School of Pharmacy

Statin-Induced Myopathy and the Benefit of Oral Administration of Coenzyme Q10

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DECLARATION

I certify that this thesis contains no material, which has been accepted for the award of any other degree or diploma in any university.

To the best of my knowledge and belief, this thesis contains no material previously published by any other person except where due acknowledgement has been made.

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ABSTRACT

Background

Muscle cramps are one of the adverse affects suffered by hypercholesterolemia patients who are treated with statins. Besides reducing cholesterol levels, statins also reduce coenzyme Q10 (CoQ10) blood levels. One of several hypotheses of pathophysiology for statin-induced muscle cramps is reduced level of CoQ10. Besides being a very important antioxidant, CoQ10 also functions as a transmembrane proton conductor and an electron carrier between NADH and succinate dehydrogenases and the cytochrome system, which is needed for phosphorylation of ADP into ATP. Therefore, a decrease in the CoQ10 tissue levels, as reflected in its reduced blood levels, may contribute to the muscle function impairment. Researchers have proven that statins, drugs used to lower cholesterol, are able to reduce CoQ10 blood levels.

Null Hypothesis

The administration of CoQ10 will have no effect on the frequency, severity and/or duration of muscle cramps amongst statin users.

Aims

This study aimed to assess factors that might influence the development of statin-induced myopathy manifested as muscle cramps, including the respondent's age and sex; the dose and duration of their statin therapy; muscle symptoms (nature, duration and whether or not they have changed with statin use); other medicines consumed; and, other diseases suffered and to investigate the efficacy of oral CoQ10 supplements in reducing muscle cramps in statin users and non-users.

Methods

The Study was comprised of two phases: Phase 1 the Muscle Adverse Effect Survey and Phase 2 the Coenzyme Q10 for Muscle Cramps Study. Data collection for Phase 1 took place from January 2006 to April 2006 in 45 community pharmacies throughout

Western Australia. The second phase of the study, the clinical trial, took place through School of Pharmacy, Curtin University of Technology, from May 2006 to December 2006.

Results

In the first phase of the study, the Muscle Adverse Effect Survey, it was found that the prevalence of myopathy amongst statin users was 22.3% (205/920). Amongst the respondents with muscle symptoms, 73/205 (35.6%) reported their muscle symptoms had worsened on using statins. Assuming non-respondents did not suffer from muscle problems reduced the overall incidence of potential statin-induced myopathy to 73/920 or 7.93%. It was found that atorvastatin was the most commonly prescribed statin (59.3%), followed by simvastatin (29.8%), then pravastatin (10.4%) and fluvastatin (0.6%). Despite the high use of atorvastatin, the incidence rate of myopathy by atorvastatin users was found to be similar with other statins. The most common muscle symptoms were night cramps (54.6%), muscle aching (52.7%), and fatigue (49.3%), while the most commonly affected area of the body was the calves (62%).

Statistical analysis with multiple logistic regression showed increasing age, heart failure and the use of cortisone-like drugs increased the risk of muscle symptoms among statin users. It was found that, for every 1-year increase in age, the odds of suffering from muscle symptoms increased 1.039 (95% CI 1.019 – 1.061). Furthermore, taking cortisone-like medication increased the odds of suffering muscle symptoms 16.4 times (95% CI; 2.2 – 124.3), while participants with heart failure were 9.3 times (95% CI 1.2 – 73.2) more likely to develop muscle symptoms when prescribed statins.

The second phase of the study, the Coenzyme Q10 for Muscle Cramps Study, was a single blind, placebo-controlled, cross over, 6-week evaluation of the benefits CoQ10 in reducing muscle cramps amongst statin users and non-users. It was found that on average, that statin users experienced a significant reduction in the severity of their muscle cramps, as indicated by lower average pain scores, during the period they were on CoQ10 (6.36 ± 0.75) compared with placebo (7.37 ± 0.85; $p = 0.028$). Furthermore,

patients also experienced significantly shorter cramp duration when they were on CoQ10 (4.88 ± 0.84) than on placebo (5.84 ± 0.84; p = 0.001). In contrast, amongst non-statin users (who were used as controls), there were no significant differences between CoQ10 and placebo efficacy in all assessed variables.

Conclusion

This study revealed that muscle symptoms were common among statin users, particularly those suffering from heart failure, taking corticosteroids, and increasing age. Furthermore, the administration of CoQ10 100 mg per day was safe and effective in reducing severity and duration of muscle cramps amongst statin users. However, these later findings need to be confirmed by larger, double blind, placebo controlled studies.

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LIST OF ABBREVIATIONS

ADP	Adenosine Diphosphate
ATP	Adenosine Triphosphate
CK	Creatine Kinase
CoQ10	Coenzyme Q10
EMG	Electromyogram
HMG-CoA	3-Hydroxy-3-methylglutaryl Coenzyme A
LDL	Low Density Lipoprotein
NA	Not Available
NADH	Nicotinamide Adenine Dinucleotide Hydrogen
NADPH	Nicotinamide Adenine Dinucletide Phoshate Hydrogen
NSAID	Non-Steroidal Anti-Inflammatory Drug
PP	Pyrophosphate
ULN	Upper Limits of Normal

WA Western Australia

CHAPTER ONE
GENERAL INTRODUCTION

1.1 MUSCLE CRAMPS

1.1.1 Definition of Muscle Cramps

The aetiology of the cramp can most likely to be traced to “cram”, from Old High German and Norse roots that means squeezing, pressing, or pinching uncomfortably[1]. Muscle cramps can be defined as an involuntarily, painful contraction of muscle, lasting seconds to minutes, often with a palpable hard knot in the affected muscle[1-8]. These cramps are painful and electromyographically show a raised frequency of motor unit potentials that spread throughout the muscles and result in a sustained muscle contraction (an electromyogram (EMG) measures this repetitive firing of motor unit potentials up to 150 per second) [1, 4]. The pain occurring may result from the accumulation of toxic metabolites or possibly the result of local ischaemia[2]. The calf is the most commonly affected, but cramps in the finger and hands also occur in 30% of patients[2, 4, 9]. Further details of clinical features of muscle cramps are summarized on Table 1.1[1, 6].

Table 1.1 Clinical features of muscle cramps[1, 6]

Cramp symptoms
Acutely painful and may result in persistent soreness, swelling, and with elevated serum CK (48-72 hours)
Occur as explosive onset and variable rate of improvement, with visible and palpable contraction.
Occur usually in one muscle or part of a muscle
Associated with both trivial movements and forceful contraction (especially in already shortened muscle)
Start and end with EMG evidence of muscle twitching that waxes and wanes independently in different part of the muscles.
Stretching the muscle terminates cramps.

These features in Table 1.1 can be used to differentiate other muscle problems, such as myalgia, myositis and myotonia, since involuntary muscle contractions are not observed in disorders such as myalgia or myositis, and pain is not featured in myotonia. Another disorder, called contracture (such as writer's cramps), also occurs involuntarily but is totally electrically silent (EMG-free activity). Involuntarily muscle contractions also occur in dystonia, where contractions of agonist and antagonist muscle groups lead to body contortions, and in tetany, where the generalized contractions result from both diffuse motor activity and sensory disturbances[1, 4] (Table 1.2[4]).

Table 1.2 Muscle cramps and muscle cramp-like phenomena[4]

Term	Definition
"True muscle cramps"	An involuntary, painful contraction associated with an increased frequency of motor unit action potentials
Dystonia	Simultaneous contraction of both agonist and antagonist muscle
Muscle contracture	An involuntary state of sustained muscle contraction that is electrically silent, and there is inability of muscle fibres to undergo relaxation
Tetany	A syndrome of sensory and motor neuron hyperexcitability, with resultant motor and sensory hyperactivities

1.1.2 Prevalence of Muscle Cramps

The proportion of cramps suffered may vary across the population. Miller and Layer in their review[1] noted that the prevalence of muscle cramps could be as high as 95% among a group of young students recently enrolled in an exercise class[1]. Other studies revealed that the prevalence of cramps in elderly people was between 35%-60%, with 40% of elderly people reporting having cramps more than three times a week in one study, and 6% reporting daily cramps[2]. Another study of 350 elderly patients found that 50% of them suffered from nocturnal leg cramps, with 20% reporting symptoms for 10 years or

more[10]. It has also been reported that one-third of the Dutch adult population had at least one muscle cramp a year, and 2% suffer from muscle cramps every week[11].

1.1.3 Pathophysiology of Muscle Cramps

There are two main views about the pathophysiology of muscle cramps. The first theory proposes that muscle cramps result from spontaneous discharges of the motor nerves[1, 6, 12], while the second theory tends to suggest that cramps result from within the muscle itself[3]. Those who support the first theory [1, 6, 12] argue that involuntary repetitive firing of motor unit action potentials at very high frequency, which happens during cramps, is more likely to represent spontaneous neuron motor activity rather than muscle activity. They also argue that a cramp is often preceded and accompanied by fasciculation in the same muscle, which is notably demonstrated at the beginning and the end of cramps on EMG.

On the other hand, Roeleveld et al[3], who favour the second theory, point out that single muscle fibers are capable of manifesting repetitive discharges independently. They also argue that neurogenic origin theory is only based on observation that cramps may occur in individuals without obvious pathophysiology and that cramps cannot be induced after the administration of curare. In their study[3], it was found that cramps present as slowly moving fraction of muscle fibres that indicate that either the spatial arrangement of the motoneurons and muscle fibres are highly related, or that cramps are initiated close to or even at the muscle fibre level.

1.1.4 Aetiology of Muscle Cramps

Muscle cramps notably occur in certain metabolic disorders; following acute extracellular volume depletion; in diseases of the lower motor neuron; in hereditary disorders; as a side effect of medication; and may also occur without clear reasons[1, 6] (Table 1.3).

Table 1.3 Aetiology of cramps[1, 4]

Aetiology of cramps	Examples
No apparent cause	Nocturnal leg cramps Exercise-related cramps
Lower motor neuron disorders	Amyitropic lateral sclerosis After poliomyelitis Multifocal motor neuropathy Peripheral nerve injury Nerve root compression Polyneuropathies
Metabolic disorders	Pregnancy Uraemia Cirrhosis Hypothyroidsm Hypoadrenalism
Acute extracellular volume depletion	Perspiration or “heat cramps” Hemodialysis Diarrhoea Vomiting
Hereditary disorders	Autosomal-dominant inherited generalized muscle cramps
Medications	Statins (cholesterol-lowering medication) Beta-adrenergic agonists Donepezil Neostigmine Raloxifene Nifedipine Terbutaline Salbutamol Diuretics

1.1.4.1 Cramps with no apparent cause

Nocturnal leg cramps typically involve the calf and foot, and are common in the elderly, but may also occur in any age of group. Although cramps are generally benign, they may cause considerable distress for patients as cramps frequently awaken patients from sleep[1, 2, 6].

Cramps also have been associated with exercise, especially with beginning a new exercise program. Even though cramps mostly occur after exercise, they may also occur during exercise, thus may limit performance. These exercise-associated cramps may be secondary to dehydration, electrolyte shifts or accumulation of metabolites in exercise muscles[1, 2].

1.1.4.2 Lower Motor Neuron Disorders

A few diseases associated with the damage to the lower motor neuron are associated with cramps, including amyotrophic lateral sclerosis, recovered poliomyelitis, multifocal neuropathy, peripheral nerve injury, nerve root compression, and polyneuropathies. These disorders have similar symptoms, namely wasting of muscles, weakness, and evidence of denervation and reinervation on electrodiagnostic studies[1, 6].

In the case of recovered poliomyelitis (post polio syndrome), the severity of residual weakness, cramps and disability after acute poliomyelitis tends to predict the development of this disorder. Patients who had minimal symptoms from the original illness will most likely experience only mild post polio syndrome. Patients originally hit hard by poliovirus are more likely to develop a more severe case of post polio syndrome with a greater loss of muscle function and more severe fatigue and cramps[1].

1.1.4.3 Metabolic Disorders

Around 30% of pregnant women suffer from cramps in the third trisemester of pregnancy. The cause is unknown, but it is assumed as secondary either to the metabolic

changes associated with pregnancy or to the fluid retention and joint laxity that accompany the later stages of pregnancy[1].

Endocrine disorders, such as hypoadrenalism, uraemia and hypothyroidism, can be associated with cramps. It has been reported that 20%-50% of hypothyroid patients complain of muscle pain or cramps[13]. Hypothyroid-associated muscle problems typically manifest as polymyositis-like with proximal muscle weakness, cramps and an increase in CK levels[13]. In patients suffering from uraemia, up to 50% of them experience muscle cramps, and seem to not have any secondary association with neuropathy that is caused by kidney disease[1].

Liver disease and cirrhosis are also associated with increased cramps, which may be due to decreased intravascular volume in cirrhosis patients. The prevalence of muscle cramps among cirrhosis patients may vary, and was reported at around 22% to 88%[1].

Performing intense muscular work in a hot environment has been associated with heat cramps. Miners, stokers, cane-cutters, firemen and athletes are among those who are susceptible to this type of cramps. People suffering from heat cramps present evidence of hyponatraemia and volume depletion; thus, taking salt tablets during the work may prevent these cramps[1, 5].

1.1.4.4 Acute Extracellular Volume Depletion

It is noted that around one third of patients undergoing haemodialysis complain of muscle cramps. Sodium profiling, a procedure conducted by varying the sodium content of the dialysis fluid during the dialysis session can be helpful in reducing the cramps incidence. Similar to heat cramps, any acute extracellular volume depletion may precipitate cramps, which may occur by having excessive perspiration, diarrhoea, diuretic therapy or vomiting[1, 6].

1.1.4.5 Hereditary Disorders

Several families have been described with autosomal-dominant inherited generalized muscle cramps. In these families, the cramping is often first recognized and most severe during adolescence[1, 6].

