blind RCT, 2x2 factorial design, 3 months	Reported symptoms: pain, muscle weakness, tiredness and cramps	Change in plasma CoQ10 and improved symptoms of statin-associated myopathy are reported

In the study of Langsjoen (2005)¹⁷² patients on statin therapy were evaluated for possible adverse effects, including myalgia and fatigue, amongst other. The prevalence of patient symptoms on initial visit and on most recent follow-up (an average of 22.4 months later) demonstrated a decrease in fatigue from 84% to 16%, and myalgia from 64% to 6%. Although the study explored the efficacy of CoQ10 for side effects of statins, including myalgia, the study is not a RCT and statin therapy was discontinued when CoQ10 supplementation commenced (two simultaneous interventions) – the predominant reasons for exclusion of the study in the review.

The study of Glover et al (2010)¹⁸³ was on patients with mitochondrial disease recruited from the Neuromuscular/Neurometabolic Clinic at McMaster University Medical Centre. Although plasma CoQ10 and CK were measured, main outcomes related to CoQ10 and cycle ergometry (V_{O_2} and lactate), magnetic resonance spectroscopy (MRS), activities of daily living (ADL) and quality of life (QOL). The study was excluded from the review as the said mitochondrial disorders were not statin-induced and benefits of CoQ10 related to exercise performance, not symptoms of myopathy.

The study of Mabuchi et al (2007)¹⁸⁴ examined the effects of CoQ10 and placebo in the hypercholesterolaemic patient treated with atorvastatin. Adverse effects were recorded throughout the treatment phase. Unfortunately outcomes of the study were not related to the side effects of statin use: changes in total cholesterol, plasma LDL-C levels, serum

triglycerides, apolipoprotein A1 and B, as well as plasma total CoQ10, ubiquinol-10 and ubiquinone-10 were measured. No complaints of myalgia or muscle weakness were found, which is the main area of interest in the current review. Although the study is a RCT, the main reason for exclusion is because patients were not experiencing symptoms of myopathy at baseline.

Table 3.8: Particulars of studies excluded from the review

Study	Intervention	Control	Participants	Methods	Outcomes	Reasons for exclusion
Langsjoen (2005) ¹⁷²	CoQ10, 240mg once daily	No control	50 male and female adult and elderly (44-84 years, mean age of 66 years) outpatients, Texas USA	Prospective analysis, average of 22.4 months follow-up (between 2 and 41 months)	Prevalence of statin adverse effects were reported	<ul style="list-style-type: none"> • Not a RCT • Patients' mean age was not between 18 and 64.99 years • Efficacy of CoQ10 not measured • Patients not experiencing myopathic symptoms at baseline
Glover et al (2010) ¹⁸³	CoQ10 (Q-Gel), 600mg twice daily	Placebo (soybean oil)	30 male and female adults (48±3 years in MELAS group; 56±3 years in the control group), Canada	Double-blind, placebo-controlled cross over study, 60 days with mean 67 ± 8.3 days washout between trials	Cycle exercise aerobic capacity, post-exercise lactate, resting lactate and strength were reported	<ul style="list-style-type: none"> • Patients not experiencing myopathic symptoms • Patients not on statin therapy
Mabuchi et al (2007) ¹⁸⁴	CoQ10, 100mg once daily	Placebo (safflower oil)	49 male and female adult and elderly (60±8 years in intervention group; 61±8 years in control group) outpatients, Japan	RCT, 12 weeks	Effect of Atorvastatin on plasma CoQ10, AST, ALT and CK were reported	<ul style="list-style-type: none"> • Patients not experiencing myopathic symptoms

3.3. RISK OF BIAS IN INCLUDED STUDIES

The Cochrane Collaboration's tool for assessing risk of bias in included studies was used to assess the risk of bias.¹⁸⁵ The two-part tool addressed the following six domains of methodological design: sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting and 'other sources of bias'.

3.3.1. Sequence Generation

In the study of Caso (2007)⁷⁰, randomization of the dispensing of supplements was carried out by the pharmacist without contact with the patients – sequence generation was thus adequate. In the study of Young et al (2007)²⁷, randomization was performed in permutation blocks of size-6 from a computer-generated randomization list by an independent statistician - sequence generation was thus also adequate.

3.3.2. Allocation Concealment

In the study of Caso (2007)⁷⁰, allocation concealment is adequate as the pharmacist from the research centre who dispensed the supplements did not have contact with the patients. In the study of Young et al (2007)²⁷, study treatments were dispensed by an independent hospital pharmacist in identical numbered bottles, with the lowest available number allocated to each sequential participant. Allocation concealment was thus also adequate.

3.3.3. Blinding

In the study of Caso (2007)⁷⁰, adequate blinding of the study was confirmed: "randomization and dispensing of supplements was carried out by the pharmacist at the General Clinical Research Centre at Stony Brook University without direct contact with patients, and patients as well as investigators were blinded throughout the protocol to which supplement was administered to whom". The study of Young et al (2007)²⁷ is double-blinded – identically matched placebo and CoQ10 capsules were used and no access to the CoQ10 results were allowed until the study was un-blinded.

3.3.4. Incomplete Outcome Data

No incomplete outcome data was identified in the study of Caso (2007)⁷⁰. In the study of Young et al (2007)²⁷, only one patient's results were not reported. Details from author correspondence confirmed that this patient did not return his/her diary containing visual analogue scales that documented myalgia symptoms – no re-inclusions in the analyses were performed by the review authors.

3.3.5. Selective Outcome Reporting

The studies of Caso (2007)⁷⁰ and Young et al (2007)²⁷ are free of selective outcome reporting.

3.3.6. Other Sources of Bias

No other sources of bias were identified.

In summary, the study of Caso (2007)⁷⁰ has mostly a low risk of bias as risk of bias was low for six of the seven domains (Figure 3.3 and 3.4, Table 3.9). In the study of Young et al (2007)²⁷, information regarding the risk of bias was obtained via author correspondence. This study has mostly a low risk of bias as risk of bias was low for six of the seven domains (Figure 3.3 and 3.4, Table 3.10). Blinding of outcome assessment was unclear for both studies, which may introduce detection and/or performance bias.

Table 3.9: Risk of bias in the study of Caso (2007)⁷⁰

	Judgement: Yes (low risk of bias)/ No (high risk of bias)/ Unclear	Description
Adequate Sequence Generation	Yes	Quote: “randomization and dispensing of supplements was carried out by the pharmacist at the General Clinical Research Centre at Stony Brook University without direct contact with patients” Comment: the key word here is “randomization”
Adequate Allocation Concealment	Yes	Quote: “randomization and dispensing of supplements was carried out by the pharmacist at the General Clinical Research Centre at Stony Brook University without direct contact with patients”
Blinding of participants and personnel	Yes	Quote 1: “double-blind randomised study” Quote 2: “patients as well as investigators were blinded throughout the protocol to which supplement was administered to whom”
Blinding of outcome assessment	Unclear	Insufficient information given
No Incomplete Outcome Data	Yes	All outcome data reported in study results
No Selective Outcome Reporting	Yes	All outcomes reported in study results
Other sources of bias	Yes	No other sources of bias detected

Table 3.10: Risk of bias in the study of Young et al (2007)²⁷

	Judgement: Yes (low risk of bias)/ No (high risk of bias)/ Unclear	Description
Adequate Sequence Generation	Yes	Quote from author correspondence: “randomization was performed in permutation blocks of size-6 from a computer-generated randomization list by an independent statistician”
Adequate Allocation Concealment	Yes	Quote from author correspondence: “study treatments were dispensed by an independent hospital pharmacist in identical numbered bottles, with the lowest available number allocated to each sequential participant.”
Blinding of participants and personnel	Yes	Quote: “double-blinded, placebo-controlled pilot study” Quote from author correspondence: “identically matched placebo and CoQ10 capsules were used and no access to the CoQ10 results were allowed until the study was unblinded”
Blinding of outcome assessment	Unclear	Insufficient information given
No Incomplete Outcome Data	Yes	All outcome data reported in study results
No Selective Outcome Reporting	Yes	All outcomes reported in study results
Other sources of bias	Yes	No other sources of bias detected

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Caso 2007	+	+	+	?	+	+	+
Young 2007	+	+	+	?	+	+	+

Figure 3.3. Risk of bias summary: review authors' judgments about each risk of bias item for Caso (2007)⁷⁰ and Young et al (2007)²⁷

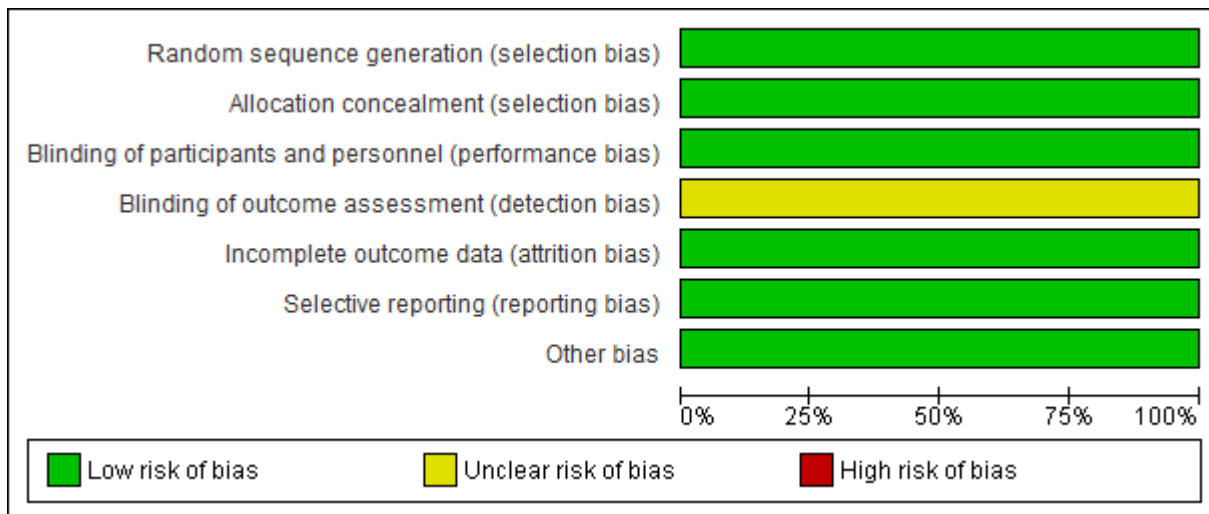


Figure 3.4. Risk of bias graph: review authors' judgments about each risk of bias item presented as percentages

3.4. EFFECTS OF INTERVENTIONS

3.4.1. Primary Objectives

3.4.1.1. The severity of statin-induced myopathic symptoms

The study of Caso (2007)⁷⁰ evaluated myopathic pain using the BPI questionnaire before and after treatment and rated pain intensity on a VAS of 0 (no pain) to 10cm (worst pain). Results were reported in terms of PSS, which is the average of pain intensity scores of the four pain intensity items. Supplementation with CoQ10 significantly improved the severity of myopathic pain compared to the control group, as measured by the change in PSS after minus before supplementation (MD 2.37, 95%CI: 1.29 to 3.45, 1 trial, 32 participants, Figure 3.5, Table 3.11). Significantly more participants in the CoQ10 group reported pain relief compared to the control group (RR 4.15, 95%CI: 1.50 to 11.46, 1 trial, 32 participants, Figure 3.6). Pain relief included a decrease in pain, ache, burning sensation and overall muscle fatigue. The authors concluded that these findings suggest that CoQ10 may be beneficial for patients using statins by ameliorating myopathic symptoms and improving subject’s well-being and functioning in daily life activities.

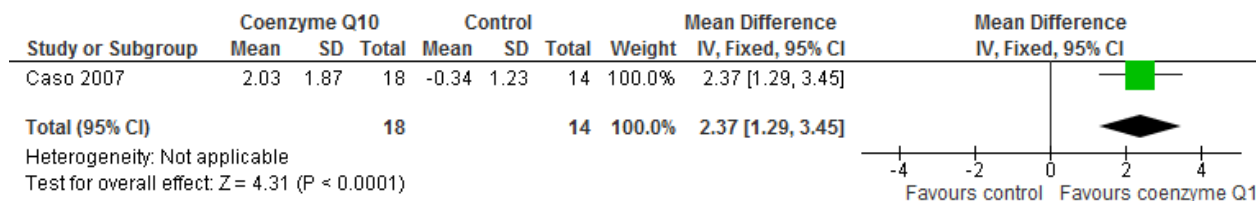


Figure 3.5: Forest plot of the comparison of CoQ10 versus controls for severity of myopathic symptoms

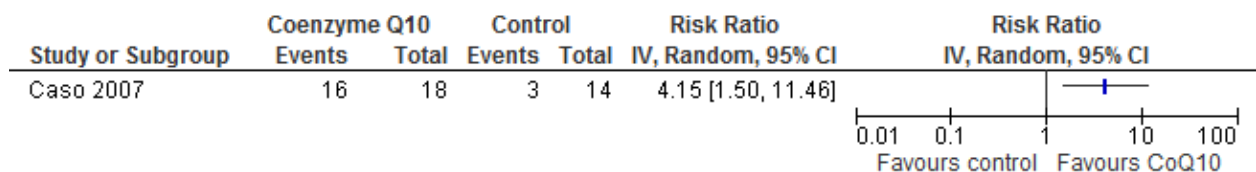


Figure 3.6: Forest plot of the comparison of CoQ10 versus controls for the number of participants reporting decrease in pain

The study of Young et al (2007)²⁷ assessed myalgia daily using a VAS of 0 (no pain) to 100mm (worst pain) adapted from Landstad (2001)¹⁸² and reported the change in these myalgia scores. The study authors reported that although there were significant increases in myalgia score from baseline to the end of study for both the CoQ10 and placebo groups, there were no significant differences in changes between the two groups ($p=0.63$, 43 participants, 1 trial, Table 3.12). When adjusted for the number of sites affected by pain, the pain score increased by a median (IQR) of 4.2mm (1.0 to 6.4) in the CoQ10 group and 2.1mm (0 to 11.4) in the control group – there remained no difference between the two groups ($p=0.73$). The authors concluded they could not demonstrate any significant beneficial effect of oral CoQ10 supplementation on simvastatin tolerability and myalgic symptoms in patients.