1.1.4.6 Medications

A few medications are notable for causing muscle cramps, such as statins (cholesterol-lowering medication), beta-adrenergic agonists, donezepil, neostigmine, raloxifene, nifedipine, terbutaline, salbutamol, and diuretics. Muscle cramps can also happen during withdrawal from sedative effect-substances, such as anxiolytics and barbiturates[1, 6, 14].

1.1.5 Treatment of Cramps

1.1.5.1 Non-pharmacological treatment

Lengthening or stretching the cramped muscle and activating the antagonist muscles are the most common, effective and non-pharmacological treatments for cramps[1, 15]. Stretching a cramped muscle may trigger temporary increased pain, but provides eventual relief[5]. Stretching can also be a preventive strategy, as a study with 44 patients having nocturnal leg cramps showed a reduction in cramp frequency after stretching their calf three times daily[1].

Adding sodium (50 mmol/L) to fluid replacement in order to prevent exercise-related fluid losses may be helpful as it can maximize fluid retention[16]. Typical sport drinks may not be very helpful as they only contain sodium levels of 10-25 mmol/L, and it has been proven these sport drinks only have slight benefit over water[16]. A combination of water and ingestion of food with salt content can perhaps be helpful in preventing exercise-related cramps.[17]

1.1.5.2 Pharmacological Treatment

According to Jansen et al[18], quinine and its derivatives, hydroquinone and quinidine, have been used for more than 50 years to treat muscle cramps. Quinine is very effective in reducing cramps by increasing the muscle refractory period and decreasing the excitability of the motor endplate to nerve stimulation[1, 19, 20]. Despite its effectiveness in treating cramps, quinine can cause toxicity, called cinchonism, which occurs with quinine levels of 5-10 mg/L. The symptoms include temporary visual and hearing disturbances, dizziness, fever, nausea, vomiting and diarrhea, blindness (can be permanent when the levels of quinine exceed 10 mg/L), and thrombocytopenia. From 1969-1992, there have been 157 reports of adverse drug reactions related to quinine sulfate use in the US, including 23 that resulted in death[1]. Since 2004, NPS no longer recommends quinine for cramps treatments.

Sodium channel-blocking agents, such as carbamazepine and phenytoin, can be used to treat muscle cramps even though their side effects are not favorable[1, 6, 21]. Table 1.4 summarizes the examples of pharmacological therapies for muscle cramps and their side effects[1, 21].

Table 1.4 Pharmacological treatments for muscle cramps and their side effects[1, 21]

Medication	Typical dose	Side effects
Quinine sulfate	300 mg at bedtime	Headache, hypoglycaemia, nausea or vomiting, dysphagia, rash, thrombocytopenia, disseminated intravascular coagulation, haemolytic-uraemic syndrome, ototoxicity, hepatotoxicity, and interstitial nephritis

Table 1.4 Pharmacological treatments for muscle cramps and their side effects[1, 21] contd..

Carbamazepine	100 to 200 mg at bedtime	Blurred vision, double vision, dizziness, clumsiness, hypertension, hypotension, nausea, vomiting, drowsiness, pruritic rash, bone marrow depression, thrombocytopenia, renal toxicity, hyponatraemia, hypocalcaemia, arrhythmias, AV heart block, congestive heart failure, syncope, hepatitis, Steven-Johnson syndrome.
Phenytoin	100 to 200 mg at bedtime	Ataxia, dizziness, encephalopathy, gingival hyperplasia confusion, osteomalacia, rash, leukopenia, pancytopenia, Steven-Johnson syndrome, thrombocytopenia, liver damage, toxic hepatitis.

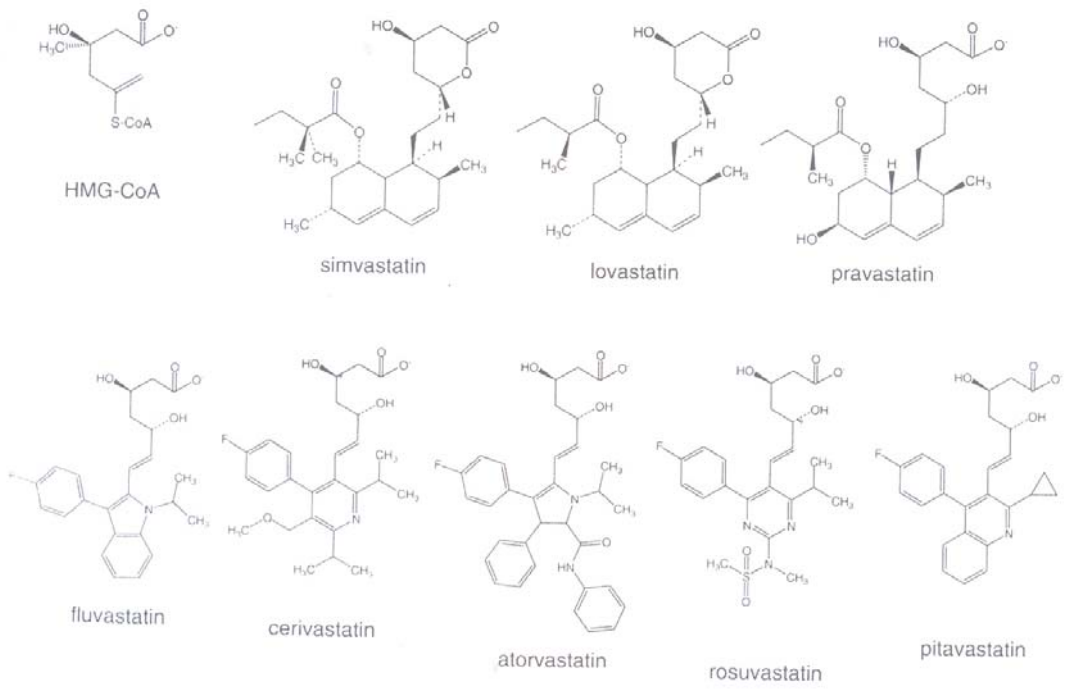
1.2 STATIN-INDUCED MYOPATHY AND MUSCLE CRAMPS

1.2.1 Statins

Statins, or 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, are cholesterol-lowering medications. A lead compound of statins, mevastatin, was extracted from *Penicillium citrinum* by Endo et al in 1971[22]. The second type of statin, lovastatin, was extracted from *Aspergillus terreus* in 1978[22, 23].

Other types of statins, such as simvastatin and pravastatin, are semi-synthetic. Simvastatin is derived from lovastatin by adding a methyl group on the carbon α to the carboxyl group, while pravastatin is a mevastatin analogue with a hydroxyl group on the decalin ring, which is prepared from mevastatin by microbial transformation using *Streptomyces carbophilus.* The next generation of statins, namely fluvastatin, cerivastatin, atorvastatin, and rosuvastatin, are completely synthetic statins with very different structures from the statins derived from fungal products[22] (Figure 1.1).

Figure 1.1 Chemical Structures of HMG-CoA and Statins (Source: Endo A[22])



In Australia, there are four statins that are widely used, namely atorvastatin (Lipitor®), fluvastatin (Lescol®, Vastin®), pravastatin (Pravachol®) and simvastatin (Zocor®, Lipex®)[21] (Table 1.5). Recently, rosuvastatin (Crestor®) has been released onto the market.

Table 1.5 Statins distributed in Australia[21]

Generic Name	Patent Name®	Dosage and Availability
Atorvastatin	Lipitor	Tablet 10, 20, 40 and 80 mg
Fluvastatin	Lescol Vastin	Capsule 20 and 40 mg
Pravastatin	Pravachol	Tablet 10, 20 and 40 mg
Simvastatin	Lipex Zocor	Tablet 5, 10, 20, 40 and 80 mg
Rosuvastatin	Crestor	Tablet 5, 10, 20 and 40 mg

1.2.1.1 Chemistry and Functional Properties

Among the statins, lovastatin and simvastatin have a lactone ring in their structure and are transformed into the active open acid form in the body while pravastatin is administrated as the biologically active open acid form. Other statins have an open acid form and have a similar structure to flurophenyl groups[22, 23]. The clinical importance of the structural variations between statins is that they determine their pharmacological effects and differing pharmacokinetic properties (Table 1.6)[24]. It can be seen from Table 1.6 (row 2) that atorvastatin and rosuvastatin are considered the most efficacious among all statins in lowering LDL cholesterol[24].

Table 1.6 Pharmacological and Pharmacokinetic Properties of Statins[24]

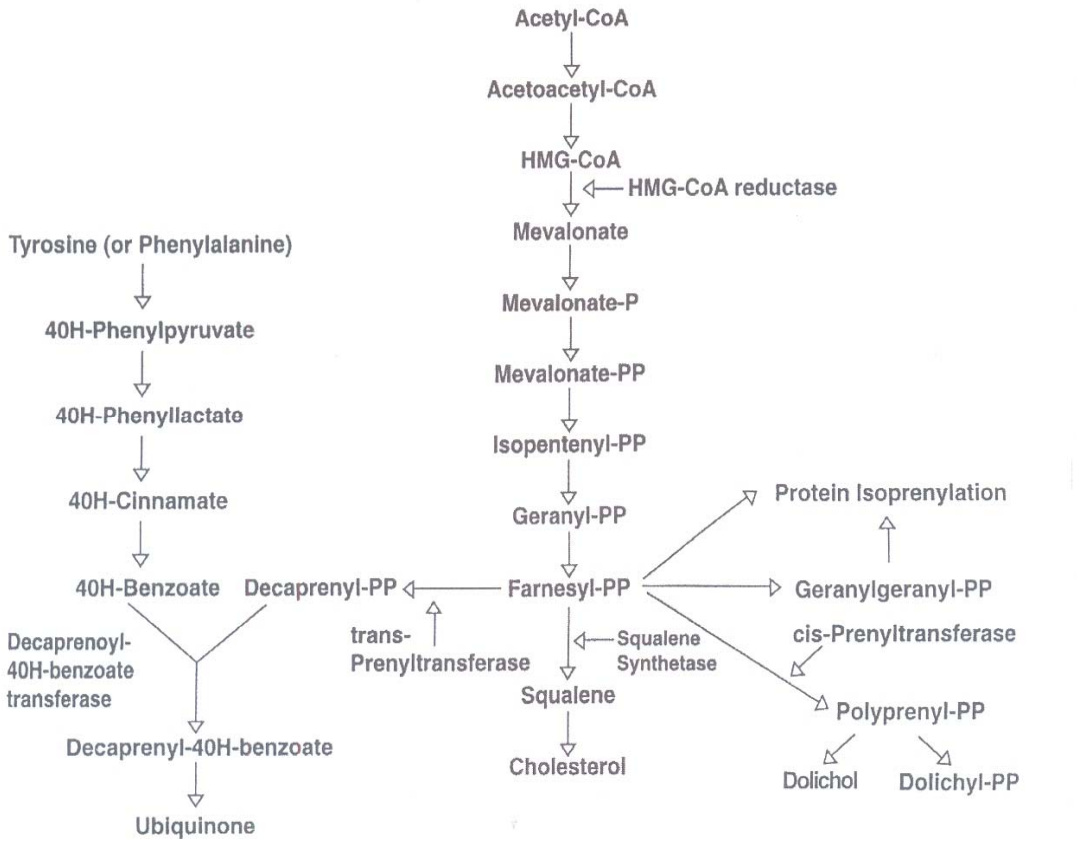
Variable	Atorvastatin	Cerivastatin#	Fluvastatin	Lovastatin	Pravastatin	Rosuvastatin	Simvastatin
LDL cholesterol reductions (Dose range, mg)	38%-54% (10-80)	25%-44% (0.2-0.8)	17%-33% (20-80)	29-48% (20-80)	19%-40% (10-40)	52-63% (10-40)	28-48% (10-80)
IC50 purified human HMG CoA reductase	8.2	10.0	27.6	NA	44.1	5.4	11.2
Specify for hepatocytes +	2.2	-0.14	-0.44	NA	3.3	3.3	0.54
Elimination half-life (hours)	15-30	2.1-3.1	0.5-2.3	2.9	1.3-2.8	19	2-3
Bioavailability (%)	12	60	19-29	5	18	20	5
Protein Binding (%)	80-90	>99	>99	>95	43-55	88	94-98
Solubility *	Lipophilic	Lipophilic	Lipophilic	Lipophilic	Hydrophilic	Hydrophilic	Lipophilic
CP450 metabolism and isozyme	3A4	3A4, 2C8	2C9	3A4	-	Limited 2C9	3A4, 3A5

Withdrawn from the market worldwide
+ Log ratio of IC_{50} in rat hepatocytes to IC_{50} in rat fibroblasts
* Determined according to log D at PH 7.4

1.2.1.2 Cholesterol-Lowering Effect of Statins

Statins inhibit the formation of mevalonate, a precursor of cholesterol produced by HMG-CoA reductase[23, 25-31]. Inhibition of this enzyme leads to a reduction in cholesterol levels (see Figure 1.2). A decline in serum cholesterol level leads to an up regulation of LDL-receptors by transcription regulation to maintain the intracellular cholesterol homeostasis. However, cytochrome P450 7A1 that is specific to the liver, transforms intracellular cholesterol to bile acids, resulting in a decline of cholesterol in hepatocytes, even though it is taken up via up regulated LDL-receptors. Biodegradation of cholesterol in the liver results in a decline of total cholesterol in the body[23, 24, 26, 32-34].

Figure 1.2 Reaction pathway of the biosynthesis of cholesterol, CoQ10 (Ubiquinone) and dolichols (Source: Bliznakov[35]).



1.2.1.3 Other Pharmacological Effects of Statins

In addition to the inhibition of cholesterol biosynthesis, statins also have other effects related to anti-atherosclerosis. Mevalonic acid, a substance whose synthesis is inhibited by statins, is a precursor of not only cholesterol, but also other metabolites, such as farnesyl pyrophosphate and geranylgeranyl pyrophosphate. These substances mediate the prenyalation of specific proteins, which are involved in cell signal transduction, differentiation, proliferation, myelanation and cytoskeleton dynamics. Therefore, statins possess anti-atherosclerosis effects by modulating such cell function triggered by the inhibition of protein prenylation[23, 36]. Table 1.7 shows further details of the mechanisms of anti-atherosclerotic effects of statins[23].

Table 1.7 Mechanisms of anti-atherosclerotic effects of statins[23]

No.	Mechanisms of anti-atherosclerotic effects
1.	Inhibition of migration and proliferation of arterial myocytes
2.	Inhibition of macrophage growth
3.	Inhibition of cell adhesion
4.	Inhibition of superoxide generation
5.	Inhibition of cholesterol accumulation in macrophages
6.	Inhibition of tissue factor expression and activity
7.	Inhibition of endotherlin-1 synthesis and expression
8.	Induction of myocytes apoptosis in proliferative lesions

1.2.2. Statin-Induced Myopathy

Patients taking statins may suffer from a number of adverse effects, including muscle problems (myopathy)[24, 37-47]. In 2001, Baycol® (Cerivastatin) was withdrawn from the market after 31 cases of fatal rhabdomyolysis in the US and 52 deaths worldwide[33, 35, 39, 40].

The terminology to describe myopathy is not quite consistent. For example, myopathy has been defined as muscle pain, weakness or tenderness associated with abnormal elevations in CK levels (over 10 times the upper limit of normal), while the American College of Cardiology/American Heart Association/National Heart, Lung, and Blood Institute (ACC/AHA/NHLBI) refers to myopathy in general terms of muscle diseases[24, 39, 48].

In 2006, The National Lipid Association's (NLA) Muscle Safety Expert Panel was charged to assess statin safety and re-examine the definition used to define myopathy, particularly statin-induced myopathy[49]. The panel suggested that myopathy is the general term for all of the following muscle problems:

1. Symptomatic myopathy: this term refers to skeletal muscle complaints, including myalgia, muscle weakness, and muscle cramps.
2. Asymptomatic myopathy: this term refers to CK elevations without symptoms or objective evidence of weakness.
3. Clinically important rhabdomyolysis: this term refers to any evidence of muscle leakage, regardless of the CK levels, and is considered to be causally related to a change in renal function.

The panel also suggested that the term rhabdomyolysis may be replaced by classes of absolute CK elevations, including:

a. Mild CK increase: this term refers to CK levels greater than normal, but less than 10 times of ULN.
b. Moderate CK increase: this term refers to CK levels more than 10 times the ULN but less than 50 times the ULN.
c. Marked CK increase: this term refers to CK levels over 50 times the ULN.

1.2.3 Statin-Induced Muscle Cramps

As part of statin-induced myopathy, unfortunately there is very little literature dealing specifically with statins-induced muscle cramps, since most of the statin-induced muscle disorders study are focused more on other types of statin-induced muscle disorders, namely myalgia, myositis and rhabdomyolysis. Sinzinger et al[50], in their review, stated that there was a 25% increase in the probability of suffering from cramp and ache-like symptoms and muscle weakness for patients doing exercise and treated with statins. Another muscle cramp related review by Ucar et al[46] point out that, in a trial with 10 to 20 mg per day of simvastatin, from 2085 patients, 41 patients suffered from myalgia, 7 patients suffered from muscle weakness, 6 patients suffered from muscle cramps, while arthralgia and gout were suffered by 4 and 1 patients respectively.

Even though muscle cramps only accounted for a small number of total muscle disorders, Thompson et al[37]stated that less serious adverse effects of statin (including muscle cramps) are underreported, and may vary between 1% and 5%. Furthermore, since muscle cramp, particularly nocturnal leg cramp, is commonly experienced by about 35-60% of older people, some of whom may take statins, they may not realize that their muscle cramps may be caused by or worsened by statins. This statement is strengthened by Gaist et al[51] who believed people taking statins are 7.6-fold more likely to suffer from myopathy, including muscle cramps, than people not taking statins.

1.2.4 Pathophysiology of Statin-Induced Muscle Cramps

As statin-induced muscle cramps are classified as one of the statin-induced myopathies[48], their pathophysiology has the same basis as other statin associated muscle problems. The most widely supported mechanism for statin-induced myopathies is statin-induced lowering of CoQ10 levels[35, 38, 42, 48, 52-56].

Human[57] showed that there was a decline in CoQ10 as well as vitamin E blood levels amongst hypercholesterolaemia patients after 14 weeks treatment with 10 and 20 mg per day of simvastatin. Colquhoun[58] reported simvastatin 20 mg per day reduced CoQ10

and vitamin E blood levels after 6 months treatment. Other researchers, Rundek[54], Strey[59] and Mabuchi[60], reported that atorvastatin also reduced CoQ10 blood levels. Another study conducted by Mortensen revealed that there was a reduction in CoQ10 serum levels in patients taking pravastatin and lovastatin[61]. It was also reported that CoQ10 muscle levels were below 50% of control values in a patient who had been treated first with simvastatin (2 years) and then atorvastatin (2 years)[62].

As CoQ10 and cholesterol have the same biochemical pathway (Figure 1.2), the inhibition of HMG-CoA reductase by statins does not only reduce cholesterol levels but also CoQ10 blood levels[38, 42, 48, 63]. Furthermore, since CoQ10 is carried in the circulation by serum lipoproteins, the reduction of cholesterol and triglyecerides by statins also contributes to further reduced CoQ10 blood levels[55, 64, 65]. Beside being an important antioxidant, CoQ10 also functions as a transmembrane proton conductor and an electron carrier between NADH and succinate dehydrogenases and the cytochrome system, which is needed for phosphorylation of ADP into ATP[66-71]. As muscles need ATP to meet energy demands, a decline in the CoQ10 tissue may contribute to muscle impairment[35, 38, 42, 48, 52-56].

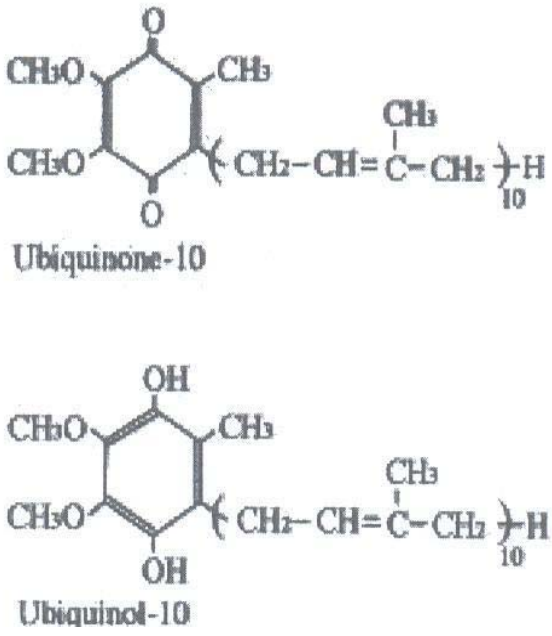
1.3 COENZYME Q10

1.3.1 Biosynthesis of Coenzyme Q10

Coenzyme Q10 (2,3-dimethoxy-5-methyl-6-decaprenyl-1,4-benzoquinone), also known as ubiquinone, is a naturally occurring and extremely hydrophobic molecule, with characteristics common to vitamins. This substance is called CoQ10 as this compound has 10 isoprenoid units in the side chain. CoQ10 is widely found in living organisms, including yeast, plants, animals and humans. CoQ10 plays a critical role as an antioxidant and electron transfer in the mitochondrial inner membrane involved in the efficient production of high-energy phosphates necessary for muscle contraction and other cellular function[42, 67, 71-74].

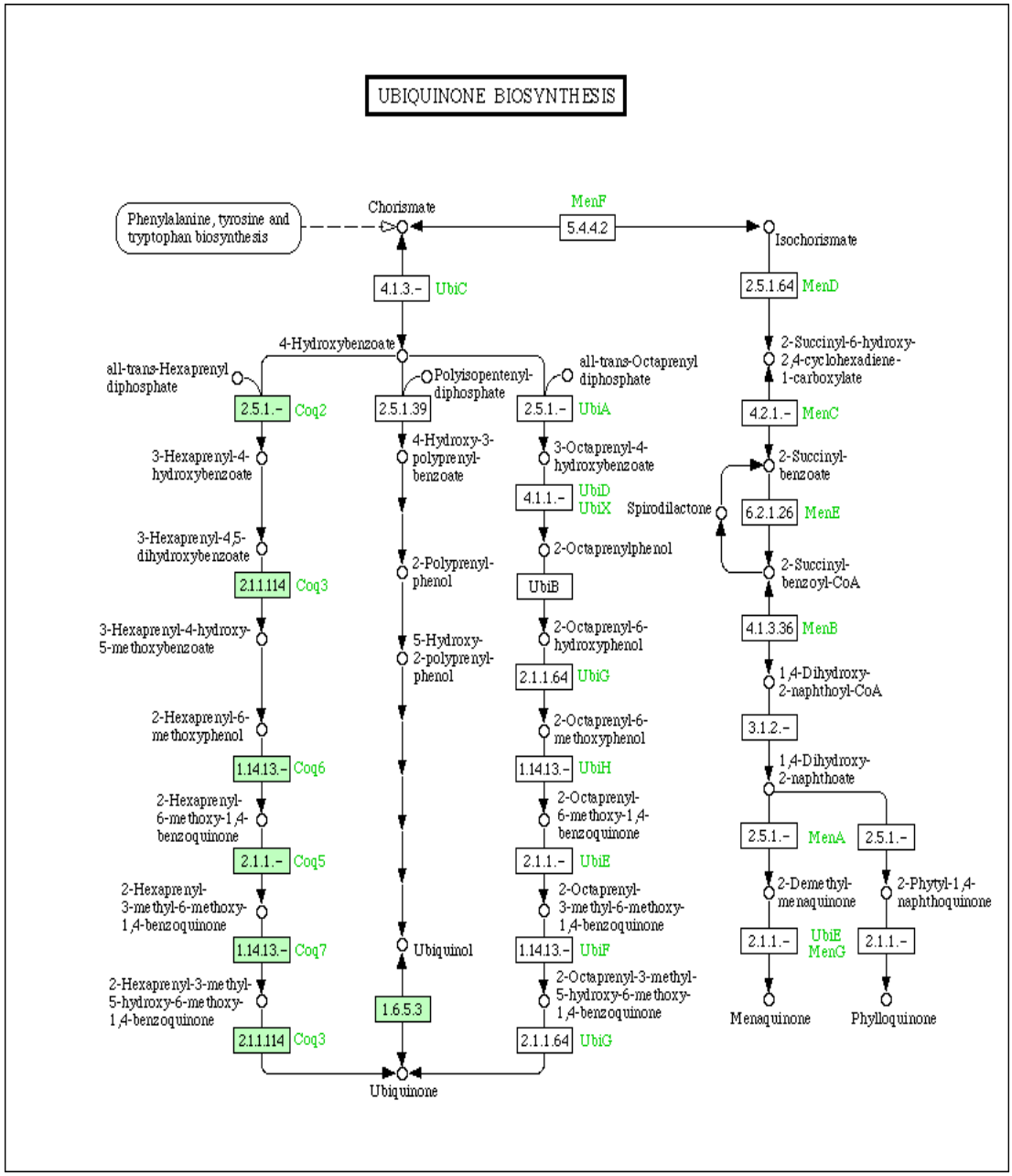
Crane et al discovered CoQ10 in 1957 as a component of beef heart mitochondria. In 1958, Folkers et al successfully determined the chemical structure of CoQ10[68] (see figure 1.3). The content of CoQ10 in organs decreases with age, and its content vary between human tissues, with heart, liver, kidneys, muscle, pancreas and thyroid gland containing 114 μg/g, 66.5 μg/g, 55 μg/g, 40 μg/g, 33 μg/g, 24.7 μg/g tissue respectively[66, 72, 75, 76].

Figure 1.3 Chemical Structures of Ubiquinone-10 and Ubiquinol-10 (Source: Bliznakov[35])



CoQ10 is synthesized in all cells from mevalonate and tyrosine, and requires the availability of multiple vitamins in their coenzyme forms, such as vitamin B2, B6, B12, C, folic acid, niacinamide, pantothenic acid and other trace elements[35]. Figure 1.4 shows further details of CoQ10 biosynthesis in the human body.