Table 3.11: Results of intervention on pain severity score and plasma creatine kinase levels (Caso 2007)⁷⁰

Outcome	Study ID	Results						Comment
		Intervention (n=18)			Control (n=14)			
		Baseline Mean (SD)	Study End Mean (SD)	Change Mean (SD)	Baseline Mean (SD)	Study End Mean (SD)	Change Mean (SD)	
Pain Severity Score (PSS)	Caso (2007) ⁷⁰	5 (1.44)	2.97 (2.04)	2.03 (1.87)	4.39 (2.24)	4.73 (2.54)	-0.34 (1.23)	SD=SEM $\times\sqrt{n}$
Plasma CK (U/L)	Caso (2007) ⁷⁰	129 (63.64)	157 (97.58)	-28	133 (138.44)	103 (52.38)	30	SD=SEM $\times\sqrt{n}$

SD = standard deviation; SEM = Standard Error of the Mean; \sqrt{n} = square root of sample size

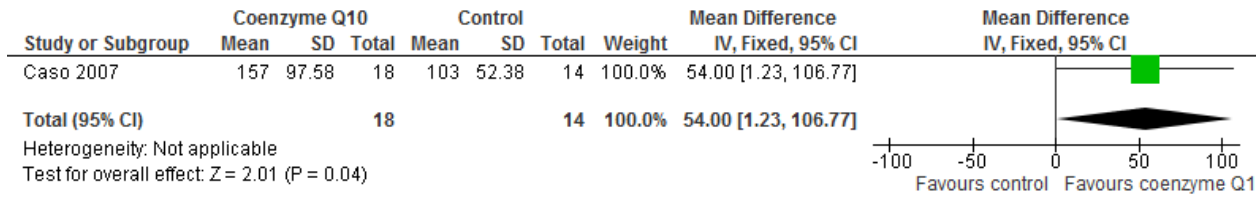


Figure 3.7: Forest plot of comparison of CoQ10 versus controls for plasma creatine kinase (U/L)

Table 3.12: Results intervention on the myalgic scale, plasma creatine kinase and CoQ10 levels Young et al (2007)²⁷

Outcome	Study ID	Results		
		Intervention	Control	p-value for difference in change between the intervention and control groups
		(n=22) Change Median (IQR)	(n=22) Change Median (IQR)	
Myalgia scale (0-100mm)	Young et al (2007) ²⁷	6.0 (2.1 to 8.8)	2.3 (0 to 12.8)	0.63
Plasma CK (U/L)	Young et al (2007) ²⁷	17 (-15 to 46)	19 (-3 to 48)	0.85
Plasma CoQ10 (µmol/L)	Young et al (2007) ²⁷	1.7 (0.3 to 2.2)	-0.5 (-0.6 to -0.3)	<0.001

3.4.1.2. The effect of CoQ10 supplementation on plasma CK levels

In Caso (2007)⁷⁰, plasma CK concentration (U/L) at the end of the intervention period was significantly higher in the CoQ10 compared to the control group (MD 54.00, 95%CI: 1.23 to 106.77, 1 trial, 32 participants, Table 3.11, Figure 3.7). There was no correlation (data not

published) between the pain score and plasma CK concentration before or after the intervention.

In the study of Young et al (2007)²⁷, there was no significant difference in changes from baseline plasma CK levels between the CoQ10 group and the placebo group ($p=0.85$, 44 participants, 1 trial, Table 3.12), no significant increase in the CoQ10 group ($p=0.14$), and a significant increase with the placebo group ($p=0.02$) from baseline to end of study.

3.4.1.3. The effect of CoQ10 supplementation on intramuscular and plasma CoQ10 levels

The study of Young et al (2007)²⁷ reported that plasma CoQ10 ($\mu\text{mol/L}$) levels significantly increased after the CoQ10 supplementation ($p<0.001$) but significantly decreased after the placebo treatment ($p<0.001$). Further, the differences between the two groups were statistically significant according to the study authors ($p<0.001$, 44 participants, 1 trial, Table 3.12). Intramuscular CoQ10 was not measured in this study.

Plasma and intramuscular CoQ10 were not measured in the study of Caso (2007)⁷⁰.

3.4.1.4. Adverse effects of CoQ10 supplementation; such as abdominal pain, nausea and vomiting or headaches

No adverse effects of CoQ10 were reported in either of the studies.

3.4.2. Secondary Objectives

3.4.2.1. The average duration of CoQ10 supplementation required to elicit a positive response

In the study of Caso (2007)⁷⁰, patient follow-up was after 30 days of intervention with CoQ10. By day 30, pain intensity decreased significantly in the CoQ10 group. However, in the study of Young et al (2007)²⁷, patient follow-up was after 12 weeks of intervention with CoQ10. By the 12th week, although pain scores had significantly increased (Table 3.12) in both the CoQ10 and the control group, there were no significant changes between the two groups. Thus, despite the longer duration of intervention in the study of Young et al (2007)²⁷, CoQ10 did not elicit a positive response.

3.4.2.2. The average dose of CoQ10 supplementation required to elicit a positive response

In the study of Caso (2007)⁷⁰, CoQ10 was given at 100 mg daily and elicited a positive response after 30 days (Table 3.11). In the study of Young et al (2007)²⁷, CoQ10 was given at 200 mg daily. Although the dose of CoQ10 given in the study of Young et al (2007)²⁷ was higher, it did not elicit a positive response (Table 3.12). Dose-response was, however, not explored in the two studies.

CHAPTER 4: DISCUSSION

4.1. SUMMARY OF THE MAIN RESULTS

In this systematic review, two small RCTs met the inclusion criteria, which included a total of 76 participants. A meta-analysis could not be performed as initially planned as one study reported results as means with SDs, and the other as medians with IQRs. The results of the two RCTs were conflicting, thus a conclusion could not be drawn regarding the efficacy of CoQ10 in statin-induced myopathy. The differences between the RCTs in terms of what they measured, how they measured it as well as other factors, such as the type and dose statins used by participants, may be reasons for the variation in results.

Only two outcomes were considered in both of the RCTs included in the review – the improvement in myopathic symptoms and the change in participants' plasma CK concentration. The study of Young et al (2007)²⁷ also measured the change in participants' plasma CoQ10. Neither RCTs measured intramuscular CoQ10, which would have been of value in adding to the limited data on the effect of CoQ10 supplementation on participants' intramuscular CoQ10 concentration, although this measurement may be regarded as an invasive procedure. No adverse effects of CoQ10 supplementation were reported between the two RCTs, which was expected as doses up to 3000 mg/day have been reported as safe and were tolerated in other study populations.^{132,155}

Dose and duration were not investigated in the included RCTs. Despite the longer study duration and higher dose of CoQ10 supplemented in the study of Young et al (2007)²⁷, myalgia significantly increased in both groups (intervention and control). In the study of Bhagavan (2006)⁷¹, plasma CoQ10 showed a gradual increase from baseline when increasing doses of CoQ10 were administered. Although the increase of plasma CoQ10 from baseline was much greater when high doses (300 to 3000 mg) of CoQ10 were given, the increase in plasma CoQ10 per 100 mg of CoQ10 ingested was much lower compared to when lower doses (30 to 300 mg) were administered. This may indicate a decrease in the efficacy of absorption when higher doses of CoQ10 are given.⁷¹ The differentiation between low/moderate dose and high doses of CoQ10 in this study were, however, arbitrary. The 100 mg difference between the CoQ10 dose in the study of Caso (2007)⁷⁰ and the study of Young et al (2007)²⁷ may also not have been sufficient to motivate the different results regarding

symptoms of myopathy. Similarly, a study duration of 30 days versus 12 weeks in the studies of Young et al (2007)²⁷ and Caso (2007)⁷⁰ respectively may also not have had an effect on the results. In the study of Hosoe (2007)¹³⁹, 90 mg, 150 mg and 300 mg of CoQ10 were administered to participants for 4 weeks. Although plasma CoQ10 levels increased more in the participants given higher doses of CoQ10 (150 and 300 mg), all participants' plasma levels reached a plateau on day 14. Although dose and duration of supplementation may have an effect on the CoQ10 plasma concentration, it is unclear whether they would affect improvement in myopathic symptoms - dose-response studies are thus yet to be explored to establish relevance.

Results from the studies of Kelly et al (2005)¹⁸⁰ and Fedacko (2009)¹⁸¹ were not included in the review as the full-text report was not available. The study of Kelly et al (2005)¹⁸⁰ was reported in a poster abstract and was not published, whereas the study of Fedacko (2009)¹⁸¹ was published in the Atherosclerosis Supplement, but a full text of the report could not be retrieved. The data obtained from the abstracts of these studies, however, appeared supportive of CoQ10 for statin-induced myopathy. The study of Kelly et al (2005)¹⁸⁰ is similar to Caso (2007)⁷⁰ as it also used 100 mg CoQ10 for 30 days. The study also reported a significant improvement in pain after supplementation with CoQ10. The study of Fedacko (2009)¹⁸¹ reported that symptoms of myopathy significantly improved in the CoQ10 group after 3 months of intervention with CoQ10, however, the CoQ10 dosage was not given in the study abstract. This should act as encouragement for authors to publish data from RCTs in order to attempt synthesis of data in future. If these studies were included in the systematic review, conclusions may have been different and most likely in favour of CoQ10 for statin-induced myopathy.

At this stage, no treatment mechanism for statin-induced myopathy exists besides cessation of statin treatment, followed by a change in statin type and/or dose relative to patient-to-patient tolerability. Because CoQ10 is a natural supplement, is not harmful and does not interfere with the efficacy of statins, it may be routinely used by patients who are able to afford it. In the ideal clinical setting, the medical professional (physician/dietitian) will provide the patient with an informed choice regarding the use of supplements such as CoQ10. However,

many patients will purchase CoQ10 without consulting with a medical professional, thus CoQ10 will continue to be used despite the lack of research-based evidence.

4.2. DIFFERENCES BETWEEN THE STUDIES

It is difficult to compare results from the study of Caso (2007)⁷⁰ and Young et al (2007)²⁷ as the methodology and study outcomes differed. The following differences were found, which were thought to introduce heterogeneity:

The study of Young et al (2007)²⁷ is placebo-controlled, whereas the study of Caso (2007)⁷⁰ uses a similar antioxidant, Vitamin E as the comparator. In this study, Vitamin E was taken at 400IU once daily for 30 days. Although a placebo is the golden standard when conducting a RCT, Vitamin E as a control was valuable as it was chosen to control for the antioxidant actions of CoQ10. Both supplements were also similar in appearance. In the study of Mancini et al (2011)⁴⁶, Vitamin E was implicated as an emerging therapy for the treatment of statin-induced myopathy. However, the study of Caso (2007)⁷⁰ was the only study in which Vitamin E was used for this purpose, and results showed that it had no value for pain relief.⁷⁰ Whether Vitamin E has any other properties that may motivate its use for pain relief is unknown. A Vitamin D deficiency is related to non-statin related muscle disease,⁶⁹ which may be why it has been recommended as a possible treatment mechanism. However, no such data exists for Vitamin E.

The other sources of heterogeneity may have included the different dose and type of statin/s used by study participants. In the study of Caso (2007)⁷⁰, dose and type of statins were not standardized – simvastatin, atorvastatin, pravastatin as well as lovastatin were used (Table 3.3) in low (10 to 20 mg/day) as well as high (≥ 40 mg) doses (Table 3.4). In the study of Young et al (2007)²⁷, only simvastatin was used by participants and was titrated from a starting dose of 10 to 20 mg/day and then to 40 mg/day at 4-weekly intervals. The ACC/AHA/NHLBI clinical advisory board implicates high-dose statin therapy as a risk factor for myopathy. The type of statin and the extent of lipid reduction are among other proposed factors.^{52,68} Although one of the inclusion criteria for the review was that participants already experience symptoms of myopathy at baseline, the above risk factors may have influenced

individual patient recovery. Titration of low-dose statin therapy (10 to 20 mg/day) to a higher dose (40 mg/day) may have been a cause for the increase in pain experienced by the study participants in both the intervention and control groups in this study.

The measurement tools for myopathy also differed between the studies. To date, a standardized measurement tool specific to myopathy does not exist, thus the studies of Caso (2007)⁷⁰ and Young et al (2007)²⁷ adapted tools that are used to assess pain. These tools were the BPI and VAS. Although both tools are well researched, the evidence is not validated in myopathy. The tools do not account for minor symptoms of myopathy such as muscle cramps, fatigue/tiredness and weakness, symptoms that are more common than pain in most statin users. Minor symptoms may occur in the absence of CK elevation, which was seen in the study of Young et al (2007)²⁷, where no correlation between the pain score and plasma CK concentration before or after the intervention was found. The BPI and VAS were also found to differ in terms of what they measured, how often they were applied, as well as the scales they used (Table 3.5), which made it very difficult to compare the results obtained from the two studies.

The study of Caso (2007)⁷⁰ did not measure plasma or intramuscular CoQ10. Although CoQ10 supplementation had a positive response in the study population, the method of administration of CoQ10 and whether it was efficiently absorbed was unclear. The study of Young et al (2007)²⁷ measured plasma CoQ10, but the method of administration of CoQ10 was also unclear. Factors such as whether the supplement was taken with a meal containing fat to aid absorption, whether the supplement was a capsule/powder/other, and at what time of the day the supplement was taken may help ensure that the supplement is bioavailable.

4.3. OVERALL COMPLETENESS AND APPLICABILITY OF THE EVIDENCE

The two included RCTs are complete in methodological design, but the evidence would be stronger if they both had larger study populations. The total number of participants between the two RCTs is 76, which is a small number given the statistics of CVD patients. Because only two RCTs met the inclusion criteria, assessment of publication bias could not be accomplished. There were two RCTs on CoQ10 and statin-induced myopathy that could not

be included in the review as no full texts of the reports could be sourced, which means that valuable data may have been excluded. Both of these abstracts are supportive of CoQ10, whereas the two RCTs included in the review have conflicting results/conclusions, so no recommendations can be made for clinical practice based on the available evidence. A more concerted effort could have been made to contact the authors of the said abstracts, however time was limited. The measurement of myopathy was not standardized, and results between the two included RCTs were expressed in means with SDs as well as medians with IQRs, thus a meta-analysis could also not be performed as planned. The primary outcome of the review, the improvement of symptoms of myopathy, is poorly researched. Even if the inclusion criteria were less rigid, for example if statin use could have been discontinued at the time of the intervention or if the participants were not restricted to adults, it appears that still only the two RCTs would be included. The only other study that explored CoQ10 for statin-induced myopathy is that of Langsjoen (2005)¹⁷² which is a prospective analysis. In this study, the prevalence of patient symptoms of myopathy on initial visit and on most recent follow-up demonstrated a decrease in fatigue from 84% to 16%, and myalgia from 64% to 6%.

4.4. QUALITY OF THE EVIDENCE

The five factors that decrease the quality level of a body of evidence are:

- limitations in the design and implementation,
- indirectness of evidence,
- unexplained heterogeneity or inconsistency of results,
- imprecision of results and
- a high probability of publication bias.

Because a meta-analysis could not be performed as planned, risk of bias could not be determined across studies, and were thus reported separately. The study of Caso (2007)⁷⁰ and Young et al (2007)²⁷ have a low risk of bias as all applicable domains of methodology are classified as having a low risk (Table 3.9 and 3.10). The only clear limitation for both studies is that they include only a small number of participants.

4.5. POTENTIAL BIASES IN THE REVIEW PROCESS

A funnel plot could not be used to detect potential biases in the review process as less than 10 studies were included in the review. When there are fewer studies, the power of the test is too low to distinguish chance from real asymmetry.

Hand searches of reference lists were one of the methods used to search for studies for inclusion in the review. The abstracts of Kelly et al (2005)¹⁸⁰ and Fedako (2009)¹⁸¹ were sourced in this manner. The scanning of reference lists may produce a biased sample of studies, thus causing citation bias. Motivation for citing certain articles may include persuasiveness to advocate a personal opinion or to justify a point of view. Over-citation of supportive versus unsupportive studies is not present in this review as only two studies were included, of which one is supportive of CoQ10, and the other is unsupportive. Electronic searches were conducted with language restrictions – all non-English studies were thus excluded from the review - language bias may thus have been present.

4.6. AGREEMENTS AND DISAGREEMENTS WITH OTHER STUDIES OR REVIEWS

The results of this review are consistent with those in a previous systematic review on CoQ10 for statin-induced myopathy by Marcoff (2007)¹⁷³. It was anticipated that more RCTs on CoQ10 for statin-induced myopathy would have been published since this review, which was published 5 years ago. Although the review also identified Caso (2007)⁷⁰ and Young et al (2007)²⁷, it did not discuss Kelly et al (2005)¹⁸⁰ which was presented as a poster abstract in 2005. The only more recent data was found in the abstract of the study of Fedacko (2009)¹⁸¹.

The review of Reinhardt (2012)¹⁸⁶ was recently published. It discussed strategies for avoiding the discontinuation of statin therapy due to muscular adverse effects. The review searched MEDLINE and the Cochrane Central Register of Controlled Trials from inception through to April 2010 using a similar search string, however also including terms for 'alternative strategies' (i.e. Vitamin D, ubiquinone, red rice yeast, red yeast rice, alternate dosing, or alternate dosage). No language restrictions were implemented. The review was not restricted to RCTs – it required that the studies included a systematic method of patient selection and that they addressed the outcomes of a strategy to maintain the use of a statin in patients with

prior muscle-related intolerance. Because studies were not RCTs, a meta-analysis was not planned. The review also did not focus solely on CoQ10 as an intervention – CoQ10 was, however, one of the strategies described in 3 out of 16 of the review's selected articles. The 3 articles described are the studies of Caso (2007)⁷⁰, Young et al (2007)²⁷ and Kelly et al (2005)¹⁸⁰. Reinhardt (2012)¹⁸⁶ reported that the differences in study design between these 3 studies (e.g., the use of a washout period, the use of vitamin E rather than a placebo in the control group) were responsible for the divergent study results and that the evidence supporting the use of CoQ10 for statin-induced myalgia was limited by inclusive results published thus far. Other differences between the studies that may also have contributed to the divergent results were the different doses and types of statins used by the study participants, as well as the different measurement tools for myopathy. Reinhardt (2012)¹⁸⁶ concluded that the limited and conflicting evidence on CoQ10, coupled with the additional costs, meant that CoQ10 was probably best recommended only for patients similar to those for whom vitamin D may be appropriate, i.e. in patients with mild symptoms who are enrolled in a well-monitored trial. However, only one clinical trial was identified for Vitamin D by Ahmed et al (2009)¹⁸⁷, which was given a poor bias assessment (poor being defined as the study either having no control group or having a control mechanism but was deemed to have severe methodological shortcomings).

The exact pathophysiology of statin-induced myopathy has also not yet been confirmed. The review of Marcoff (2007)¹⁷³ highlights the insufficiency of evidence to implicate a CoQ10 deficiency as the cause of statin-induced myopathy. This is supported by other studies where the efficacy of CoQ10 is hypothesised due to a decreased serum CoQ10 in statin users.³¹ There remain several possible causes of statin-induced myopathy as well as numerous factors that may increase the risk of myopathy in statin users. This number of confounding factors may be the reason/s why funding agencies and pharmaceutical companies are not investing their time and money in further investigating whether CoQ10 depletion as a result of statin therapy is the cause of myopathy, as well as whether routine CoQ10 supplementation is a definitive treatment mechanism.

Thus far, no other review on CoQ10 for statin-induced myopathy, besides Thompson (2006)⁵², was identified that raises concern regarding the lack of a standardized measurement tool for myopathy. Patient reports of symptoms of myopathy have thus far been subjective, and measurement tools not specific to myopathy have been used. In the prospective analysis of Langsjoen (2005)¹⁷², the measurement tool for myalgia in study participants was not stipulated. However, participants were tested for proximal muscle weakness (details not stipulated) and CK levels. The only other studies that used the same/similar tools to those used by the study of Caso (2007)⁷⁰ and Young et al (2007)²⁷ (the BPI and VAS) used the tools to diagnose pain in mostly cancer patients and for reasons relating to palliative care.

The study of Koumis (2004)³¹ discusses the benefits of statin therapy and that they outweigh the risk of statin-induced myopathy. Although statins are far more extensively researched, their side effects may be underreported and thus may be more commonly seen in clinical practice. This warrants high-quality research to explore treatment mechanisms for this adverse effect. One should keep in mind that although the prevalence is low, statin-induced myopathy can result in fatal rhabdomyolysis if left untreated. Although rare, rhabdomyolysis can be life-threatening and may result in permanent kidney damage, muscle fatigue and pain.¹⁸⁸ These long-term effects as well as the mild symptoms of statin-induced myopathy (namely muscle weakness and fatigue, which mirror the long term effects of rhabdomyolysis), may have an effect on patient quality of life and thus everyday functioning.

CHAPTER 5: AUTHOR'S CONCLUSIONS

Based on the two studies included in the review, there is inconclusive evidence to support the recommendation of CoQ10 supplementation for statin-induced myopathy, especially in developing countries considering the high cost of such therapy. More RCTs on the efficacy of CoQ10 as a treatment for statin-induced myopathy are, however, warranted to establish whether CoQ10 should form a part of future management guidelines. Researchers are also encouraged to publish results of RCTs on CoQ10 and statin-induced myopathy, regardless of whether the data support the use of CoQ10 in clinical practice or not.

5.1. IMPLICATIONS FOR PRACTICE

- CoQ10 is a natural nutritional supplement. If supplementation is advised for patients with statin-induced myopathy, the typical doses remain between 60 and 200 mg daily, which may serve as a guideline in clinical practice.
- No adverse effect directly related to CoQ10 supplementation in healthy humans exists. CoQ10 supplements are available without prescription and can thus be used without medical supervision.
- Adverse effects of CoQ10 in chronic care are very rare and mostly apparent when doses above 1200 mg/day (the OSL) of CoQ10 are supplemented. If a patient is supplemented above this level, be aware of gastrointestinal symptoms (loss of appetite, abdominal pain, nausea and vomiting), central nervous system changes (dizziness, photophobia, irritability and headaches), as well as itching, rash, fatigue and flu-like symptoms.
- CoQ10 supplements can be taken as an adjunct to statin therapy without affecting their cholesterol-lowering effects.
- Many factors that may increase a patient's risk to statin-induced myopathy have been suggested. To date, the statin dose appears to be the most common risk factor.
- Other popular drugs also deplete or interfere with the biosynthesis of coenzyme Q10. Blitznakov (2002)¹⁸⁹ cited a roster that includes a list of 49 drugs that may have this effect. In these patients, plasma and/or intramuscular CoQ10 levels may be lower/depleted at baseline.
- Cost remains important and should be discussed with each patient individually. Statin therapy should continue when/if CoQ10 supplements are taken, a cost that is already a

burden to most CVD patients. Some practical recommendations to enhance the cost-benefit relationship of routine supplementation would be to:

- Advise the patient to purchase a bioavailable form of CoQ10. Thus far, a solubilized form of CoQ10 remains the most bioavailable supplement.
- Encourage the patient to take the CoQ10 supplement with a meal that includes healthy, unsaturated fats to enhance the absorption of the supplement as it is lipophilic.⁴³

Implications for practice from the study of Thompson (2006)⁵² are reemphasized:

- Statin-induced myopathy may not be accompanied by CK elevation or pain. The physician should be aware of minor patient complaints such as muscle weakness and cramps, which may affect patient quality of life.
- A validated measurement instrument for symptoms of myopathy needs to be developed.

5.2. IMPLICATIONS FOR RESEARCH

Many narrative reviews exist regarding the use of CoQ10 for statin-induced myopathy. Larger RCTs are warranted to investigate the effect of CoQ10 on statin-induced myopathy to provide more conclusive results and implications for medical practice. Specific attention should be given to outcomes measured such as minor symptoms of myopathy (muscle complaints), and a standardized measurement tool should be developed and validated for use in future research to measure these outcomes. Major symptoms (CK elevation) of myopathy as well as plasma and intramuscular markers of CoQ10 should continue to be measured and reported as mean (SD) for comparison with other studies in future systematic reviews. When more and larger RCTs are available on CoQ10 and statin-induced myopathy, meta-analysis can be reattempted to provide for more conclusive evidence and thus to assist with medical management guidelines.