Figure 1.4 The Biosynthesis of Coenzyme Q10 (Source: Chan et al[71])



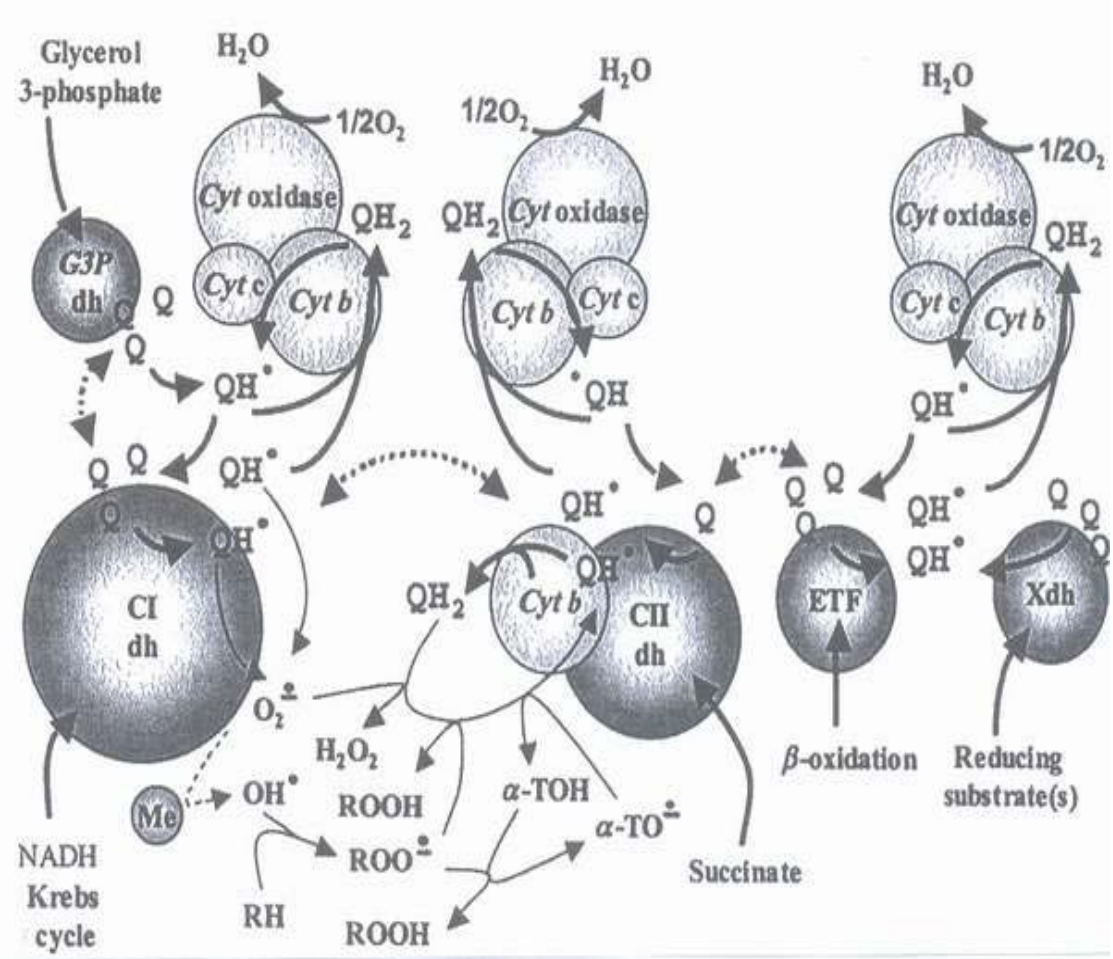
The biosynthesis of CoQ10 can be reduced by statins, due to the fact that they inhibit the formation of mevalonate. Furthermore, a reduction in CoQ10 blood levels of statin users could also be related to the fact that statins lower plasma LDL-C level, and CoQ10 is mainly transported by LDL-C. Although CoQ10 can be obtained from foods, such as

meat and fish, its content in them is very low. Therefore, some nutritionists have considered the use of CoQ10 as a dietary supplement[35, 55, 66, 70, 75].

1.3.2 The Role of Coenzyme Q10 in the Respiratory Chain

CoQ10 plays a crucial role in the mitochondrial respiratory chain, distributing the electrons between the various dehydrogenases and the cytochrome segments of the respiratory chain (Figure 1.5[72]).

Figure 1.5 The Central Role of CoQ10 (Q) in the Respiratory Chain (Source: Rustin et al[72]). Thick lines symbolize electron flow through the respiratory chain. Dotted lines correspond to electron exchanges between kinetically compartmentalized CoQ10 pools. Thin lines represent the antioxidant activity of CoQ10.



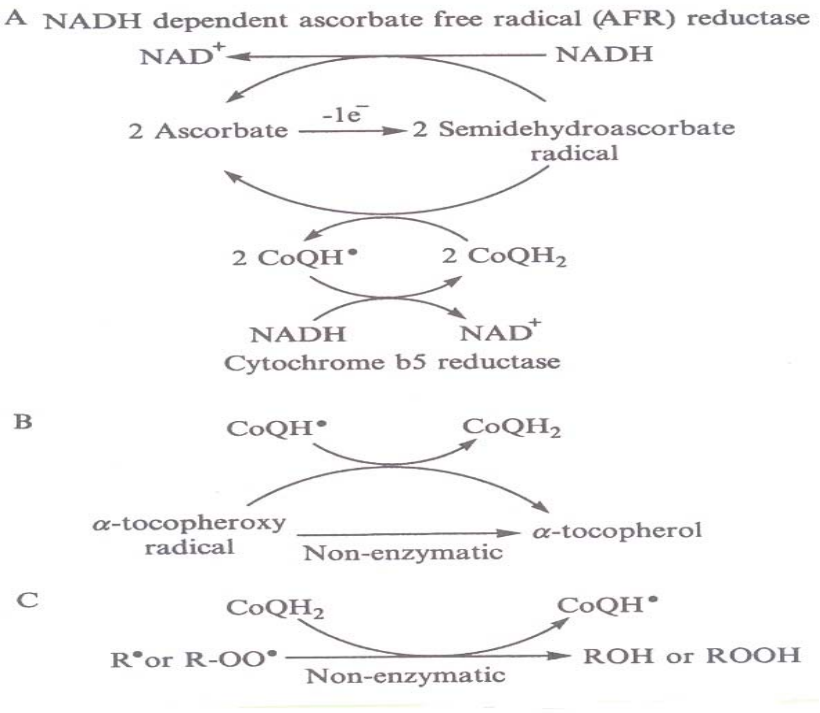
A CoQ10 cycle at the respiratory chain complex III allows protons to be extruded from the mitochondrial matrix to the inter membrane space along with electrons flowing through the complex. Furthermore, depending on its redox and protonation status, CoQ10 can react with molecular oxygen to produce superoxides. Besides the pro-oxidant effect of CoQ10, the fully reduced form of CoQ10, ubiquinol, can reduce a number of radical species, such as superoxides, hence acting as an antioxidant. Therefore, CoQ10 can act as both a pro- and an antioxidant molecule[71, 72].

CoQ10 is a very crucial antioxidant and playing a pivotal role in the mitochondrial respiratory chain, distributing the electrons between the various dehydrogenases and the cytochrome segments of respiratory chain. A decline in CoQ10 levels may result in an increase of NADH/NAD ratio, a decrease in mitochondrial ATP formation, an increase of superoxide formation, and the functional impairment of numeric metabolic pathways requiring the respiratory chain function. Furthermore, since quinone-dependent oxidative phosphorylation supplies most organs and tissues (such as muscle) with energy, CoQ10 depletion should theoretically result in various clinical manifestations[71, 72].

1.3.3 The Role of Coenzyme Q10 as an Antioxidant

The reduced form of CoQ10, ubiquinol, mediates the antioxidant role of endogenous CoQ10, which is able to prevent lipid peroxidation-mediated protein damage (Figure 1.6[71]). Ubiquinol can be formed from the activity of mitochondrial Complex I (NADH dependent ubiquinone oxireductase), Complex II (succinate dependent FADH or ubiquinone oxireductase), NAD(P)H dependent quinone oxidoreductase (NQO1), and NADPH dependent ubiquinone reductase (UQR)[35, 55, 71, 75].

Figure 1.6 The Antioxidant Activity of Ubiquinol (Source: Chan et al[71]). (A) NADH dependent regeneration of ascorbate from ascorbyl radical. (B) NAD(P)H dependent regeneration of tocopherol from its chromanoxyl radical. (C) Scavenging of lipid peroxyl and carbon-centered radicals in a direct lipid peroxidation chain-breaking role.



As can be seen from Figure 1.6 above, ubiquinol is also able to supplement other antioxidants, such as vitamin E (α-tocopherol) and C (ascorbate). Ubiquinol can mediate the regeneration of α-tocopherol from its chromanoxyl radical. However, another form of CoQ10, called ubisemiquinone, is noted to be able to auto-oxidize to form superoxide, if allowed access to H_2O. This pro-oxidant activity may only be significant if cellular antioxidant mechanisms are severely compromised[71].

Another antioxidant, ascorbate, is regenerated across the plasma membrane with the aid of ubiquinol, cytochrome b_5 reductase, and a heme containing enzyme responsible for mediating the transfer of electrons from intracellular NADH to extracellular electron acceptors such as the ferrycyanide and ascorbyl radical[71].

1.3.4 The Safety of Coenzyme Q10

Ikematsu et al[75] conducted a double-blind, randomized, placebo-controlled study in order to assess the safety of CoQ10 in a total of 88 healthy subjects. In this 4-week study, participants were given CoQ10 at doses of 300, 600, and 900 mg per day. It was reported that there were no serious adverse events observed in any group. The most common adverse effects were common colds and flu symptoms and gastrointestinal problems (such as abdominal pain and soft faeces).

Hatchcock and Shao[77] carried out another risk assessment. After examining 54 studies associated with CoQ10 clinical trials, they reported that the adverse effects of CoQ10 are mild, such as nausea, and upset stomach. Reports of nausea and other gastrointestinal effects of CoQ10 cannot be causally related to the active ingredient because there is no dose-response relationship. The absence of a dose relationship between CoQ10 and nausea suggests that the capsule or oil vehicle, and not CoQ10 itself, may have been responsible for the nausea effect.

Other possible adverse effects of CoQ10 are reported by Weiss[78]. Weiss states that besides nausea, vomiting and upset stomach, people taking CoQ10 may also experience heartburn, diarrhoea, loss of appetite, skin itching, rash, insomnia, headache, dizziness, fatigue or flu-like symptoms. These side effects will stop without requiring any treatment[78, 79]. CoQ10 may also lower blood sugar and blood pressure levels, and reduce the effectiveness of warfarin[80, 81]. Furthermore, there is not enough information about the safety of CoQ10 amongst pregnant and breastfeeding women[80, 81].

In terms of the safety of CoQ10 in statin users, it is reported that CoQ10 therapy prevents a reduction in both platelet and plasma CoQ10 levels without affecting the cholesterol lowering effect of the statin[55, 56]. Authors of a small number of studies[35, 58, 60] together with associations such as the International Coenzyme Q10 Association to the United State Food and Drug Administration[82], and the International College of Cardiology [82], have recommended the use of CoQ10 for statin users.

CoQ10 efficacy has been examined by Caso et al[83] who assessed the effectiveness of CoQ10 and vitamin E in reducing muscle pain (myalgia) associated with statin treatment. It was revealed that after a 30-day intervention, pain severity decreased by 40%, and pain interference with daily activities decreased by 38% in the group treated with CoQ10. On the other hand, there were no changes in pain severity and pain interference with daily activity in the group treated with vitamin E.

In 2002, Whitaker[84] filled a citizen petition to the FDA to change the labeling for all statin drugs and insisted that all labels of statin products should contain the recommendation for statin users to take 100 mg to 200 mg per day of CoQ10. To support his petition, Whitaker[84] noted that Merck, the manufacturer of Mevacor® (lovastatin) and Zocor® (Simvastatin), holds two patents that cover doses containing up to 80 mg of an HMG CoA reductase inhibitor with 25 mg to 1 g of CoQ10. One patent (No. 4,933,165)[85] specifically mentions that the combination of statins with CoQ10 will be effective in reducing adverse effects of statins.

CHAPTER TWO
OBJECTIVES OF THE STUDY

The objective of the study were as follows:

1. To determine the frequency and nature of muscle symptoms among statin users in Western Australia.

2. To assess factors that may influence the development of statin-induced muscle symptoms, including the dose and the duration of statin medication, age and sex of patients, history of muscle cramps, other medicines consumed concomitantly with statins, and other diseases suffered.

3. To investigate the efficacy of CoQ10 in reducing muscle cramps amongst statin users and non-users.

4. To document any adverse reactions associated with the use of CoQ10.

CHAPTER THREE
METHODOLOGY

3.1 ETHICS

Ethics approval for the study was obtained from the Curtin University of Technology Human Research Ethics Committee (Appendices A and B). Patient Information Sheet and Informed Written Consent forms were developed in accordance with the requirements of the Curtin University of Technology Ethics Committee (Appendices C and D).

3.2 DATA COLLECTION AND ANALYSIS

The study was comprised of two phases: Phase 1 the "Muscle Adverse Effects Survey" and Phase 2 the "Coenzyme Q10 for Muscle Cramps Study".

3.2.1 Muscle Adverse Effects Survey

3.2.1.1 Setting

Data collection for this survey took place from January 2006 to April 2006 in 45 community pharmacies throughout Western Australia (metropolitan 32, rural 13).

3.2.1.2 Study Design

This was an observational study adopting a prospective approach.

3.2.1.3 Recruitment

In this study patients were enrolled at the time of presenting a repeat prescription for a statin. Each patient was asked to complete a standardized questionnaire, either at the time in the pharmacy or at home, and return it to the Investigator using a prepaid envelope provided.

3.2.1.4 Questionnaire Design

The questionnaire was adopted from a myopathy survey of IMPOSTER ("Is Myopathy Part of Statin Therapy?") Study[86]. The following data were recorded: the respondent's

age and sex; the dose and duration of their statin therapy; muscle symptoms (nature, duration and whether or not they have changed with statin use); other medicines consumed; and other diseases suffered.

3.2.1.5 Definition of Terms

For the purpose of this survey, the following definitions were used:

1. Diabetes mellitus is defined as a disorder that results from insulin hyposecretion and/or insulin insensitivity, and is associated with hyperglycemia[87].
2. Hypertension is defined as a condition notified by an increase in blood pressure to an extent where clinical benefit is obtained from blood pressure lowering[88].
3. Heart attack (ischaemia heart disease) is defined as a condition where the vascular supply to the heart is obstructed by thrombosis, atheroma or spasm of coronary arteries, which may impair the supply of oxygenated blood to cardiac tissue[89].
4. Heart failure is defined as a condition where the heart fails to sustain an adequate delivery of blood, with symptoms including fatigue, and shortness of breath[90].
5. Hypothyroidism is defined as a condition that mostly results from reduced production of thyroid hormones, which can cause weakness, lethargy, cold intolerance, slowness, memory loss, and weight gain[91].
6. Acute renal failure is defined as a condition signified by a decline in the excretory function of the kidneys over a period of days or weeks leading to an accumulation of nitrogenous waste products and other toxins[92].