Guidelines for future research:

- To develop and validate a measurement tool which explores the different symptoms and signs specific to myopathy, including plasma CK elevation.
- Conduct and publish high-quality RCTs, which will entail larger study populations.
- Race/ethnicity, gender and age (elderly) may affect the patients' risk to myopathy, so these groups should be investigated separately.
- CoQ10 should be taken as an adjunct to statin therapy in all future controlled trials – discontinuing statin therapy when commencing CoQ10 may be seen as two interventions, which may limit applicability of study findings.
- Only bioavailable forms of CoQ10 should be used as the intervention. Administration of the CoQ10 with a meal containing unsaturated (healthy) fats to aid in absorption is recommended.
- Future studies should explore patients' dose response to CoQ10 by monitoring improvement in the patients' symptoms of myopathy with increasing doses. A higher dose of CoQ10 will result in higher plasma CoQ10 levels.
- The type of statin as well as the dose of statin should be standardized across study participants so as to avoid introducing heterogeneity. It is recommended that the type and dose of statin be stratified to determine whether a certain statin dose may require a certain CoQ10 dose to improve symptoms of myopathy.
- More studies are required that measure the relationship between intramuscular and plasma CoQ10 concentrations. No data exists that may implicate a deficient intramuscular CoQ10 as the cause/one of the causes for statin-induced myopathy.

DECLARATIONS OF INTEREST

No conflict of interest to report.

DIFFERENCES BETWEEN PROTOCOL AND THE REVIEW

Inclusion criteria in the protocol were for human adult participants, defined as a participant between 18 and 59.99 years of age. In the review, an adult is defined as a participant between 18 and 64.99 years (WHO)¹⁷⁴ as most participants in the available reports are ≥ 60 years of age.

FUNDING

None.

REFERENCES

GENERAL

1. Acute renal failure (ARF). In Mosby's Dictionary of Medicine, Nursing, & Health Professions [homepage on the internet]. c2009 [updated 2009; cited 2012 Aug]. Available from: http://www.credoreference.com.ez.sun.ac.za/entry/ehsmosbymed/acute_renal_failure_arf
2. Amyotrophic lateral sclerosis. In McGraw-Hill Dictionary of Scientific and Technical Terms [homepage on the internet]. c2003 [updated 2003; cited 2012 Aug]. Available from: http://www.credoreference.com.ez.sun.ac.za/entry/mhscience/amyotrophic_lateral_sclerosis
3. Coronary artery disease (CAD). In Mosby's Dictionary of Medicine, Nursing, & Health Professions [homepage on the internet]. c2009 [updated 2009; cited 2012 Aug]. Available from: http://www.credoreference.com.ez.sun.ac.za/entry/ehsmosbymed/coronary_artery_disease_cad
4. Cardiovascular disease. In Mosby's Dictionary of Medicine, Nursing, & Health Professions [homepage on the internet]. c2009 [updated 2009; cited 2012 Aug]. Available from: http://www.credoreference.com.ez.sun.ac.za/entry/ehsmosbymed/cardiovascular_disease
5. Diabetes Mellitus. In Black's Medical Dictionary, 42nd Edition [homepage on the internet]. c2010 [updated 2010; cited 2012 Aug]. Available from: http://www.credoreference.com.ez.sun.ac.za/entry/blackmed/diabetes_mellitus
6. Huntington's disease. In Mosby's Dictionary of Medicine, Nursing, & Health Professions [homepage on the internet]. c2009 [updated 2009; cited 2012 Aug]. Available from: http://www.credoreference.com.ez.sun.ac.za/entry/ehsmosbymed/huntington_s_disease
7. Hypertrophic cardiomyopathy. In Mosby's Dictionary of Medicine, Nursing, & Health Professions [homepage on the internet]. c2009 [updated 2009; cited 2012 Aug]. Available from: http://www.credoreference.com.ez.sun.ac.za/entry/ehsmosbymed/hypertrophic_cardiomyopathy

8.Hypothyroidism. In Mosby's Dictionary of Medicine, Nursing, & Health Professions [homepage on the internet]. c2009 [updated 2009; cited 2012 Aug]. Available from: <http://www.credoreference.com.ez.sun.ac.za/entry/ehsmosbymed/hypothyroidism>

9.Idiopathic. In Black's Veterinary Dictionary [homepage on the internet]. c2005 [updated 2005; cited 2012 Aug]. Available from: <http://www.credoreference.com.ez.sun.ac.za/entry/acbvvet/idiopathic>

10.Infertility. In McGraw-Hill Concise Encyclopedia of Science and Technology [homepage on the internet]. c2006 [updated 2006; cited 2012 Aug]. Available from: <http://www.credoreference.com.ez.sun.ac.za/entry/conscitech/infertility>

11.Lipophilic. In Mosby's Dictionary of Complementary and Alternative Medicine [homepage on the internet]. c2005 [updated 2005; cited 2012 Aug]. Available from: <http://www.credoreference.com.ez.sun.ac.za/entry/mosbycompmed/lipophilic>

12.Lymphatic system. In Mosby's Dictionary of Medicine, Nursing, & Health Professions [homepage on the internet]. c2009 [updated 2009; cited 2012 Aug]. Available from: http://www.credoreference.com.ez.sun.ac.za/entry/ehsmosbymed/lymphatic_system

13.Mitochondria. In McGraw-Hill Concise Encyclopedia of Science and Technology [homepage on the internet]. c2006 [updated 2006; cited 2012 Aug]. Available from: <http://www.credoreference.com.ez.sun.ac.za/entry/conscitech/mitochondria>

14.Cytopathy. In Dorland's Illustrated Medical Dictionary [homepage on the internet]. c2007 [updated 2007; cited 2012 Aug]. Available from: <http://www.credoreference.com.ez.sun.ac.za/entry/ehsdorland/cytopathy>

15.Multiple sclerosis. In Mosby's Dictionary of Complementary and Alternative Medicine [homepage on the internet]. c2005 [updated 2005; cited 2012 Aug]. Available from: http://www.credoreference.com.ez.sun.ac.za/entry/mosbycompmed/multiple_sclerosis

16.Parkinson's disease. In Mosby's Dictionary of Medicine, Nursing, & Health Professions [homepage on the internet]. c2009 [updated 2009; cited 2012 Aug]. Available from: http://www.credoreference.com.ez.sun.ac.za/entry/ehsmosbymed/parkinson_s_disease

17. Blinding. In Mosby's Dictionary of Complementary and Alternative Medicine [homepage on the internet]. c2005 [updated 2005; cited 2012 Aug]. Available from: <http://www.credoreference.com.ez.sun.ac.za/entry/mosbycompmed/blinding>

18. Confidence interval. In McGraw-Hill Dictionary of Scientific and Technical Terms [homepage on the internet]. c2003 [updated 2003; cited 2012 Aug]. Available from: http://www.credoreference.com.ez.sun.ac.za/entry/mhscience/confidence_interval

19. Presenting results and 'summary of findings' tables. In Higgins JPT, Deeks JJ ed. Cochrane Handbook for Systematic Reviews of Interventions. England: John Wiley & Sons Ltd., 2008; p. 337.

20. Salkind NJ ed. Meta-Analysis Encyclopedia of Measurement and Statistics. Thousand Oaks, CA: Sage Reference, 2007; p. 595-8.

21. Analyzing data and undertaking meta-analysis. In Higgins JPT, Deeks JJ ed. Cochrane Handbook for Systematic Reviews of Interventions. England: John Wiley & Sons Ltd., 2008; p. 276.

22. Introduction. In Higgins JPT, Deeks JJ ed. Cochrane Handbook for Systematic Reviews of Interventions. England: John Wiley & Sons Ltd., 2008; p. 6.

23. Analyzing data and undertaking meta-analysis. In Higgins JPT, Deeks JJ ed. Cochrane Handbook for Systematic Reviews of Interventions. England: John Wiley & Sons Ltd., 2008; p. 245.

24. Randomized controlled trial. In Merriam-Webster's Medical Desk Dictionary, Revised Edition [homepage online] [updated; cited 2012 Aug]. Available from: http://www.credoreference.com.ez.sun.ac.za/entry/mwmedicaldesk/randomized_controlled_trial

25. Glossary. In the Cochrane Collaboration [homepage on the internet] c2012 [updated 2012; cited 2012 Aug]. Available from: <http://www.cochrane.org/glossary/5#letterb>.

- 26.Littarru GP, Langsjoen P. Coenzyme Q10 and statins: biochemical and clinical. *Mitochondrion* [serial online]. 2007 Jun [cited 2012 May]; 7S: S168-74. Available from: PubMed.
- 27.Young JM, Florkowski CM, Molyneux SL, et al. Effect of coenzyme Q10 supplementation on simvastatin-induced myalgia. *Am J Cardiol* [serial online]. 2007 Nov [cited 2012 May]; 100(9): 1400-3. Available from: PubMed.
- 28.The Merck Manuals Online Medical Library. Dyslipidaemia [homepage on the internet]. C2004-2011 [updated 2009 May; cited 2012 May]. Available from: <http://www.merckmanuals.com/professional/sec22/ch331/ch331f.html?qt=coenzymeQ10&alt=sh 04>.
- 29.Marshall T. Coronary heart disease prevention: insights from modelling incremental cost effectiveness. *BMJ* [serial online]. 2003 Nov [cited 2012 Jun]; 327(7426): 1264. Available from: PubMed.
- 30.Mitka M. Expanding statin use to help more at-risk patients is causing financial heartburn. *JAMA* [serial online]. 2003 Nov [cited 2012 May]; 290(17): 2243-5. Available from: Academic Search Premier.
- 31.Koumis T, Nathan J, Rosenberg J, Cicero L. Strategies for the prevention and treatment of statin-induced myopathy: Is there a role for ubiquinone supplementation? *Am J Health Syst Pharm* [serial online]. 2004 Mar [cited 2012 May]; 61(5): 515-519. Available from: Academic Search Premier.
- 32.Joy TR, Hegele RA. Narrative Review: Statin-related myopathy. *Ann Intern Med* [serial online]. 2009 Jun [cited 2012 May 10]; 150(12): 858-868. Available from: PubMed.
- 33.Blitznakov EG. Lipid-lowering drugs (statins), cholesterol, and Coenzyme Q10. The Baycol case – a modern Pandora’s box. *Biomed Pharmacother* [serial online]. 2002 Feb [cited 2012 May]; 56(1): 56-9. Available from: PubMed.

- 34.Schachter M. Chemical, pharmacokinetic and pharmacodynamic properties of statins: an update. *Fundam Clin Pharmacol* [serial online]. 2005 Feb [cited 2012 Nov]; 19 (1): 117-25. Available from: PubMed.
- 35.Tunstall-Pedoe H. In: the WHO MONICA Project ed. *MONICA Monograph and Multimedia Sourcebook*. Geneva: World Health Organization, 2003.
- 36.Armitage J. The safety of statins in clinical practice. *Lancet* [serial online]. 2007 Nov [cited 2012 Apr]; 370(9601): 1781–90. Available from: PubMed.
- 37.Hepatic and Biliary Disorders. In: Beers MH et al. ed. *The Merck Manual of Diagnosis and Therapy*. New Jersey: Merck Research Laboratories, 2006; p.210.
- 38.Pasternak RC, Smith SC Jr, Bairey-Merz CN, et al. ACC/AHA/NHLBI clinical advisory on the use and safety of statins. *Stroke* [serial online]. 2002 Sept [cited 2012 Apr]; 40(9): 567-72. Available from: PubMed.
- 39.Bruckert E, Hayem G, Dejager S, Yau C, Be´Gaud B. Mild to moderate muscular symptoms with high-dosage statin therapy in hyperlipidemic patients— the PRIMO study. *Cardiovasc Drugs Ther* [serial online]. 2005 Dec [cited 2012 Apr];19(6): 403-14.Available from: PubMed.
- 40.The Merck Manuals Online Medical Library. Quality of life in the elderly [homepage on the internet]. C2004-2011 [updated 2009 Aug; cited 2012 Jun]. Available from: [http://www.merckmanuals.com/professional/geriatrics/aging_and_quality_of_life/quality_of_life_in_the_elderly.html?qt=quality of life&alt=sh](http://www.merckmanuals.com/professional/geriatrics/aging_and_quality_of_life/quality_of_life_in_the_elderly.html?qt=quality%20of%20life&alt=sh).
- 41.Jackevicius CA, Mamdani M, Tu JV. Adherence with statin therapy in elderly patients with and without acute coronary syndromes. *JAMA* [serial online]. 2002 Jul [cited 2012 May]; 288(4): 462–467. Available from: PubMed.
- 42.Crane FL. Biochemical functions of coenzyme Q10. *J Am Coll Nutr* [serial online]. 2001 Dec [cited 2012 May]; 20(6): 591-8. Available from: PubMed.

43. Nukui K, Yamagishi T, Miyawaki H, et al. Blood CoQ10 levels and safety profile after single-dose or chronic administration of PureSorb Q-40: animal and human studies. *Biofactors* [serial online]. 2008 [cited 2012 May]; 32(1-4): 209-19. Available from: PubMed.
44. Sewright KA, Clarkson PM, Thompson PD. Statin myopathy: incidence, risk factors, and pathophysiology. *Curr Atheroscler Rep* [serial online]. 2007 Nov [cited 2012 May]; 9(5): 389-96. Available from: PubMed.
45. McKenney JM, Davidson MH, Jacobson TA, Guyton JR. National Lipid Association Statin Safety Assessment Task Force. Final conclusions and recommendations of the National Lipid Association Statin Safety Assessment Task Force. *Am J Cardiol*. [serial online]. 2006 Apr [cited 2012 May]; 97(8A): 89C-94C. Available from: PubMed.
46. Mancini J, Baker S, Bergeron J, et al. Diagnosis, prevention and management of statin adverse effects and intolerance: proceedings of a Canadian Working Group Consensus Conference. *Can J Cardiol* [serial online]. 2011 Sept [cited 2012 Apr]; 27(5): 635-62. Available from PubMed.
47. Phillips PS, Haas RH, Bannykh S, et al. Statin-associated myopathy with normal creatine kinase levels. *Ann Intern Med* [serial online]. 2002 Oct [cited 2012 May]; 137(7): 581-5. Available from: Academic Search Premier.
48. Harper CR, Jacobson TA. The broad spectrum of statin myopathy: from myalgia to rhabdomyolysis. *Curr Opin Lipidol* [serial online]. 2007 Aug [cited 2012 May]; 18(4): 401-8. Available from: PubMed.
49. Sinzinger H, Wolfram R, Peskar BA. Muscular side effects of statins. *J Cardiovasc Pharmacol* [serial online]. 2002 Aug [cited 2012 May]; 40(2): 163-71. Available from: PubMed.
50. Franc S, Dejager S, Bruckert E, Chauvenet M, Giral P, Turpin G. A comprehensive description of muscle symptoms associated with lipid-lowering drugs. *Cardiovasc Drugs Ther* [serial online]. 2003 Sept-Nov [cited 2012 May]; 17(5-6): 459-65. Available from: PubMed.

51. Eckel RH. Approach to the patient who is intolerant of statin therapy. *J Clin Endocrinol Metab* [serial online]. 2010 May [cited 2012 May]; 95(5):2015-22. Available from: PubMed.
52. Thompson PD, Clarkson PM, Rosenson RS. An Assessment of Statin Safety by Muscle Experts. *Am J Cardiol* [serial online]. 2006 Apr [cited 2012 Apr]; 97(8A): 69C-76C. Available from: PubMed.
53. Law M, Rudnicka AR. Statin safety: a systematic review. *Am J Cardiol* [serial online]. 2006 Apr [cited 2012 May]; 97(8A): 52C–60C. Available from: PubMed.
54. Fuhrmans V. Bayer discloses higher death toll from Baycol. *Wall Street Journal* [serial online]. 2002 Jan [cited 2012 May]; 239(14): A10. Available from: Academic Search Premier.
55. Staffa JA, Chang J, Green L. Cerivastatin and reports of fatal rhabdomyolysis. *N Engl J Med* [serial online]. 2002 Feb [cited 2012 May]; 346(7): 539–40. Available from: PubMed.
56. Kashani A, Phillips CO, Foody JM, et al. Risks associated with statin therapy: an overview of randomized clinical trials. *Circulation* [serial online]. 2006 Dec [cited 2012 May]; 114(25): 2788–97. Available from: PubMed.
57. Thompson PD, Clarkson P, Karas RH. Statin-associated myopathy. *JAMA* [serial online]. 2003 Apr [cited]; 289(13): 1681–90. Available from: PubMed.
58. Graham DJ, Staffa JA, Shatin D, et al. Incidence of hospitalized rhabdomyolysis in patients treated with lipid-lowering drugs. *JAMA* [serial online]. 2004 Dec [cited 2012 May]; 292(21): 2585–90. Available from: Academic Search Premier.
59. Hansen KF, Hilderbrand JP, Ferguson EE, Stem JH. Outcomes in 45 patients with statin-associated myopathy. *Arch Intern Med* [serial online]. 2005 Dec [cited 2012 May]; 165(22): 2671-6. Available from: PubMed.
60. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet* [serial online]. 2002 Jul [cited 2012 Apr]; 360(9326): 7–22. Available from: Academic Search Premier.

- 61.Venero CV, Thompson PD. Managing statin myopathy. *Endocrinol Metab Clin N Am* [serial online]. 2009 Mar [cited 2012 Apr]; 38(1): 121-36. Available from PubMed.
- 62.Clark CW, Ferrer-Brechner T, Janal MN, Carroll JD, Yang JC. The dimensions of pain: a multidimensional scaling comparison of cancer patients and healthy volunteers. *Pain* [serial online]. 1989 Apr [cited 2012 May]; 37(1): 23–32. Available from: PubMed.
- 63.Keller S, Bann CM, Dodd SL, Schein J, Mendoza TR, Cleeland CS. Validity of the Brief Pain Inventory for use in documenting the outcomes of patients with noncancer pain. *Clin J Pain* [serial online]. 2004 Sept-Oct [cited 2012 May]; 20(5): 309–18. Available from: PubMed.
- 64.Caraceni A, Cherny N, Fainsinger R, et al. Pain measurement tools and methods in clinical research in palliative care: recommendations of an Expert Working Group of the European Association of Palliative Care. *J Pain Symptom Manage* [serial online]. 2002 Mar [cited 2012 May]; 23(3): 239–55. Available from: ScienceDirect.
- 65.Price DD, McGrath PA, Rafii A, Buckingham B. The validation of visual analogue scales as ratio scale measures for chronic and experimental pain. *Pain* [serial online]. 1983 Sept [cited 2012 May]; 17(1): 45–56. Available from: PubMed.
- 66.Scott J, Huskinsson EC. Graphic representation of pain. *Pain* [serial online]. 1976 Jun [cited 2012 May]; 2(2): 175–84. Available from: PubMed.
- 67.de Lemos JA, Blazing MA, Wiviott SD, et al. Early intensive vs a delayed conservative simvastatin strategy in patients with acute coronary syndromes: phase Z of the A to Z trial. *JAMA* [serial online]. 2004 Sept [cited 2012 May]; 292(11): 1307–16. Available from: Academic Search Premier.
- 68.Morales DCV, Parker B, Lørsen L, White M, Polk D, Thompson P. Greater reductions in total and low density lipoprotein cholesterol are associated with concomitant development of statin myopathy. *JACC* [serial online]. 2011 Apr [cited]; Volume 57, issue 14.
- 69.Gupta A, Thompson PD. The relationship of vitamin D deficiency to statin myopathy. *Atherosclerosis* [serial online]. 2011 Mar [cited]; 215(1): 23-9. Available from PubMed.

70.Caso G, Kelly P, McNurlan MA, Lawson WE. Effect of coenzyme q10 on myopathic symptoms in patients treated with statins. *Am J Cardiol* [serial online]. 2007 May [cited 2012 May]; 99(10): 1409-12. Available from: PubMed.

71.Bhagavan HN, Chopra RK. Coenzyme Q10: absorption, tissue uptake, metabolism and pharmacokinetics. *Free Radic Res* [serial online]. 2006 May [cited 2012 Apr]; 40(5):445-53. Available from: MEDLINE (Proquest).

72.Duncan AJ, Heales SJR, Mills K, Eaton S, Land JM, Hargreaves IP. Determination of coenzyme Q10 status in blood mononuclear cells, skeletal muscle, and plasma by HPLC with di-propoxy-coenzyme Q10 as an internal standard. *Clin Chem* [serial online]. 2005 Dec [cited 2012 May]; 51(12): 2380–82. Available from: PubMed.

73.Steele PE, Tang PH, DGrauw AJ, Miles MV. Clinical laboratory monitoring of coenzyme Q10 use in neurologic and muscular diseases. *Am J Clin Pathol* [serial online]. 2004 Jun [cited 2012 May]; 121 Suppl: S113–S120. Available from: PubMed.

74.Lang JK, Packer L. Quantitative determination of vitamin E and oxidized and reduced coenzyme Q by HPLC with in-line ultraviolet and electrochemical detection. *J Chromatogr* [serial online]. 1987 Jan [cited 2012 May]; 385:109–17. Available from: PubMed.

75.Edlund PO. Determination of coenzyme Q10, α -tocopherol and cholesterol in biological samples by coupled-column liquid chromatography with coulometric and ultraviolet detection. *J Chromatogr* [serial online]. 1988 Mar [cited 2012 May]; 425(1): 87–97. Available from: PubMed.

76.Grossi G, Bargossi AM, Fiorella PL, Piazzzi S. Improved highperformance liquid chromatographic method for the determination of coenzyme Q10 in plasma. *J Chromatogr* [serial online]. 1992 Feb [cited 2012 May]; 593(1-2): 217–26. Available from: PubMed.

77.Finckh B, Kontush A, Commentz J, Hubner C, Burdelski M, Kohlschutter A. Monitoring of ubiquinol-10, ubiquinone-10, carotenoids, and tocopherols in neonatal plasma microsamples using high-performance liquid chromatography with coulometric electrochemical detection. *Anal Biochem* [serial online]. 1995 Dec [cited 2012 May]; 232(2): 210-16. Available from: PubMed.

78.Lagendijk J, Ubbink JB, Delpont R, Hayward WJ, Human JA. Measurement of the ratio between the reduced and oxidized forms of CoQ10 in human plasma as a possible marker of oxidative stress. *J Lipid Res* [serial online]. 1996 Jan [cited 2012 May]; 37(1): 67–75. Available from: PubMed.

79.Kaikkonen J, Nyysönen K, Tuomainen T-P, Ristonmaa U, Salonen JT. Determinants of plasma coenzyme Q10 in humans. *FEBS Lett* [serial online]. 1999 Jan [cited 2012 Apr]; 443(2): 163–6. Available from: PubMed.

80.Tang PH, Miles MV, DeGrauw A, Hershey A, Pesce A. HPLC analysis of reduced and oxidized coenzyme Q(10) in human plasma. *Clin Chem* [serial online]. 2001 Feb [cited 2012 May]; 47(2): 256–65. Available from: PubMed.

81.Kaikkonen J, Tuomainen E-P, Nyysönen K, Salonen JT. Coenzyme Q10: Absorption, antioxidative properties, determinants, and plasma levels. *Free Radic Res* [serial online]. 2002 Apr [cited 2012 Apr]; 36(4): 389–97. Available from: PubMed.

82.Miles MV, Horn PS, Morrison JA, Tang PH, DeGrauw T, Pesce AJ. Plasma coenzyme Q10 reference intervals, but not redox status, are affected by gender and race in self-reported healthy adults. *Clin Chim Acta* [serial online]. 2003 Jun [cited 2012 Apr]; 332(1-2): 123–32. Available from: PubMed.

83.Duncan AJ, Heales SJR, Mills K, Eaton S, Land JM, Hargreaves IP. Determination of coenzyme Q10 status in blood mononuclear cells, skeletal muscle, and plasma by HPLC with di-propoxy-coenzyme Q10 as an internal standard. *Clin Chem* [serial online]. 2005 Dec [cited 2012 May]; 51(12): 2380–82. Available from: PubMed.

84.Groneberg DA, Kindermann B, Althammer M, et al. Coenzyme Q10 affects expression of genes involved in cell signalling, metabolism and transport in human CaCo-2 cells. *Int J Biochem Cell Biol* [serial online]. 2005 Jun [cited 2012 May]; 37(6): 1208–18. Available from: PubMed.

85.Schulz C, Obermüller-Jevic U, Hasselwander O, Bernhardt J, Biesalski H. Comparison of the relative bioavailability of different coenzyme Q10 formulations with a novel solubilizate

(Solu™ Q10). *Int J Food Sci Nut* [serial online]. 2006 Nov [cited 2012 May]; 57(7-8): 546-55. Available from: Academic Search Premier.

86.Mitchell P. Possible molecular mechanisms of the protonmotive function of cytochrome systems. *J. Theor Biol* [serial online]. 1976 Oct [cited 2012 May]; 62(2): 327–67. Available from: PubMed.

87.Ghirlanda G, Oradei A, Manto A, et al. Evidence of plasma CoQ10-lowering effect by HMG-CoA reductase inhibitors: a double-blind, placebo-controlled study. *J Clin Pharmacol* [serial online]. 1993 Mar [cited 2012 Apr]; 33(3): 226 –29. Available from: PubMed.

88.Folkers K, Langsjoen P, Willis R, et al. Lovastatin decreases coenzyme Q levels in humans. *Proc Natl Acad Sci U S A* [serial online]. 1990 Nov [cited 2012 Apr]; 87(22):8931–34. Available from: PubMed.

89.Bargossi AM, Grossi G, Fiorella PL, et al. Exogenous CoQ10 supplementation prevents plasma ubiquinone reduction induced by HMG-CoA reductase inhibitors. *Mol Aspects Med* [serial online]. 1994 [cited]; 15 Suppl: s187–s193. Available from: Academic Search Premier.