3.2.1.6 Sample Size

Based on estimates of myopathy rates of 1-5% amongst statin users[37], a minimum of 700 participants were needed for the "Muscle Adverse Effects Survey" to identify 35 potential participants for Group A in phase 2 of the study ("Coenzyme Q10 for Muscle Cramps Study").

3.2.1.7 Data Analysis

Window based Statistical Package of the Social Sciences (SPSS) Version 13 was used to perform the following statistical analyses: the Pearson chi square statistical test, independent-t test, and logistic regression test.

The data obtained from the questionnaires were numerically coded and entered into an SPSS package. All coding and data entry were checked upon completion in comparison with original questionnaires. A *P*-value less than 0.05 was considered statistically significant.

3.2.2 Coenzyme Q10 for Muscle Cramps Study

3.2.2.1 Setting

This clinical trial took place through the School of Pharmacy, Curtin University of Technology, from May 2006 to December 2006.

3.2.2.2 Study Design

This study had a single blind, placebo-controlled, cross over design.

3.2.2.3 Advertisement for the trial

This study was advertised at 45 community pharmacies in WA, and through Curtin University's Radio station, and in two Western Australia community newspapers.

3.2.2.4 Recruitment

For patients to be eligible for the study they had to fulfill the following criteria:

1. Suffered from muscle cramps at least once a week
2. Be aged over 18 years
3. Be able to consent to participate in the study

Patients were excluded from the study if they:

1. Were pregnant or breastfeeding
2. Had cognitive impairment and /or language barrier
3. Had unfavourable health condition(s) as advised by their general practitioner, such as severe hypertension, severe hypotension, renal failure, and uncontrolled diabetes mellitus
4. Had been taking CoQ10
5. Were taking warfarin.

Patients who were interested in joining this study were given the Participant Information Sheet, and asked to sign the Consent Form. They were required to come to the research centre at the School of Pharmacy, Curtin University of Technology, to meet the Investigator. The Investigator explained further details of the study design and answered any questions that they might have at that time. As taking part in this study was voluntary, participants were free to choose not to take part or may leave the study at any time without penalty. Participants were separated into two groups; Group A was those suffering from muscle cramps who were taking statins, and Group B (Controls) was those suffering from muscle cramps but not taking statins.

3.2.1.5 Clinical Trial Protocol

The trial consisted of four phases: Phase 1 - a 1-week assessment period, during which the baseline frequency of muscle cramps was assessed; Phase 2 - a 2-week treatment period, during which participants of Group A were allocated CoQ10 100 mg/day, and Group B were allocated placebo; Phase 3 - a 1-week wash out period during which participants did not take either CoQ10 or placebo; and Phase 4 - a second 2-week period of the second treatment during which participants of Group A took placebo, and Group B took CoQ10 100 mg per day.

The CoQ10 capsules used in this study were manufactured by Blackmore Ltd, and each capsule contained CoQ10 50 mg. The placebo capsules contained extra virgin olive oil, and were manufactured by the School of Pharmacy, Curtin University of Technology.

As it was not possible to have identical placebo capsules to the commercial Blackmores' CoQ10, the study had to be a single blind study.

During the treatment periods (Weeks 2, 3, 5 and 6), participants were advised to take the medication (either CoQ10 or placebo), two capsules daily with the evening meal. Patients were then given a diary to record the following data across the 6-week period of the study:

1. Days on which cramps were experienced
2. Number of cramps suffered per day
3. Average pain score associated with muscle cramps (on a scale of 0 to 10)
4. Maximum pain score associated with muscle cramps (on a scale of 0 to 10)
5. The duration of the cramps (in minutes)
6. The part(s) of the body affected by the cramps
7. Any adverse reactions suffered over the duration of the study

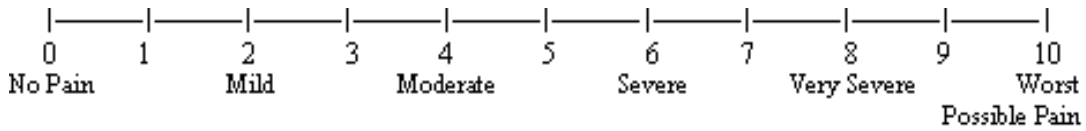
During the study, the Investigator monitored the condition of participants by interviewing them once a week (by face-to-face meetings or by telephone interviews). At the end of the study, their diaries were collected by the Investigator, and participants were given the opportunity to receive a copy of the results of the study.

3.2.1.6 Definition of Terms

For the purpose of this study, the following definitions were used:

1. "Average pain score" was defined as the average score of pain intensity associated with the muscle cramps, which is determined by using the pain severity scale (Figure 3.1).

Figure 3.1 Numeric Rating Scale



The pain severity scale used in this study has been adopted from the numeric rating scale (NRS) of the Office of Academic Affiliations, US Department of Veteran Affairs [93]. On the NRS, 0 is marked as no muscle pain associated with the muscle cramps, while 10 means the worst possible pain of muscle cramp.

The numeric rating scale (NRS) adopted in this study has already been proven valid and reliable[94-96]. A study conducted by Ferraz et al[95] found that NRS had higher reliability in both literate and illiterate patients compared to other scales, namely the visual analogue scale (VAS) and the verbal rating scale (VRS).

2. "Maximum pain score" was defined as the maximum score of pain intensity associated with the muscle cramps, which is determined by using the pain severity scale (Figure 3.1).

3. "Duration of the cramps" was defined as the length of the cramp episode that may last for a few seconds or up to 10 minutes. The limitation for the contraction of muscle cramps up to 10 minutes is used in order to distinguish muscle cramp from painful muscle stiffness[18]. The duration of the cramps was determined by using either a wristwatch or a stopwatch.

4. "Adverse effects" were defined as unfavourable medical events, including subjective symptoms and objective symptoms, that participants commented on after taking the medication, regardless of whether they appeared related to the test material[75].

3.2.1.7 Sample Size

A total number of 70 patients were expected to be recruited for this trial. This sample size is based on previous research on muscle cramps using hydroquinone, which was conducted by Jansen et al[18].

3.2.1.8 Data Analysis

Window based Statistical Package of the Social Sciences (SPSS) Version 13 was used to perform the following statistical analyses: repeated measures ANOVA, Scheffè test, and paired t-test.

The data obtained from the diary were numerically coded and entered into an SPSS package. All coding and data entry were checked upon completion in comparison with original diaries. A *P*-value less than 0.05 was considered statistically significant.

CHAPTER FOUR
RESULTS

4.1. MUSCLE ADVERSE EFFECTS SURVEY

4.1.1 Recruitment

Participants for the study were recruited through 45 community pharmacies in Western Australia (metropolitan 32, rural 13). Participants enrolled into the study were asked to complete a questionnaire, which was adopted from a myopathy survey of IMPOSTER ("Is Myopathy Part Of Statin Therapy?")[86], either at the time in the pharmacy or at home and return it by post. Of the 920 participants enrolled into the study who took the questionnaire, 356 (38.7%) returned the questionnaire.

4.1.2 Patient Demographics

The 356 respondents were made up of 202 males and 156 females. The average age of male respondents was 60.5 ± 11.1 (SD) years and the average age of female respondents was 64.1 ± 11.3 (SD) years. Two hundred and five of the 356 (57.6%) respondents, 111 men and 94 women, reported muscle symptoms (Table 4.1). T testing for the equality of the mean was undertaken, and the results demonstrated that respondents suffering from muscle symptoms were significantly older than those who did not experience any muscle symptoms (Mean difference 4.89 years; 95% CI: 2.65 – 7.31, p value= 0.000) [Table 4.1].

Table 4.1 the Age and Gender of Participants

Group	Number	Males	Females	Mean of Age (95% CI)	SD	p value (Mean of Age)
Myopathy	205	111	94	64.2 (62.7-65.7)	10.8	0.000
Non myopathy	151	91	60	59.2 (57.4-61.0)	11.4	

For the purpose of analysis it was assumed that non-respondents did not suffer from muscle symptoms, which reduced the overall incidence to 205/920 or 22.3%. Amongst the respondents with muscle symptoms, 73 (35.6%) reported their muscle symptoms had worsened on using their statins, 42 (20.6%) admitted they experienced darkening of their urine after exercise or fasting, and 26 (12.7%) admitted they had a family history of muscle disorders.

Furthermore, amongst the respondents with muscle symptoms, 98 respondents (49.8%) had liver function tests done, and 44 (21.5%) and 10 (4.9%) had CK and myoglobinuria tests done respectively. However, there's no further information obtained regarding these tests, as their test results were not attached to the questionnaire.

4.1.3 Lipid Lowering Therapy Used

The survey found that atorvastatin was the most commonly prescribed statin (59.3%), followed by simvastatin (29.8%) and then pravastatin (10.4%) and fluvastatin (0.6%). As can be seen from the Table 4.2 below, despite the high use of atorvastatin, the incidence rate of myopathy amongst individual atorvastatin users was found to be similar to that of other statins.

Table 4.2 Statin Therapy Used

Statin Used	Group		Total Number of Respondents	Proportion of Total Respondents (%)
	Myopathy N (%)	Non-Myopathy N (%)		
Atorvastatin	121(59.0%)	90 (59.6%)	211	59.3
Fluvastatin	2 (0.98%)	0 (0%)	2	0.6
Pravastatin	26 (12.7%)	11 (7.3%)	37	10.4
Simvastatin	56 (27.3%)	50 (33.1%)	106	29.8
Total responses	**205 (100%)**	**151 (100%)**	**356**	**100**

From a total of 356 participants, seven (1.9%) took a combination of statins with other cholesterol lowering medications, namely gemfibrozil, ezetimibe, and fenofibrate. Table 4.3 summarizes the type of statins (including their combination), and their doses used by respondents. It can be seen from the table that the incidence rates for myopathy and non-myopathy amongst statin doses remained statistically indistinguishable ($p>0.05$).

Table 4.3 Complete Lists of Statin Therapy Used

Statin Used	Group		Number of Respondents	Proportion of Respondents (%)
	Myopathy n (%)	Non-Myopathy n (%)		
Atorvastatin 10 mg	56 (27.3%)	34 (22.5%)	90	25.3
Atorvastatin 10 mg + Gemfibrozil 600 mg	1 (0.5%)	1 (0.7%)	2	0.6
Atorvastatin 20 mg	26 (12.7%)	24 (15.9%)	50	14.0
Atorvastatin 40 mg	20 (9.8%)	21 (13.9%)	41	11.5
Atorvastatin 40 mg + Fenofibrate 160 mg	1 (0.5%)	0 (0%)	1	0.3
Atorvastatin 60 mg (40 mg + 20 mg)	2 (0.9%)	0 (0%)	2	0.6
Atorvastatin 80 mg	14 (6.8%)	10 (6.6%)	24	6.7
Atorvastatin 80 mg + Ezetimibe 10 mg	1 (0.5%)	0 (0%)	1	0.3

Table 4.3 Complete Lists of Statin Therapy Used Contd…

Fluvastatin 20 mg	2 (0.9%)	0 (0%)	2	0.6
Pravastatin 10 mg	13 (6.3%)	4 (2.6%)	17	4.8
Pravastatin 20 mg	3 (1.5%)	7 (4.6%)	10	2.8
Pravastatin 40 mg	9 (4.4%)	0 (0%)	9	2.5
Pravastatin 80 mg	1 (0.5%)	0 (0%)	1	0.3
Simvastatin 5 mg	12 (5.9%)	8 (5.3%)	20	5.6
Simvastatin 10 mg	14 (6.8%)	12 (7.9%)	44	12.4
Simvastatin 20 mg	8 (3.9%)	19 (12.6%)	27	7.6
Simvastatin 20 mg + Ezetimibe 10 mg	1 (0.5%)	0 (0%)	1	0.3
Simvastatin 40 mg	13 (6.3%)	7 (4.6%)	20	5.6
Simvastatin 40 mg + ezetimibe 10 mg	0 (0%)	1 (0.7%)	1	0.3
Simvastatin 80 mg	7 (3.4%)	2 (1.3%)	9	2.5
Simvastatin 80 mg + Fenofibrate 160 mg	0 (0%)	1 (0.7%)	1	0.3
Total Responses	**205 (100%)**	**151 (100%)**	**356**	**100**

In terms of the duration of medication use, the majority of participants in both the myopathy and non-myopathy groups had been taking a statin for over 1 year (301; 84.6%) [Table 4.4].

Table 4.4 the Duration of Statin Used

Duration of statin taken by participants	**Group**		**Number of Respondents**	**Proportion of Respondents (%)**
	Myopathy n (%)	**Non-Myopathy n (%)**		
Less than 1 year	33 (16.1%)	22 (14.6%)	55	15.4
More than 1 year	172 (83.9%)	129 (85.4%)	301	84.6
Total responses	**205(100%)**	**151 (100%)**	**356**	**100**

4.1.4 Other Suffered Diseases besides Hypercholesterolemia

It was found that besides hypercholesterolaemia, there were 301 cases of other diseases suffered by participants that might be associated to myopathy. The most commonly reported concomitant diseases were hypertension (n =140 cases or 39.3% cases of total respondents), followed by diabetes mellitus with 65 cases (18.3%), ischaemic heart disease with 41 cases (11.5%) and hypothyroidism with 36 cases (10.1%) [Table 4.5].