90.Berthold HK, Naini A, Di Mauro S, et al. Effect of ezetimibe and/or simvastatin on coenzyme Q10 levels in plasma: a randomised trial. *Drug Saf* [serial online]. 2006 [cited 2012 May]; 29(8): 703–12. Available from: Academic Search Premier.

91.Laaksonen R, Ojala JP, Tikkanen MJ, Himberg JJ. Serum ubiquinone concentrations after short- and long-term treatment with HMG-CoA reductase inhibitors. *Eur J Clin Pharmacol* [serial online]. 1994 [cited 2012 May]; 46(4): 313–17. Available from: MEDLINE.

92.Laaksonen R, Jokelainen K, Sahi T, et al. Decreases in serum ubiquinone concentrations do not result in reduced levels in muscle tissue during short-term simvastatin treatment in humans. *Clin Pharmacol Ther* [serial online]. 1995 Jan [cited 2012 May]; 57(1): 62–6. Available from: PubMed.

93.Watts GF, Castelluccio C, Rice-Evans C, et al. Plasma coenzyme Q (ubiquinone) concentrations in patients treated with simvastatin. *J Clin Pathol* [serial online]. 1993 Nov [cited 2012 May]; 46(11): 1055–57. Available from: PubMed.

94. Mortensen SA, Leth A, Agner E, Rohde M. Dose-related decrease of serum coenzyme Q10 during treatment with HMG-CoA reductase inhibitors. *Mol Aspects Med* [serial online]. 1997; 18 Suppl [cited 2012 May]: S137–S144. Available from: Pubmed.
95. Rundek T, Naini A, Sacco R, et al. Atorvastatin decreases the coenzyme Q10 level in the blood of patients at risk for cardiovascular disease and stroke. *Arch Neurol* [serial online]. 2004 Jun [cited 2012 May]; 61(6): 889–92. Available from: PubMed.
96. Laaksonen R, Jokelainen K, Laakso J, et al. The effect of simvastatin treatment on natural antioxidants in low-density lipoproteins and high-energy phosphates and ubiquinone in skeletal muscle. *Am J Cardiol* [serial online]. 1996 Apr [cited 2012 Apr]; 77(10): 851–54. Available from: PubMed.
97. De Pinieux G, Chariot P, Ammi-Said M, et al. Lipid-lowering drugs and mitochondrial function: effects of HMG-CoA reductase inhibitors on serum ubiquinone and blood lactate/pyruvate ratio. *Br J Clin Pharmacol* [serial online]. 1996 Sept [cited 2012 Apr]; 42(3): 333–37. Available from: MEDLINE.
98. de Lorgeril M, Salen P, Bontemps L, et al. Effects of lipid-lowering drugs on left ventricular function and exercise tolerance in dyslipidemic coronary patients. *J Cardiovasc Pharmacol* [serial online]. 1999 Mar [cited 2012 May]; 33(3): 473–78. Available from: PubMed.
99. Human JA, Ubbink JB, Jerling JJ, et al. The effect of Simvastatin on the plasma antioxidant concentrations in patients with hypercholesterolaemia. *Clin Chim Acta* [serial online]. 1997 Jul [cited 2012 May]; 263(1): 67–77. Available from: PubMed.
100. Jula A, Marniemi J, Huupponen R, et al. Effects of diet and simvastatin on serum lipids, insulin, and antioxidants in hypercholesterolemic men: a randomized controlled trial. *JAMA* [serial online]. 2002 Feb [cited 2012 May]; 287(5): 598–605. Available from: PubMed.
101. Päivä H, Thelen KM, Van Coster R, et al. High-dose statins and skeletal muscle metabolism in humans: a randomized, controlled trial. *Clin Pharmacol Ther* [serial online]. 2005 Jul [cited 2012 Apr]; 78(1): 60–68. Available from: PubMed.

102. Davidson M, McKenney J, Stein E, et al. Comparison of one-year efficacy and safety of atorvastatin versus lovastatin in primary hypercholesterolemia. Atorvastatin Study Group I. *Am J Cardiol* [serial online]. 1997 Jun [cited 2012 May]; 79(11): 1475–81. Available from PubMed.
103. Passi S, Stancato A, Aleo E, et al. Statins lower plasma and lymphocyte ubiquinol/ubiquinone without affecting other antioxidants and PUFA. *Biofactors* [serial online]. 2003 Mar [cited 2012 May]; 18(3): 113–24. Available from: PubMed.
104. Miyake Y, Shouzu A, Nishikawa M, et al. Effect of treatment with 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors on serum coenzyme Q10 in diabetic patients. *Arzneimittelforschung* [serial online]. 1999 Apr [cited 2012 May]; 49(1): 324–29. Available from: PubMed.
105. Palomäki A, Malminiemi K, Metsä-Ketelä T. Enhanced oxidizability of ubiquinol and alpha-tocopherol during lovastatin treatment. *FEBS Lett* [serial online]. 1997 Jun [cited 2012 May]; 410(2-3): 254–8. Available from: MEDLINE.
106. Palomäki A, Malminiemi K, Solakivi T, Malminiemi O. Ubiquinone supplementation during lovastatin treatment: effect on LDL oxidation ex vivo. *J Lipid Res* [serial online]. 1998 Jul [cited 2012 May]; 39(7): 1430-7. Available from: MEDLINE.
107. Mabuchi H, Higashikata T, Kawashiri M, et al. Reduction of serum ubiquinol-10 and ubiquinone-10 levels by atorvastatin in hypercholesterolemic patients. *J Atheroscler Thromb* [serial online]. 2005 [cited 2012 May]; 12(2):111-9. Available from: PubMed.
108. Diebold BA, Bhagavan NV, Guillory RJ. Influences of lovastatin administration on the respiratory burst of leukocytes and the phosphorylation potential of mitochondria in guinea pigs. *Biochim Biophys Acta* [serial online]. 1994 Jul [cited 2012 May]; 1200(2): 100–8. Available from: MEDLINE.
109. Laaksonen R, Riihimäki A, Laitila J, Martensson K, Tikkanen MJ, Himberg JJ. Serum and muscle tissue ubiquinone levels in healthy subjects. *J Lab Clin Med* [serial online]. 1995 Apr [cited 2012 May]; 125(4): 517–21. Available from: MEDLINE.

- 110.Palomaki A, Malminiemi K, Solakivi T, Malminiemi O. Ubiquinone treatment during lovastatin treatment: effect on LDL oxidation ex vivo. *J Lipid Research* [serial online]. 1998 Jul [cited 2012 Jun]; 39(7): 1430-7. Available from: PubMed.
- 111.Aberg F, Appelkvist EL, Dallner G, Ernster L. Distribution and redox state of ubiquinones in rat and human tissues. *Arch Biochem Biophys* [serial online]. 1992 Jun [cited 2012 May]; 295(2): 230–4. Available from: MEDLINE.
- 112.ElMBERGER PG, Kalen A, Brunk UT, Dallner G. Discharge of newly-synthesized dolichol and ubiquinone with lipoproteins to rat liver perfusate and to the bile. *Lipids* [serial online]. 1989 Nov [cited 2012 May]; 24(11): 919–30. Available from: PubMed.
- 113.Traber MG, Lane JC, Lagmay NR, Kayden HJ. Studies on the transfer of tocopherol between lipoproteins. *Lipids* [serial online]. 1992 Sep [cited 2012 May]; 27(9): 657–63. Available from: PubMed.
- 114.Kalén A, Appelkvist EL, Dallner G. Age-related changes in the lipid compositions of rat and human tissues. *Lipids* [serial online]. 1989 Jul [cited 2012 May]; 24(7):579–84. Available from: PubMed.
- 115.Seshadry Sastry P, Jayaraman J, Ramasarma T. Distribution of coenzyme Q in rat liver cell fractions. *Nature* [serial online]. 1961 Feb [cited 2012 May]; 189: 577. Available from: PubMed.
- 116.Kálen A, Appelkvist EL, Dallner G. Age-related changes in the lipid compositions of rat and human tissues. *Lipids* [serial online]. 1989 Jul [cited 2012 May]; 24(7): 579-84. Available from: PubMed.
- 117.The Merck Manuals Online Medical Library. Coenzyme Q10 [homepage on the internet]. C2004-2011 [updated 2009 May; cited 2012 Jun]. Available from: <http://www.merckmanuals.com/professional/sec22/ch331/ch331f.html?qt=coenzymeQ10&alt=sh>

118. Ernster L, Dallner G. Biochemical, physiological and medical aspects of ubiquinone function. *Biochim Biophys Acta* [serial online]. 1995 May [cited 2012 May]; 1271(1): 195–204. Available from: MEDLINE.
119. Hoppe U, Bergemann J, Diembeck W, et al. Coenzyme Q10, a cutaneous antioxidant and energizer. *Biofactors* [serial online]. 1999 [cited 2012 May]; 9(2-4): 371–8. Available from: MEDLINE.
120. Rosenfeldt FL, Pepe S, Ou R, et al. Coenzyme Q10 improves the tolerance of the senescent myocardium to aerobic and ischemic stress: studies in rats and in human atrial tissue. *Biofactors* [serial online]. 1999 [cited 2012 May]; 9(2-4): 291–30. Available from: MEDLINE.
121. Willis R, Anthony M, Sun L, House Y, Qiao G. Clinical implications of the correlation between coenzyme Q10 and vitamin B6 status. *Biofactors* [serial online]. 1999 [cited 2012 May]; 9(2-4): 359–63. Available from: PubMed.
122. Hodges S, Hertz N, Lockwood K, Lister R. CoQ10: could it have a role in cancer management. *Biofactors* [serial online]. 1999 [cited 2012 May]; 9(2-4): 365–70. Available from: PubMed.
123. Rötig A, Appelkvist EL, Geromel V, et al. Quinone-responsive multiple respiratory-chain dysfunction due to widespread coenzyme Q10 deficiency. *Lancet* [serial online]. 2000 Jul [cited 2012 May]; 356(9225): 391–5. Available from: PubMed.
124. Folkers K, Osterborg A, Nylander M, Morita M, Melstedt H. Activities of vitamin Q in animal models and a serious deficiency in patients with cancer. *Biochem Biophys Res Commun* [serial online]. 1997 May [cited 2012 May]; 234(2): 296–9. Available from: PubMed.
125. Weber C, Bysted A., Holmer G. The coenzyme Q10 content of the average Danish diet. *Int J Vitam Nutr Res* [serial online]. 1997 [cited 2012 May]; 67(2): 123–9. Available from: PubMed.

126. Mattila P, Kumpulainen J. Coenzymes Q9 and Q10: Contents in foods and dietary intake. *J Food Compos Anal* [serial online]. 2001 [cited 2012 May]; 14: 409–17. Available from: CAB Abstracts.
127. Pravst I, Zmitek K, Zmitek J. Coenzyme Q10 contents in foods and fortification strategies. *Crit Rev Food Sci Nutr* [serial online]. 2010 Apr [cited 2012 May]; 50(4): 269-80. Available from: PubMed.
128. Lester R, Crane FL. The natural occurrence of coenzyme Q and related compounds. *J Biol Chem* [serial online]. 1959 Aug [cited 2012 May]; 234(8): 2169–75. Available from: PubMed.
129. Weber C, Bysted A, Holmer G. Coenzyme Q10 in the diet. Daily intake and relative bioavailability. *Mol Asp Med* [serial online]. 1997 [cited 2012 May]; 18 Suppl: 251–4. Available from: PubMed.
130. Zita C, Overvad K, Mortensen SA, Sindberg CD, Moesgaard S, Hunter DA. Serum coenzyme Q10 concentrations in healthy men supplemented with 30 mg or 100 mg coenzyme Q10 for two months in a randomised controlled study. *Biofactors* [serial online]. 2003 [cited 2012 May]; 18(1-4): 185–93. Available from: MEDLINE.
131. Rosenfeldt F, Marasco S, Lyon W, et al. Coenzyme Q10 therapy before cardiac surgery improves mitochondrial function and in vitro contractility of myocardial tissue. *J Thorac Cardiovasc Surg* [serial online]. 2005 Jan [cited 2012 May]; 129(1), 25–32. Available from: MEDLINE.
132. Shults CW, Beal MF, Song D, Fontaine D. Pilot trial of high dosages of coenzyme Q10 in patients with Parkinson's disease. *Exp Neurol* [serial online]. 2004 Aug [cited 2012 May]; 188(2): 491–4. Available from: Academic Search Premier.
133. Chopra RK, Goldman R, Sinatra ST, Bhagavan HN. Relative bioavailability of coenzyme Q10 formulations in human subjects. *E Int J Vitam Nutr Rev* [serial online]. 1998 [cited 2012 May]; 68(2): 109-13. Available from: MEDLINE.

134. Bhagavan HN, Chopra RK. Plasma coenzyme Q10 response to oral ingestion of coenzyme Q10 formulations. *Mitochondrion* [serial online]. 2007 Jun [cited 2012 May]; 7 Suppl: S78-S88. Available from: MEDLINE.
135. Weber C, Jakobsen TS, Mortensen SA, Paulsen G, Holmer G. Antioxidative effect of dietary coenzyme Q10 in human blood plasma. *Mol Aspects Med* [serial online]. 1994 [cited 2012 May]; 64 Suppl: 311–15. Available from: PubMed.
136. Tomono Y, Hasegawa J, Seki T, Motegi K, Morishita N. Pharmacokinetic study of deuterium-labelled coenzyme Q10 in man. *Int J Clin Pharmacol Ther Toxicol* [serial online]. 1986 Oct [cited 2012 May]; 24(10): 536-41. Available from: PubMed.
137. Miles MV, Horn P, Miles L, Tang P, Steele P, DeGrauw T. Bioequivalence of coenzyme Q10 from over-the-counter supplements. *Nutr Res* [serial online]. 2002 Aug [cited 2012 May]; 22(8): 919–29. Available from: Academic Search Premier.
138. Kaikkonen J, Nyssonen K, Porkkala-Sarataho E, et al. Effect of oral coenzyme Q10 supplementation on the oxidation resistance of human VLDL+LDL fraction: Absorption and antioxidative properties of oil and granule-based preparations. *Free Radic Biol Med* [serial online]. 1997 [cited 2012 May]; 22(7): 1195–202. Available from: MEDLINE.
139. Hosoe K, Kitano M, Kishida H, Kubo H, Fujii K, Kitahaara M. Study on safety and bioavailability of ubiquinol (Kaneka QH) after single and 4-week multiple oral administration to healthy volunteers. *Regul. Toxicol. Pharmacol* [serial online]. 2007 Feb [cited May 2012]; 47(1): 19–28. Available from: MEDLINE.
140. Lyon W, Van Den Brink O, Pepe V, et al. Similar therapeutic serum levels attached with emulsified and oil-based preparations of CoQ10. *Asia Pac J Clin Nutr* [serial online]. 2001 Sept [cited 2012 May]; 10(3): 212-15. Available from: Academic Search Premier.
141. Kurowska EM, Dresser G, Deutsch L, Bassoo E, Freeman DJ. Relative bioavailability and antioxidant potential of two coenzyme Q10 preparations. *Ann Nutr Metab* [serial online]. 2003 [cited 2012 May]; 47(1): 16-21. Available from: MEDLINE.

142. Weis M, Mortensen SA, Rassing MR, et al. Bioavailability of four oral coenzyme Q10 formulations in healthy volunteers. *Mol Aspects Med* [serial online]. 1994 [cited 2012 May]; 15 Suppl: S273-S280. Available from: PubMed.
143. Folkers K, Moesgaard S, Morita M. A one year bioavailability study of coenzyme Q10 with 3 months withdrawal period. *Mol Aspects Med* [serial online]. 1994 [cited 2012 May]; 15 Suppl: S281-85. Available from: PubMed.
144. Lonrot K, Metsa-Katela T, Molnr G, et al. The effect of ascorbate and ubiquinone supplementation on plasma and CSF total antioxidant capacity. *Free Rad Biol Med* [serial online]. 1996 [cited 2012 May]; 21(2):211–17. Available from: PubMed.
145. Miles MV. The uptake and distribution of coenzyme Q(10). *Mitochondrion* [serial online]. 2007 Jun [cited 2012 May]; 7 Suppl: S72-7. Available from: PubMed.
146. Bonakdar RA, Guarneri E. Coenzyme Q10. *Am Fam Phys* [serial online]. 2005 Sep [cited 2012 May]; 72(6): 1065–70. Available from: PubMed.
147. Challem J. Nutrients that enhance energy and prevent DNA damage. In: *Feed Your Genes Right*. Hoboken, New Jersey: John Wiley & Sons, 2005; p. 41–53.
148. Jones K, Hughes K, Mischley L, McKenna DJ. Coenzyme Q10: Efficacy, safety, and use. *Alt Ther Health Med* [serial online]. 2002 May-Jun [cited 2012 May]; 8(3): 42–55. Available from: PubMed.
149. Hidaka K, Fujii K, Funahashi I, Fukutomi N, Hosoe K. Safety Assessment of Coenzyme Q10 (CoQ10). *Biofactors* [serial online]. 2008 [cited 2012 May]; 32(1-4):199-208. Available from: Academic Search Premier.
150. Williams KD, Maneke JD, AbdelHameed M, et al. 52-week oral gavage chronic toxicity study with ubiquinone in rats with a 4-week recovery. *J Agric Food Chem* [serial online]. 1999 Sep [cited 2012 May]; 47(9): 3756–63. Available from: PubMed.
151. Hathcock JN, Shao A. Risk assessment for Coenzyme Q10 (Ubiquinone). *Regul Toxicol Pharmacol* [serial online]. 2006 Aug [cited 2012 May]; 45(3): 282-8. Available from: PubMed.

152. Shults CW, Oakes D, Kieburtz K, et al. Effect of Coenzyme Q10 in early Parkinson disease. *Arch Neurol* [serial online]. 2002 Oct [cited 2012 May]; 59(10): 1541–50. Available from: MEDLINE.
153. The Huntington Study Group. A randomized, placebo-controlled trial of coenzyme Q10 and remacemide in Huntington's disease. *Neurology* [serial online]. 2001 Aug [cited 2012 May]; 57(3): 397–404. Available from: PubMed.
154. Gold DR, Cohen BH. Treatment of mitochondrial cytopathies. *Semin Neurol* [serial online]. 2001 Sep [cited 2012 May]; 21(3): 309–25. Available from: PubMed.
155. Ferrante KL, Shefner J, Zhang H, et al. Tolerance of high-dose (3000 mg/day) Coenzyme Q10 in ALS. *Neurology* [serial online]. 2005 Dec [cited 2012 May]; 65(11): 1834–6. Available from: PubMed.
156. Bhagavan HN, Chopra RK. Plasma Coenzyme Q10 response to oral ingestion of Coenzyme Q10 formulations. *Mitochondrion* [serial online]. 2007 Jun [cited 2012 May]; 7 Suppl: S78-88. Available from: PubMed.
157. Belardinelli R, Mucaj A, Lacalaprice F, et al. Coenzyme Q10 and exercise training in chronic heart failure. *Eur Heart J* [serial online]. 2006 Nov [cited 2012 May]; 27(22): 2675–81. Available from: PubMed.
158. Tiano L, Belardinelli R, Carnevali P, Principi F, Seddaiu G, Littarru GP. Effect of coenzyme Q10 administration on endothelial function and extracellular superoxide dismutase in patients with ischaemic heart disease: a double-blind, randomized controlled study. *Eur Heart J* [serial online]. 2007 Sep [cited 2012 May]; 28(18): 2249–55. Available from: PubMed.
159. Rosenfeldt FL, Haas SJ, Krum H, et al. Coenzyme Q10 in the treatment of hypertension: a meta-analysis of the clinical trials. *J Hum Hypertens* [serial online]. 2007 Apr [cited 2012 May]; 21(4): 297–306. Available from: PubMed.
160. Hodgson JM, Watts GF, Playford DA, Burke V, Croft KD. Coenzyme Q10 improves blood pressure and glycaemic control: a controlled trial in subjects with type 2 diabetes. *Eur J Clin Nutr* [serial online]. 2002 Nov [cited 2012 May]; 56(11): 1137–42. Available from: PubMed.

161. Chew GT, Watts GF. Coenzyme Q10 and diabetic endotheliopathy: oxidative stress and the 'recoupling hypothesis'. *QJM* [serial online]. 2004 Aug [cited 2012 May]; 97(8): 537–48. Available from: PubMed.
162. Chinnery P, Majamaa K, Turnbull D, Thorburn D. Treatment for mitochondrial disorders. *Cochrane Database Syst Rev* [serial online]. 2006 Jan [cited 2012 May]; CD004426. Available from: PubMed.
163. Lamson DW, Plaza SM. Mitochondrial factors in the pathogenesis of diabetes: a hypothesis for treatment. *Altern Med Rev* [serial online]. 2002 Apr [cited 2012 May]; 7(2): 94–111. Available from: PubMed.
164. Watts GF, Playford DA, Croft KD, Ward NC, Mori TA, Burke V. Coenzyme Q(10) improves endothelial dysfunction of the brachial artery in Type II diabetes mellitus. *Diabetologia* [serial online]. 2002 Mar [cited 2012 May]; 45(3): 420–6. Available from: PubMed.
165. Balercia G, Buldreghini E, Vignini A, Tiano L, Paggi F, Amoroso S. Coenzyme Q10 treatment in infertile men with idiopathic asthenozoospermia: a placebo-controlled, double-blind randomized trial. *Fertil Steril* [serial online]. 2009 May [cited 2012 May]; 91(5): 1785–92. Available from: PubMed.
166. Teran E, Hernandez I, Nieto B, Tavera R, Ocampo JE, Calle A. Coenzyme Q10 supplementation during pregnancy reduces the risk of preeclampsia. *Int J Gynaecol Obstet* [serial online]. 2009 Apr [cited 2012 May]; 105(1): 43–5. Available from: PubMed.
167. Langsjoen PH, Langsjoen PH, Folkers K. Long-term efficacy and safety of coenzyme Q10 therapy for idiopathic dilated cardiomyopathy. *Am J Cardiol* [serial online]. 1990 Feb [cited 2012 May]; 65(7): 421-3. Available from: PubMed.
168. Ho MJ, Bellusci A, Wright JM. Blood pressure lowering efficacy of coenzyme Q10 for primary hypertension. [Cochrane Review]. In: *The Cochrane Library*, Issue 4, 2009. Oxford: Update Software.

169. Ikematsu H, Nakamura K, Harashima S, Fujii K, Fukutomi K. Safety Assessment of Coenzyme Q10 (Kaneka Q10) in healthy subjects: a double-blind, randomized, placebo-controlled trial. *Regul Toxicol Pharmacol* [serial online]. 2006 Apr [cited 2012 May]; 44(3): 212-8. Available from: PubMed.
170. Shinozawa S, Gomita Y, Araki Y. Tissue concentration of doxorubicin (Adriamycin) in ice pretreated with alpha-tocopherol or coenzyme Q10. *Acta Med Okayama* [serial online]. 1991 Jun [cited 2012 May]; 45(3): 195-200. Available from: MEDLINE.
171. White CM. HMG CoA reductase inhibitor-induced muscle toxicity: risks, monitoring, and management. *Formulary* [serial online]. 2002 Nov [cited 2012 May]; 37(11): 583-8. Available from: CINAHL.
172. Langsjoen PH, Jangsjoen JO, Langsjoen AM, Lucas LA. Treatment of statin adverse effects with supplemental coenzyme Q10 and statin drug discontinuation. *Biofactors* [serial online]. 2005 [cited 2012 May]; 25(1-4): 147-152. Available from: PubMed.
173. Marcoff L, Thompson PD. The role of coenzyme Q10 in statin-associated myopathy: a systematic review. *J Am Coll Cardiol* [serial online]. 2007 Jun [cited 2012 May]; 49(23): 2231-7. Available from: PubMed.
174. Definition of an older or elderly person. In World Health Organisation [homepage on the internet] c2012 [updated 2012; cited 2012 Feb]. Available from: <http://www.who.int/healthinfo/survey/ageingdefnolder/en/index.html>
175. Selecting studies and collecting data. In Higgins JPT, Deeks JJ ed. *Cochrane Handbook for Systematic Reviews of Interventions*. England: John Wiley & Sons Ltd., 2008; p. 157-82.
176. Assessing risk of bias in included studies. In Higgins JPT, Deeks JJ ed. *Cochrane Handbook for Systematic Reviews of Interventions*. England: John Wiley & Sons Ltd., 2008; p. 190-3.
177. Assessing risk of bias in included studies. In Higgins JPT, Deeks JJ ed. *Cochrane Handbook for Systematic Reviews of Interventions*. England: John Wiley & Sons Ltd., 2008; p. 198-202.