Table 4.5 Other diseases suffered besides hypercholesterolaemia

Diseases	**Myopathy n = 205**	**Non-myopathy n = 151**	**Number of Respondents**	**Proportion of Respondents (%)**
Diabetes Mellitus	44	21	65	18.3
Hypertension	84	56	140	39.3
Ischaemia Heart Disease	27	14	41	11.5
Heart Failure	13	1	14	3.9
Hypothyroidism	23	13	36	10.1
Kidney Failure	4	1	5	1.4
No Diseases	74	67	141	39.6
Total Responses	**269**	**163**	**432**	**124[#]**

 # Total exceeded more than 100% as many patients suffered from more than 1 concomitant disease

4.1.5. Other Drugs Used Besides Statin

Amongst the 356 respondents, 220 (61.8%) took other drugs that might be associated with myopathy while they were on statin therapy. It was found that alcohol (more than 2 drinks daily) was the most commonly consumed drug (95 cases; 26.7% of total respondents), followed by vitamin E (47 cases; 13.2% total respondents), thyroxine (36 cases; 10.1% of total respondents), vitamin D (33 cases; 9.3% of total respondents) and cortisone (23 cases; 6.5% of total respondents) [Table 4.6].

Table 4.6 Other Drugs Used Besides Statin

Drugs	Myopathy (n = 205) N (%)	Non-Myopathy (n = 151) N (%)	Number of Respondents	Proportion of Total Respondents (%)
Diltiazem	5 (2.5%)	3 (1.9%)	8	2.2
Nifedipine	6 (2.9%)	1(0.7%)	7	1.9
Verapamil	2 (1%)	1(0.7%)	3	0.8
Alcohol (more than 2 drinks daily)	51 (24.9%)	44 (29.1%)	95	26.7
Amiodarone	1 (0.5%)	0 (0%)	1	0.3
Antimalarial	12 (5.9%)	1 (0.7%)	13	3.7
Chemotherapy	6 (2.9%)	0 (0%)	6	1.7
Colchicine	6 2.9%()	0 (0%)	6	1.7
Cyclosporin	1 (0.5%)	0 (0%)	1	0.3
Cortisone	21 (10.2%)	2 (1.3%)	23	6.5
Labetalol	1 (0.5%)	0 (0%)	1	0.3
Prednisone	16 (7.8%)	3 (2%)	19	5.3
Thyroxine	23 (11.2%)	13 (8.6%)	36	10.1
Sodium valproate	2 (1%)	1 (0.7%)	3	0.8
Vitamin D	20 (9.8%)	13 (8.6%)	33	9.3
Vitamin E	27 (13.2%)	20 (13.2%)	47	13.2
Warfarin	16 (7.8%)	5 (3.3%)	21	5.9
Other drugs	11 (5.4%)	6 (4%)	17	5.1
None	66 (32.2%)	70 (4.6%)	136	38.2
Total Responses	**293 (142.9%)**	**183 (121.2%)**	**476**	**132**

4.1.6 Statin-Induced Myopathy

On average, respondents in the myopathy group reported around 2.5 muscle symptoms, with the most commonly experienced being night cramps (54.6%), followed by muscle aching (52.7%), and fatigue/tiredness (49.3%) [Table 4.7].

Table 4.7 Muscle Symptoms Suffered in the Myopathy Group

Muscle symptoms	Respondents with myopathy n = 205	Proportion of Respondents* (%)
Cramp at night	112	54.6
Cramp after exercise	40	19.5
Muscle aching/soreness	108	52.7
Fatigue/tiredness	101	49.3
Muscle weakness	66	32.2
Breathlessness with exercise	55	26.8
Other muscle symptoms	28	13.7
Total cases	**510**	**248.8***

*** Note many participants had multiple symptoms**

It was found that the majority of respondents suffering from muscle symptoms reported their calves as the most affected area of the body, accounting for 62%; while hips were reported as the least affected area of the body, affected in only for 0.5% of respondents (Table 4.8).

Table 4.8 Part of the Body Experiencing Muscle Symptoms

Part of the body	Number of Respondents	Proportion of Respondents# (%)
Calves	127	62.0%
Thighs and buttocks	60	29.3%
Back	40	19.5%
Arms	34	16.6%
Hands/fingers	6	2.9%
Neck	9	4.4%
Feet/toes	17	8.3%
Ankles	6	2.9%
Knees	4	2.0%
Shoulders	7	3.4%
Legs	3	1.5%
Chest/ribs	3	1.5%
Hips	1	0.5%
All muscle hurt equally	11	5.4%
No specific part	9	4.4%
Other part of the body	2	1.0%
Total cases	**339**	**165.4%#**

 # Total exceeded more than 100% as many patients suffered muscle cramps in more that one site in the body

The responses revealed that the majority of people in the myopathy group had been suffering from muscle symptoms for a period of 1 to 5 years (Figure 4.1). The symptoms were reported to most likely come and go throughout the day, but least likely to appear after exercise or on awaking (Table 4.9).

Figure 4.1 Duration of myopathy suffered

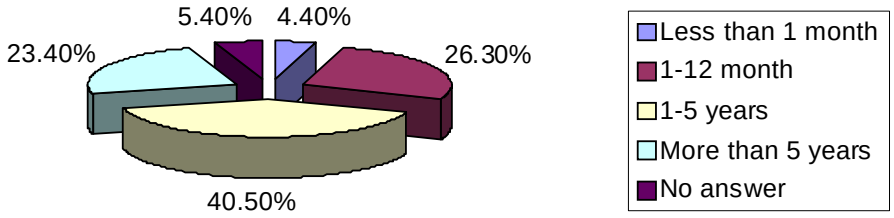


Table 4.9 Frequency of Muscle Symptoms Suffered

Frequency	**Number of Respondents**	**Proprotion of Respondents (%)**
Constant throughout the day	26	12.7
Comes and goes throughout the day	79	38.5
Appears particularly at night	50	24.4
Appears particularly after exercise	5	2.4
Appears particularly while wake up	5	2.4
Appears particularly in the morning	10	4.9
Irregular	22	10.7
No answer	8	3.9
Total	**205**	**100%**

4.1.7 Factors Increasing the Risks of Statin-Induced Myopathy

Logistic regression was performed modeling the dependent variables (myopathy) with a series of explanatory variables including:

1. Patient age
2. Gender of participants
3. Statin therapy (Atorvastatin, Pravastatin and Simvastatin. Fluvastatin data were excluded from analysis due to low number of users)
4. Duration of statin therapy
5. Other diseases suffered (heart failure, ischemia heart disease, hypertension, hypothyroidism, diabetes mellitus and kidney failure)
6. Other medicines taken (cortisone, prednisone, sodium valproate, nifedipine, diltiazem, amiodarone, alcohol, labetolol, and chemotherapy).

Three variables were found to increase the odds of respondents suffering from myopathy. The model only accounted for 11.0 % to 14.7% of the variance in the dependent variable, which may be due to the relatively modest response rate of the respondent in the survey, and also the limited numbers of explanatory variables in explaining the incidence of myopathy. The "goodness of fit test" has a highly significant Chi-square value at 41.142 with 4 degrees of freedom ($P<0.001$). The model correctly identifies 72.9% of cases that suffered from myopathy and 48.3% who did not. Therefore the positive predictive value is 65.4% and the negative predictive value is 57%. Table 4.10 displays the extent to which the variables influenced the outcome variable.

Table 4.10 Variables in the Equation

Variable	β (SE)	p value	Exp (β)	95% CI	
				Lower	Upper
Age	0.039 (0.010)	0.000	1.039	1.019	1.061
Heart failure	2.288 (1.054)	0.034	9.285	1.177	73.217
Cortisone-like drugs	2.793 (1.034)	0.007	16.388	2.161	124.299
Sodium valproate	-2.989 (1.752)	0.088	0.050	0.002	1.560
Constant	-2.246 (0.639)	0.000	0.106	-	-

Statistical analysis with multiple logistic regression found that increasing in age, having heart failure and taking cortisone-like drugs increased statin users susceptible to myopathy. Table 4.10 column Exp (β) shows that, for every 1-year increase in age, the odds of suffering from myopathy increased 1.039 (95% CI 1.019 – 1.061). Furthermore, taking cortisone-like medication increased the odds of suffering myopathy 16.4 times (95% CI; 2.2 – 124.3), while participants with heart failure were 9.3 times (95% CI 1.2 – 73.2) more likely to develop muscle symptoms when prescribed statins.

4.2.COENZYME Q10 FOR MUSCLE CRAMPS STUDY

4.2.1 Recruitment

A total of 61 participants initially enrolled into the study, 35 people in Group A (statin users) and 26 people in Group B (non-statin users). In the middle of the study, six participants withdrew for the following reasons:

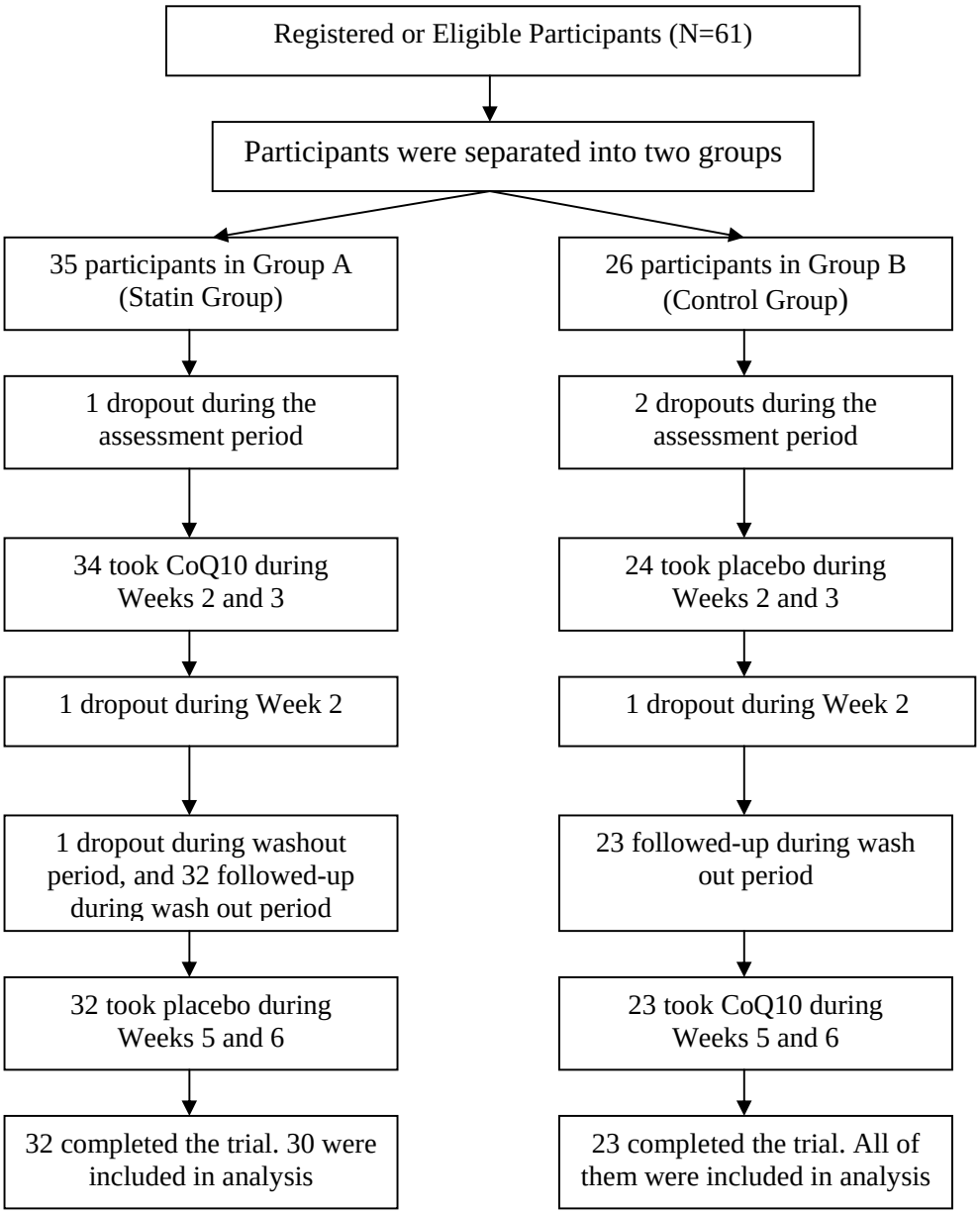
1. Two participants from the Group B and one participant from Group A withdrew during the assessment periods without stating reasons.
2. One participant from the Group B experienced a skin rash while taking placebo (on day 5 of the 2nd week of the study), and decided to withdraw from the trial, and was given antihistamine by the participant's doctor. The Primary Investigator was later informed since the participant commenced the trial in spring, participant's allergy was most probably caused by pollen, not the medicine (placebo).
3. One participant from the Group A decided to withdraw because the participant wanted to continue taking CoQ10 during the wash out period. The participant later decided to buy CoQ10 from a pharmacy and started taking it regularly.
4. One participant from the Group A fell out of the bed, and doctor advised the participant to rest (and to start taking NSAID), and the participant later withdrew from the study.

Thirty-two participants in Group A and 23 participants in Group B completed the study. Data from two participants in Group A were excluded from analysis for the following reasons:

1. One participant did not experience any cramps during the 6 weeks study period, despite having cramps before the study was commenced.
2. One participant experienced the death of sibling in the middle of the study, and then suffered from stress, and felt this increased the condition of cramps.

As a result, there were 30 participants in the Group A and 23 participants in the Group B included in statistical analysis. Flow diagram of the study is summarized in Figure 4.2.

Figure 4.2 Flow Diagram of Clinical Trial



4.2.2 Patient Demographics

The gender mix in the two groups (Table 4.11) was significantly different with the majority of the Group A being females and the majority of the Group B being males (p = 0.003).