178. Analyzing data and undertaking meta-analyses. In Higgins JPT, Deeks JJ ed. Cochrane Handbook for Systematic Reviews of Interventions. England: John Wiley & Sons Ltd., 2008; p. 278.
179. Detecting Reporting Biases. In Higgins JPT, Deeks JJ ed. Cochrane Handbook for Systematic Reviews of Interventions. England: John Wiley & Sons Ltd., 2008; p. 317.
180. Kelly P, Vasu S, Gelato M et al. Coenzyme Q10 improves myopathic pain in statin treated patients. *J Am Coll Cardiol* [serial online]. 2005 [cited 2012 Feb]; 45:3a. Abstract.
181. Fedacko J, Pella D, Rybar R, Fedackova P, Merchirova V. Coenzyme Q10 and selenium supplementation in patients with statin-associated myopathy. *Atherosclerosis* [serial online]. 2009 [cited 2012 Feb]; 10(2). Abstract.
182. Landstad BJ, Schuldt K, Ekholm J, Broman L, Bergroth A. Women at Work Despite Ill Health: Diagnoses and Pain Before and After Personnel Support. A Prospective Study of Hospital Cleaners/Home-Help Personnel with Comparison Groups. *J Rehab Med* [serial online]. 2001 Sep [cited 2012 Feb]; 33(5): 216-24. Available from PubMed.
183. Glover EI, Martin J, Maher A, Thornhill RE, Moran GR, Tarnopolsky MA. A randomized trial of coenzyme Q10 in mitochondrial disorders. *Muscle Nerve* [serial online]. 2010 Nov [cited 2012 Feb]; 42(5): 739-48. Available from PubMed.
184. Mabuchi H, Nohara A, Kobayashi J et al. Effects of CoQ10 supplementation on plasma lipoprotein lipid, CoQ10 and liver and muscle enzyme levels in hypercholesterolemic patients treated with atorvastatin: a randomized double-blind study. *Atherosclerosis* [serial online]. 2007 Dec [cited 2012 Feb]; 195(2): e182-9. Available from: PubMed.
185. Assessing risk of bias in included studies. In Higgins JPT, Deeks JJ ed. Cochrane Handbook for Systematic Reviews of Interventions. England: John Wiley & Sons Ltd., 2008; p. 190-3.
186. Reinhardt KM and Woods JA. Strategies to preserve the use of statins in patients with previous muscular adverse effects. *Am J Health-Syst Pharm* [serial online]. 2012 Feb [cited 2012 Aug]; 69(4): 291-300. Available from PubMed.

187. Ahmed W, Khan N, Glueck CJ et al. Low serum 25 (OH) vitamin D levels (<32 ng/mL) are associated with reversible myositis-myalgia in statin-treated patients. *Transl Res* [serial online]. 2009 Jan [cited 2012 Aug]; 153(1): 11-6. Available from: PubMed.

188. Rhabdomyolysis. PubMed Health [homepage on the internet] c2012 [updated Sept 2011; cited Aug 2012]. Available from: <http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0001505/>

189. Blitznakov EG. Lipid-lowering drugs (statins), cholesterol, and Coenzyme Q10. The Baycol case – a modern Pandora's box. *Biomed Pharmacother* [serial online]. 2002 Feb [cited 2012 Aug]; 56(1): 56-9. Available from: PubMed.

INCLUDED STUDIES

Young JM, Florkowski CM, Molyneux SL, et al. Effect of coenzyme Q10 supplementation on simvastatin-induced myalgia. *Am J Cardiol* [serial online]. 2007 Nov [cited 2012 May]; 100(9): 1400-3. Available from: PubMed.

Caso G, Kelly P, McNurlan MA, Lawson WE. Effect of coenzyme q10 on myopathic symptoms in patients treated with statins. *Am J Cardiol* [serial online]. 2007 May [cited 2012 May]; 99(10): 1409-12. Available from: PubMed.

EXCLUDED STUDIES

Langsjoen PH, Jangsjoen JO, Langsjoen AM, Lucas LA. Treatment of statin adverse effects with supplemental coenzyme Q10 and statin drug discontinuation. *Biofactors* [serial online]. 2005 [cited 2012 May]; 25(1-4): 147-152. Available from: PubMed.

Glover EI, Martin J, Maher A, Thornhill RE, Moran GR, Tarnopolsky MA. A randomized trial of coenzyme Q10 in mitochondrial disorders. *Muscle Nerve* [serial online]. 2010 Nov [cited 2012 Feb]; 42(5): 739-48. Available from PubMed.

Mabuchi H, Nohara A, Kobayashi J et al. Effects of CoQ10 supplementation on plasma lipoprotein lipid, CoQ10 and liver and muscle enzyme levels in hypercholesterolemic patients treated with atorvastatin: a randomized double-blind study. *Atherosclerosis* [serial online]. 2007 Dec [cited 2012 Feb]; 195(2): e182-9. Available from: PubMed.

ADDENDUM A – Data extraction form

Notes:

Form no.:	
Revision date:	
Source:	
Study ID (created by review author) – last name of the first author & year	
Report ID (created by review author)	
Review author ID number	
Citation & contact details (email & phone number)	

Eligibility:					
Confirm eligibility & reasons <i>(tick the check-list)</i>	Human subjects	English language study	Statin therapy is being taken in any dose	Effectivity of CoQ10 is measured by Plasma CK & improved myopathic symptoms	Study is a RCT
	There is a control group	Participants are all experiencing myopathic symptoms	The control is a placebo, similar antioxidant or no intervention	CoQ10 is used with their usual medication (including statins)	The mean age of participants are between 18 and 64.99 years
Or reason/s for exclusion <i>(tick the check-list)</i>	CoQ10 is used in combination with other supplemental medication		There is no control group		Study is not a RCT
	This is an Animal study		No full text is available		Participants have clinical evidence of other serious medical conditions (Hepatic, Renal, Endocrine Disease)

Methods:				
Study design				
Total study duration (weeks)				
Country				
Setting	Acute care facility (e.g. hospital)	Chronic care facility (e.g. nursing home)	General practice (outpatients)	
Diagnostic criteria of myalgia (how was myalgia determined)				

Participants receiving CoQ10 (study group):						
Total number						
Age (mean and SD)						
Gender (indicate number) e.g <i>Male 10, female 12</i>	Male	Female			Not indicated	
Ethnicity (indicate numbers as well)	Black	Caucasian	Indian	Coloured	Other (specify):	Not indicated
Participants receiving the control (control group):						
Total number						
Age (mean and SD)						
Gender (indicate numbers)	Male	Female			Not indicated	
Ethnicity (indicate numbers as well)	Black	Caucasian	Indian	Coloured	Other (specify):	Not indicated

Intervention details:				
Specific intervention		CoQ10 supplementation type/name		
		Comparator group type (e.g. placebo/vitamin E)		
	Route of administration	Dose (amount)	Frequency of delivery (/day)	Duration of intervention (weeks)
CoQ10 supplementation	Oral			
	Other (specify):			
Comparator	Oral			
	Other (specify):			

Outcomes:	
Primary Outcomes and time points	
Collected	1.
	2.
	3.
	4.
	5.
Reported	1.
	2.
	3.
	4.
	5.
Secondary Outcomes and time points	
Collected	1.
	2.
	3.
	4.
	5.

Reported	1.	
	2.	
	3.	
	4.	
	5.	
	Outcome definition (<i>diagnostic method, name of scale, definition of threshold or type of behavior</i>)	Unit of measurement
Intensity and/or frequency of myopathic pain		
Plasma creatine kinase (CK)		
Intramuscular CoQ10		
Plasma CoQ10		
Adverse effects of CoQ10 (<i>list, if any</i>)		

Results:		
Number of participants allocated to each intervention group		
CoQ10 supplementation		
Comparator (<i>placebo/similar antioxidant/no intervention</i>)		
Participants receiving CoQ10 (study group):		
	Sample size for each outcome of interest	Number of missing (withdrawal/dropout) participants for each outcome of interest
Intensity and/or frequency of myopathic pain		
Plasma creatine kinase (CK)		
Intramuscular CoQ10		
Plasma CoQ10		
Adverse effects of CoQ10		

Participants receiving the control (control group):		
	Sample size for each outcome of interest	Number of missing (withdrawal/dropout) participants for each outcome of interest
Intensity and/or frequency of myopathic pain		
Plasma creatine kinase (CK)		
Intramuscular CoQ10		
Plasma CoQ10		
Adverse effects of CoQ10		

Summary data for each intervention group						
1. Participants receiving CoQ10 (study group)						
	Baseline Measurement			Final Measurement		
	Mean	SD		Mean	SD	
Continuous data						
Plasma creatine kinase (CK)						
Intramuscular CoQ10						
Plasma CoQ10						
Myopathic pain						
Dichotomous data	YES	NO	NOT INDICATED	YES	NO	NOT INDICATED
Adverse effects of CoQ10						

2. Participants receiving the control (placebo/similar antioxidant/no intervention):						
Continuous data	Mean		SD	Mean		SD
Plasma creatine kinase (CK)						
Intramuscular CoQ10						
Plasma CoQ10						
Myopathic pain						
Dichotomous data	YES	NO	NOT INDICATED	YES	NO	NOT INDICATED
Adverse effects of CoQ10						
Subgroup analyses:						
1.						
2.						
3.						
4.						

Other/Miscellaneous:	
Funding source	
Key conclusions of study authors	
Miscellaneous comments from study author/s	
References to other relevant studies	

Correspondence required	
Miscellaneous comments by independent reviewer	

ADDENDUM B – Assessment of risk of bias form

<p>Domain</p>	<p>Review Authors' judgment</p> <p><i>Yes=low risk of bias</i></p> <p><i>No=high risk of bias</i></p>	<p>Description</p>	
<p>Adequate sequence generation?</p> <p><i>Procedure of allocation i.e. randomization procedure</i></p>	<p>YES</p> <hr/> <p>NO</p> <hr/> <p>UNCLEAR</p>		<p><i>Describe the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.</i></p>
<p>Allocation concealment?</p> <p><i>Treatment to be allocated is not known before patient is entered in the study</i></p>	<p>YES</p> <hr/> <p>NO</p> <hr/> <p>UNCLEAR</p>		<p><i>Describe the method used to conceal the allocation sequence in sufficient detail to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment.</i></p>

Was knowledge of the allocated intervention prevented during the study?

For participants	YES		<p><i>Describe all measures used, if any, to blind study participants & personnel from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective.</i></p>
	NO		
	UNCLEAR		
For personnel	YES		
	NO		
	UNCLEAR		
Intensity and/or frequency of myopathic pain	YES		
	NO		
	UNCLEAR		
Plasma creatine kinase (CK)	YES		
	NO		
	UNCLEAR		

Intramuscular CoQ10	YES		<p><i>Describe all measures used, if any, to blind study participants & personnel from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective.</i></p>
	NO		
	UNCLEAR		
Plasma CoQ10	YES		
	NO		
	UNCLEAR		
Adverse effects of CoQ10	YES		
	NO		
	UNCLEAR		

Incomplete outcome data addressed? *see data from page 9 & 10 of this form

Participants receiving CoQ10 (study group):

Intensity and/or frequency of myopathic pain	YES		<p><i>Describe the completeness of outcome data for each main outcome, including attrition and exclusions from the analysis:</i></p> <p><i>1. State whether attrition and exclusions were reported,</i></p> <p><i>2. The number excluded (compared with the total randomised participants),</i></p> <p><i>3. Reasons for attrition/exclusions where reported, and</i></p> <p><i>4. Any re-inclusions in analyses performed by the review authors.</i></p>
	NO		
	NOT APPLICABLE		
Plasma creatine kinase (CK)	YES		
	NO		
	NOT APPLICABLE		
Intramuscular CoQ10	YES		
	NO		
	NOT APPLICABLE		
Plasma CoQ10	YES		
	NO		
	NOT APPLICABLE		

Adverse effects of CoQ10	YES		
	NO		
	NOT APPLICABLE		

Participants receiving the control (<i>placebo/similar antioxidant/no intervention</i>):			
Intensity and/or frequency of myopathic pain	YES		<p><i>Describe the completeness of outcome data for each main outcome, including attrition and exclusions from the analysis:</i></p> <p><i>1. State whether attrition and exclusions were reported,</i></p> <p><i>2. The number excluded (compared with the total randomised participants),</i></p> <p><i>3. Reasons for attrition/exclusions where reported, and</i></p> <p><i>4. Any re-inclusions in analyses performed by the review authors.</i></p>
	NO		
	NOT APPLICABLE		
Plasma creatine kinase (CK)	YES		
	NO		
	NOT APPLICABLE		
Intramuscular CoQ10	YES		
	NO		
	NOT APPLICABLE		
Plasma CoQ10	YES		
	NO		
	NOT APPLICABLE		
Adverse effects of CoQ10	YES		
	NO		
	NOT APPLICABLE		

Free of selective outcome reporting?	YES		<i>State how the possibility of selective outcome reporting was examined by the review authors, and what was found.</i>
	NO		
Free of other sources of bias?			
Was Intention To Treat (ITT) analysis of data conducted?	YES	Comments:	
	NO		
Other			

ADDENDUM C: Ethics Approval



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jou kennisvenoot • your knowledge partner

17 March 2011

MAILED

Ms L Pietersen
Department of Human Nutrition
3rd Floor
Clinical Building

Dear Ms Pietersen

Coenzyme Q10 Supplementation for the Treatment of Statin-induced Myopathy: A systematic Review

ETHICS REFERENCE NO: N11/03/087

RE : ETHICAL REVIEW NOT REQUIRED

Thank you for your application. The application is for a systematic review using only data that is available in the public domain therefore the cluster head for Research Ethics has considered this proposal to be exempt from ethical review.

This letter confirms that this project is now registered and you can proceed with the work.

Yours faithfully

MS CARLI SAGER

RESEARCH DEVELOPMENT AND SUPPORT

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17 March 2011 15:57

Page 1 of 1



Fakulteit Gesondheidswetenskappe • Faculty of Health Sciences



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Afdeling Navorsingsontwikkeling en -steun • Division of Research Development and Support

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