Table 4.11 The Age and Gender of Participants

Group	Number (and gender)	Mean of Age (SD) (Years)	p value
A (Statin)	30 (7 Male and 23 Female)	64.5 (8.4)	0.021
B (Control)	23 (17 Male and 6 Female)	58.0 (11.2)	

After testing the data for equality of variance, t testing for the equality of the mean was undertaken. This demonstrated that participants in the Group A were significantly older than those in Group B (mean difference = 9.17 years; 95% CI: 1.02-11.83). Further testing with the Shapiro-Wilk test confirmed that the data of age of participants were normally distributed.

Of the total of 53 participants, 11 (20.8%) reported having a family history associated with muscle cramps. Moreover, 41 (77.4%) reported having cramps at least once a week, and 38 (71.7%) reported experiencing cramps for over 5 years.

In Group A (statin group), atorvastatin 10 mg, was reported as the most commonly prescribed statin, accounting for 30% (Table 4.12).

Table 4.12 Statin Therapy Used in Group A

Statin Used	Number of Respondents	Proportion of Respondents
Atorvastatin 10 mg	9	30.0
Atorvastatin 20 mg	5	16.7
Atorvastatin 40 mg	5	16.7
Atorvastatin80 mg	3	10.0
Fluvastatin 20 mg	1	3.3
Pravastatin 20 mg	2	6.7
Pravastatin 80 mg	1	3.3
Simvastatin 10 mg	2	6.7
Simvastatin 20 mg	1	3.3
Simvastatin 80 mg	1	3.3
Total	**30**	**100**

In the Group A, beside statins, alcohol was the most commonly consumed drug associated with myopathy; making up 11 (36.7%) cases, while in the Group B, magnesium became the most frequently used drug, accounting for 13 (56.5%) cases. (Table 4.13)

Furthermore, none of participants in the Group B (Group B) suffered from hypercholesterolaemia. The most commonly disease suffered by participants in both group was hypertension, accounting for 11 cases (20.8% of total participants) [Table 4.14].

Table 4.13 Drugs Associated with Myopathy Taken by Participants

Drug Used	Group		Number of Respondents	Proportion of Total Participants (n = 53) (%)
	Group A (Statin Users n=30) n (%)	Group B (Non-Statin Users n=23) n (%)		
Alcohol	11 (36.7%)	4 (17.4%)	15	28.3
Cortisone	3 (10%)	1 (4.3%)	4	7.5
Prednisone/Prednisolone	1 (3.3%)	0 (0%)	1	1.9
Thyroxine	2 (6.7%)	2 (8.7%)	4	7.5
Calcium	6 (20%)	10 (43.3%)	16	30.2
Magnesium	8 (26.7%)	13 (56.5%)	21	39.6
Vitamin D	3 (10%)	8 (34.8%)	11	20.7
Vitamin E	4 (13.3%)	8 (34.8%)	12	22.6
None	10 (33.3%)	4 (17.4%)	14	26.4
Total	**48 (160%)**	**50 (217.4%)**	**98**	**185**

Table 4.14 Disease Suffered by Participants

Disease Suffered	Group		Number of Respondents	Proportion of Total Participants (n = 53) (%)
	Group A (Statin Users n=30) n (%)	Group B (Non-Statin Users n=23) n (%)		
Hypertension	3 (10%)	8 (34.8%)	11	20.8
Diabetes Mellitus	3 (10%)	2 (8.7%)	5	9.4
Ischaemic Heart Disease	2 6.7(%)	0 (0%)	2	3.8
Hypothyroidism	2 (6.7%)	2 (8.7%)	4	7.5
None	20 (66.7%)	14 (60.9%)	34	64.2
Total	**30 (%)**	**26 (%)**	**56**	**105.7**

4.2.3 Part of the Body Affected by Cramps

During the study, it was found that the majority of participants reported their calves as the most commonly affected area of the body (34; 64.2% of total participants), while the fingers were reported as the least affected area of the body, only making up 1 case (1.9% of total participants) [Table 4.15].

Table 4.15 Part of the Body Affected During The Study

Part of the Body Affected	**Group**		**Number of Respondents**	**Proportion of Total Participants (n = 53) (%)**
	Group A (Statin Users n=30) n (%)	**Group B (Non-Statin Users n=23) n (%)**		
Calves	20 (66.7%)	14 (60.9%)	34	64.2
Thigh and buttocks	12 (40%)	6 (26.1%)	18	34.0
Back	5 (16.7%)	5 (21.7%)	10	18.9
Feet	7 (23.3%)	9 (39.1%)	16	30.2
Ankles	1 (3.3%)	1 (4.3%)	2	3.8
Toes	2 (6.7%)	0 (0%)	2	3.8
Knees	2 (6.7%)	0 (0%)	2	3.8
Legs	5 (16.7%)	15 (65.2%)	20	37.7
Arms	4 (13.3%)	2 8.7(%)	6	11.3
Hands	3 (10%)	1 (4.3%)	4	7.5
Fingers	1 (3.3%)	0 (0%)	1	1.9
Neck	1 (3.3%)	1 (4.3%)	2	3.8
Shoulders	1 (3.3%)	1 (4.3%)	2	3.8
Total respondents	**64 (213.3%)**	**55 (239.1%)**	**119**	**224.7**

4.2.4 Adverse Events with CoQ10

It was reported that there were no significant differences in the adverse events frequency between CoQ10 and placebo in both statin users (Group A) and non-statin users (Group B). The following symptoms were reported by participants in Group A whilst they were

on either CoQ10 or placebo: nausea, stomach upset, and insomnia. In Group B, participants reported having flu-like symptoms and nausea when they were on CoQ10; and having headache and nausea when they were on placebo (Table 4.16). There were no participants who had multiple subjective symptoms, and these symptoms stopped without requiring any treatment.

Table 4.16 Adverse Events with CoQ10 and Placebo

Symptoms	Group A		Group B	
	CoQ10 n (%)	Placebo n (%)	CoQ10 n (%)	Placebo n (%)
Nausea	1 (3.3%)	1 (4.3%)	1 (3.3%)	1 (4.3%)
Stomach upset	1 (3.3%)	1 (4.3%)	0 (0%)	0 (0%)
Flu-like symptoms	0 (0%)	0 (0%)	1 (3.3%)	0 (0%)
Headache	0 (0%)	0 (0%)	0 (0%)	1 (4.3%)
Insomnia	1 (3.3%)	1 (4.3%)	0 (0%)	0 (0%)

4.2.5 Co-Enzyme Q10 Efficacy

The efficacy of co-enzyme Q10 was assessed on the basis of changes in the following:

- The average number of days per week participants suffered muscle cramps
- The average number of muscle cramps suffered per week
- The intensity of the pain associated with the muscle cramps
- The average duration of the cramps suffered per week

4.2.5.1 Days with muscle cramps

4.2.5.1.1 Group A – Statin Users

Table 4.17 below shows the number of days per week each patient in the Group A reported suffering muscle cramps across the 6 weeks of the study; which varied considerably between the participants.

Table 4.17 Group A – Days per week with muscle cramps

Patient No.	Days per week with muscle cramp					
	Week 1	**Week 2**	**Week 3**	**Week 4**	**Week 5**	**Week 6**
	Baseline	Co-Enzyme Q10		Washout	Placebo	
1	3	2	2	4	3	5
2	5	2	3	5	2	2
3	5	4	4	5	5	6
4	2	0	1	2	1	1
5	7	7	7	7	7	7
6	4	1	1	2	2	1
7	7	7	7	7	7	7
8	1	2	2	1	0	0
9	4	5	4	3	5	5
10	3	5	4	3	2	4
11	5	4	2	5	3	4
12	7	6	6	7	6	5
13	1	0	0	1	0	1
14	3	1	0	1	2	1
15	6	6	6	6	4	4
16	2	1	1	2	1	2
17	2	1	1	4	3	2
18	3	0	1	2	2	2
19	7	6	6	6	4	4
20	6	3	3	5	4	5
21	0	0	0	1	0	1
22	7	3	3	5	4	3
23	3	3	1	2	2	2
24	2	1	1	2	2	2
25	2	1	2	1	1	1
26	2	1	1	1	3	3
27	2	2	1	3	3	3
28	4	2	3	6	5	4
29	3	4	4	2	3	4
30	2	1	2	3	4	3
MEAN	**3.7**	**2.7**	**2.6**	**3.5**	**3.0**	**3.1**
SD	**2.1**	**2.2**	**2.1**	**2.0**	**1.9**	**1.9**

As an overall trend, the average numbers of days per week with muscle cramps were lowest when the participants received CoQ10 100 mg daily (Weeks 2 and 3), and highest when they were not on a trial "medication" (i.e. either CoQ10 or placebo), that being the baseline period (Week 1) and the wash out period (Week 4). On average, participants suffered more days with cramps during the time they were on placebo (Week 5 and 6) than on CoQ10 (Weeks 2 and 3), but less that when they were on no medication at all (Weeks 1 and 4) (Table 4.17).

Amongst the 30 participants in the Group A, 19 people (63.3%) showed positive responses with CoQ10 (i.e. they experienced fewer days with muscle cramps) while eight people (26.7%) showed positive responses with placebo. The remaining three participants (10%) did not experience any differences in their leg cramp frequency on either CoQ10 or placebo.

Repeated Measures ANOVA was performed to determine whether or not there were any differences in the number of days per week with muscle cramps in the Group A over a 6-week period of time. The data were found to have violated the sphericity assumption (the variances across the weeks were not equal), thus Greenhouse-Geisser correction was then used to provide a valid F-ratio[97]. It was then found that the frequency of muscle cramps differed significantly over the 6 weeks of the study, with $F(3.391, 98.351) = 6.407$, $p = 0.000$ (using Greenhouse-Geisser correction).

Scheffè testing was then undertaken to determine where significant differences existed in the frequency of muscle cramps between the weeks of the study (Table 4.18). Here (I) equals the index week and (J) the comparator week. A result in (I – J) represents mean difference in the muscle cramp frequency between weeks. Those differences marked with an asterisk are statistically significant at the 0.05 levels.

Table 4.18 Group A- Significant Inter-Week Differences in Cramp Frequency as Identified by Scheffè testing

(I) Week	(J) Week	Mean Difference (I-J) Lower Bound	SE	p value (a)	95% Confidence Interval for Difference (a)	
					Lower Bound	Upper Bound
1	2	0.967(*)	0.251	0.001	0.453	1.481
	3	1.033(*)	0.232	0.000	0.558	1.509
	4	0.200	0.188	0.297	-0.185	0.585
	5	0.667(*)	0.237	0.009	0.183	1.150
	6	0.533	0.274	0.062	-0.028	1.094
2	1	-.967(*)	0.251	0.001	-1.481	-0.453
	3	0.067	0.143	0.645	-0.226	0.360
	4	-.767(*)	0.270	0.008	-1.319	-0.215
	5	-0.300	0.263	0.264	-0.838	0.238
	6	-0.433	0.238	0.079	-0.921	0.054
3	1	-1.033(*)	0.232	0.000	-1.509	-0.558
	2	-0.067	0.143	0.645	-0.360	0.226
	4	-0.833(*)	0.230	0.001	-1.304	-0.362
	5	-0.367	0.237	0.133	-0.852	0.119
	6	-0.500(*)	0.234	0.041	-0.978	-0.022
4	1	-0.200	0.188	0.297	-0.585	0.185
	2	0.767(*)	0.270	0.008	0.215	1.319
	3	0.833(*)	0.230	0.001	0.362	1.304
	5	0.467(*)	0.208	0.032	0.042	0.891
	6	0.333	0.237	0.169	-0.150	0.817
5	1	-0.667(*)	0.237	0.009	-1.150	-0.183
	2	0.300	0.263	0.264	-0.238	0.838
	3	0.367	0.237	0.133	-0.119	0.852
	4	-0.467(*)	0.208	0.032	-0.891	-0.042
	6	-0.133	0.157	0.403	-0.455	0.188
6	1	-0.533	0.274	0.062	-1.094	0.028
	2	0.433	0.238	0.079	-0.054	0.921
	3	0.500(*)	0.234	0.041	0.022	0.978
	4	-0.333	0.237	0.169	-0.817	0.150
	5	0.133	0.157	0.403	-0.188	0.455

Based on estimated marginal means

* The mean difference is significant at the .05 level.

a Adjustment for multiple comparisons: Least Significant Difference (equivalent to no adjustments).

The Scheffè test showed there was a significant difference in the number of days per week with muscle cramp during the time when participants were on no medication (Weeks 1 and 4), on CoQ10 (Weeks 2 and 3) and on placebo (Weeks 5 and 6). Furthermore, there was a significant difference between the number of days per week with muscle cramps in Week 3 (the second week participants received CoQ10) and that in Week 6 (the second week participants received placebo), $p<0.05$.

Further thorough testing using t-paired analysis was performed to determine whether there were any differences in the frequency of muscle cramps between the two medication periods, namely the periods participants were on CoQ10 **(Weeks 2 + 3)** and the periods they were on placebo **(Weeks 5 + 6).** From t-paired analysis, on average, participants suffered fewer days with cramps during the periods they were on CoQ10 (Weeks 2 + 3; mean score= 5.33 ± 0.77 days) than on placebo (Weeks 5 + 6; mean score= 6.13 ± 0.67 days). However, the differences were not statistically significant ($t(29) = -1.827$, 95% CI= -1.696 – 0.096; $p=0.078$)

4.2.5.1.2 Group B –non-statin users (Controls)

Table 4.19 below shows the number of days per week each patient in the Group B reported muscle cramps across the 6 weeks of the study, which varied considerably between the participants.

Table 4.19 Group B – Days per week with muscle cramps

Patient No	Days per week with muscle cramps					
	Week 1	**Week 2**	**Week 3**	**Week 4**	**Week 5**	**Week 6**
	Baseline	Placebo		Washout	CoQ10	
1	6	3	2	2	2	6
2	6	6	7	6	6	5
3	4	2	3	3	1	1
4	5	4	3	5	3	5
5	2	1	1	1	1	0
6	1	1	1	2	1	1
7	6	5	5	6	6	6
8	5	4	5	4	3	3
9	1	0	0	2	2	1
10	4	3	5	6	4	3
11	3	2	2	4	2	3
12	3	5	3	4	4	2
13	4	3	5	3	4	4
14	3	1	2	2	1	1
15	2	1	1	2	1	0
16	6	6	5	6	4	4
17	4	2	3	3	4	2
18	4	4	2	3	1	2
19	5	4	2	4	2	2
20	4	2	2	2	1	2
21	7	6	5	6	7	5
22	5	4	6	5	7	7
23	7	6	4	6	6	6
MEAN	**4.2**	**3.3**	**3.2**	**3.8**	**3.2**	**3.1**
SD	**1.7**	**1.9**	**1.9**	**1.7**	**2.1**	**2.1**

In general, the average numbers of days per week with muscle cramps were lowest when the participants received CoQ10 100 mg (Weeks 5 and 6), and highest when they were not on medication, namely the baseline period (Week 1) and the wash out period (Week 4). On average, participants suffered less cramps when they were on placebo (Weeks 2

and 3) than on the baseline and washout periods (Weeks 1 and 4), but slightly more than when they were on CoQ10 (Weeks 2 and 3) [Table 4.19].

Amongst the 23 participants in the Group B, 11 (47.8%) showed positive responses with CoQ10 (i.e. they experienced fewer days with muscle cramps), and 10 (43.5%) experienced positive responses with placebo. The remaining two participants (8.7%) did not experience any differences in the number days per week with muscle cramps with both CoQ10 and placebo.

Repeated measures ANOVA analysis was performed to determine whether or not there were any differences in the number of days per week with muscle cramps in the Group B over a 6-week period of time. This demonstrated that the frequency of muscle cramps differed significantly over the 6 weeks of the study, with $F(5,110) = 5.93$, $p=0.000$.

Scheffè testing was then undertaken to determine where significant differences existed in the frequency of muscle cramps between the weeks of study (Table 4.20).

Table 4.20: Group B- Significant Inter-Week Differences in Cramp Frequency as Identified by Scheffè testing

(I) Week	(J) Week	Mean Difference (I-J)	SE	p value (a)	95% Confidence Interval for Difference (a)	
					Lower Bound	Upper Bound
1	2	0.957(*)	.204	0.000	0.534	1.379
	3	1.000(*)	.281	0.002	0.417	1.583
	4	0.435	.258	0.106	-0.100	0.970
	5	1.043(*)	.324	0.004	0.373	1.714
	6	1.130(*)	.254	0.000	0.604	1.657
2	1	-0.957(*)	.204	0.000	-1.379	-0.534
	3	0.043	.270	0.874	-0.517	0.604
	4	-0.522(*)	.207	0.020	-0.952	-.092
	5	0.087	.294	0.770	-0.523	0.697
	6	0.174	.312	0.583	-0.473	0.821
3	1	-1.000(*)	.281	0.002	-1.583	-0.417
	2	-0.043	.270	0.874	-0.604	0.517
	4	-0.565(*)	.234	0.024	-1.050	-0.080
	5	0.043	.247	0.862	-0.469	0.556
	6	0.130	.316	0.684	-0.525	0.786
4	1	-0.435	.258	0.106	-0.970	0.100
	2	0.522(*)	.207	0.020	0.092	0.952
	3	0.565(*)	.234	0.024	0.080	1.050
	5	0.609(*)	.249	0.023	0.091	1.126
	6	0.696(*)	.311	0.036	0.051	1.340
5	1	-1.043(*)	.324	0.004	-1.714	-0.373
	2	-0.087	.294	0.770	-0.697	0.523
	3	-0.043	.247	0.862	-0.556	0.469
	4	-0.609(*)	.249	0.023	-1.126	-0.091
	6	0.087	.281	0.760	-0.495	0.669
6	1	-1.130(*)	.254	0.000	-1.657	-0.604
	2	-0.174	.312	0.583	-0.821	0.473
	3	-0.130	.316	0.684	-0.786	0.525
	4	-0.696(*)	.311	0.036	-1.340	-0.051
	5	-0.087	.281	0.760	-0.669	0.495

Based on estimated marginal means

* The mean difference is significant at the .05 level.

A Adjustment for multiple comparisons: Least Significant Difference (equivalent to no adjustments).

The Scheffè test showed there was a significant difference in the number of days per week with muscle cramps during the time when participants were on no medication (Weeks 1 and 4) and on CoQ10 (Weeks 5 and 6), and placebo (Weeks 2 and 3); $p<0.05$.
Further t-test (paired analysis) was performed to determine whether there were any differences in the frequency of muscle cramps between the two medication periods, namely the periods when participants were on CoQ10 **(Weeks 5 + 6)** and those when they were on placebo **(Weeks 2 + 3).** From t-paired analysis, on average, participants suffered more days with cramps during the periods they were on placebo (Weeks 2 + 3; mean score= 6.486 ± 0.73), than on CoQ10 (Weeks 5 + 6; mean score = 6.26 ± 0.83). However, these differences were not statistically significant (t (22) = 0.494; (95% CI= -0.695 – 1.130; p=0.626).

4.5.2.2 Number of muscle cramps

4.5.2.2.1 Group A - Statin group

Table 4.21 below shows the number of muscle cramps per week suffered by each patient in the Group A, which varied considerably across the participants.

Table 4.21 Group A – Number of muscle cramps per week

Patient No	Number of muscle cramps per week					
	Week 1	**Week 2**	**Week 3**	**Week 4**	**Week 5**	**Week 6**
	Baseline	CoQ10		Washout	Placebo	
1	5	4	5	6	5	5
2	5	2	3	5	2	2
3	10	7	7	9	9	10
4	4	0	2	2	3	2
5	15	13	11	11	12	12
6	4	1	1	3	4	3
7	7	7	7	7	7	7
8	1	2	2	1	0	0
9	4	6	5	4	7	6
10	3	5	4	4	3	3
11	7	6	4	7	8	7
12	11	11	10	12	8	8
13	1	0	0	1	0	1
14	3	1	0	1	2	1
15	7	9	8	7	5	5
16	2	1	1	2	1	2
17	2	1	1	4	3	2
18	3	0	1	2	2	2
19	8	8	7	6	6	5
20	7	5	4	8	5	6
21	0	0	0	1	0	1
22	8	5	5	8	7	8
23	3	3	1	2	3	2
24	2	1	1	2	2	2
25	2	1	2	1	1	1
26	3	2	1	3	4	4
27	2	2	2	3	4	3
28	4	2	3	6	5	5
29	3	5	5	2	3	4
30	2	1	2	3	4	3
MEAN	**4.6**	**3.7**	**3.5**	**4.4**	**4.2**	**4.1**
SD	**3.4**	**3.5**	**3.0**	**3.0**	**2. 9**	**2.9**

In general, the average numbers of muscle cramps per week were highest when participants were on no medication (Weeks 1 and 4), and lowest when they were on CoQ10 100 mg (Weeks 2 and 3). Furthermore, participants suffered less cramps when they were on placebo (Weeks 5 and 6) than on the baseline and washout periods (Weeks 1 and 4), but more than when they were on CoQ10 (Weeks 2 and 3) [Table 4.21].

Of the 30 participants in the Group A, 20 (66.7%) showed positive responses to CoQ10 (i.e. they experienced fewer cramps) while eight of them (26.7%) experienced positive responses to placebo. The remaining two participants (6.7%) did not experience any differences in their cramps frequency with both CoQ10 and placebo.

Repeated measures ANOVA analysis was performed to determine whether or not there were any differences in the number of cramps in the Group A over a 6-week period of time. The data were found to have violated the sphericity assumption (the variances across the weeks were not equal), thus Greenhouse-Geisser correction was then used to provide a valid F-ratio[97]. It was then found that the number of cramps was significantly different over the weeks of treatment, $F(3.015, 87.440) = 4.609$, $p=0.005$ (using Greenhouse-Geisser correction).

Scheffè testing was then undertaken to determine where the significant differences existed in the numbers of muscle cramps between the weeks of study (Table 4.22).

Table 4.22 Group A- Significant Inter-Week Differences in the number of muscle cramps as Identified by Scheffè testing

(I) Week	(J) Week	Mean Difference (I-J)	SE	p value (a)	95% Confidence Interval for Difference (a)	
					Lower Bound	Upper Bound
1	2	0.900(*)	0.301	0.006	0.285	1.515
	3	1.100(*)	0.281	0.001	0.525	1.675
	4	0.167	0.235	0.484	-0.315	0.648
	5	0.433	0.270	0.119	-0.119	0.985
	6	0.533(*)	0.252	0.043	0.017	1.050
2	1	-0.900(*)	0.301	0.006	-1.515	-0.285
	3	0.200	0.182	0.281	-0.172	0.572
	4	-0.733(*)	0.332	0.035	-1.412	-0.054
	5	-0.467	0.345	0.186	-1.172	0.239
	6	-0.367	0.334	0.281	-1.049	0.316
3	1	-1.100(*)	0.281	0.001	-1.675	-0.525
	2	-0.200	0.182	0.281	-0.572	0.172
	4	-0.933(*)	0.283	0.003	-1.513	-0.354
	5	-0.667(*)	0.316	0.043	-1.312	-0.021
	6	-0.567	0.294	0.064	-1.169	0.035
4	1	-0.167	0.235	0.484	-0.648	0.315
	2	0.733(*)	0.332	0.035	0.054	1.412
	3	0.933(*)	0.283	0.003	0.354	1.513
	5	0.267	0.271	0.333	-0.287	0.821
	6	0.367	0.237	0.133	-0.119	0.852
5	1	-0.433	0.270	0.119	-0.985	0.119
	2	0.467	0.345	0.186	-0.239	1.172
	3	0.667(*)	0.316	0.043	0.021	1.312
	4	-0.267	0.271	0.333	-0.821	0.287
	6	0.100	0.139	0.476	-0.183	0.383
6	1	-0.533(*)	0.252	0.043	-1.050	-0.017
	2	0.367	0.334	0.281	-0.316	1.049
	3	0.567	0.294	0.064	-0.035	1.169
	4	-0.367	0.237	0.133	-0.852	0.119
	5	-0.100	0.139	0.476	-0.383	0.183

Based on estimated marginal means

* The mean difference is significant at the .05 level.

A Adjustment for multiple comparisons: Least Significant Difference (equivalent to no adjustments).

The Scheffè test showed there were significant differences in the number of muscle cramps between Week 1 (the baseline period) and Weeks 2 and 3 (CoQ10 period) and also Week 6 (placebo period). It was also revealed that the number of muscle cramps differed significantly between the washout period (Week 4) and CoQ10 period (Weeks 2 and 3). Furthermore, there was a significant difference in cramps numbers between Week 3 (the second week when participants received CoQ10) and week 5 (the first week when participants received placebo), with $p<0.05$.

Further thorough testing using t-paired analysis was performed to determine whether there were any differences in the number of muscle cramps between two medication periods, namely the periods when participants were on CoQ10 **(Weeks 2 + 3)** and those when they were on placebo **(Weeks 5 + 6).** From t-paired analysis, on average, participants suffered fewer muscle cramps during the periods they were on CoQ10 (Weeks 2 + 3; mean score= 7.20 ± 1.16), than on placebo (Weeks 5 + 6; mean score= 8.23 ± 1.05). However, these differences were not statistically significant ($t(29)= -1.712$, 95% CI= -2.268 – 0.201; $p=0.098$).

4.2.5.2.2 Group B – non statin users (Controls)

Table 4.23 below presents the number of cramps per week suffered by each patient in the Group B over the 6 weeks of the study, which varied considerably between the participants.

In general, the average numbers of muscle cramps per week were highest when they were on no medication, namely the baseline period (Week 1) and the wash out period (Week 4), and lowest when they were on CoQ10 100 mg daily (Weeks 5 and 6). On average, participants suffered slightly more muscle cramps when they were on placebo (Weeks 2 and 3) than on COQ10, but less that when they were on no medication at all (Weeks 1 and 4) [Table 4.23].

Table 4.23 Group B – Number of muscle cramps per week

Patient No	Number of muscle cramps per week					
	Week 1	**Week 2**	**Week 3**	**Week 4**	**Week 5**	**Week 6**
	Baseline	Placebo		Washout	CoQ10	
1	6	3	3	4	2	6
2	10	9	8	9	8	7
3	3	2	2	3	1	1
4	13	14	13	15	14	16
5	3	2	1	1	1	0
6	1	1	1	2	1	1
7	12	10	10	12	11	11
8	6	6	7	6	6	5
9	2	0	0	2	2	0
10	4	4	6	6	5	5
11	3	3	2	4	2	3
12	6	5	5	6	4	4
13	9	7	8	9	7	6
14	3	1	2	2	1	1
15	2	2	1	4	1	0
16	10	9	9	10	9	10
17	5	2	3	4	4	2
18	5	4	2	3	3	2
19	6	4	4	5	3	3
20	4	3	3	3	1	2
21	12	10	9	12	11	9
22	9	7	8	9	8	8
23	11	8	8	10	9	9
MEAN	**6.3**	**5.0**	**5.0**	**6.1**	**5.0**	**4.8**
SD	**3.7**	**3.6**	**3.6**	**3.7**	**3.9**	**4.2**

Of the 23 people assigned to Group B, 11 of them (47.8%) noted that they experienced fewer cramps when they were on CoQ10 (Weeks 5 and 6); whereas, nine people (39.1%) reported they had fewer cramps while they were on placebo. The remaining three participants (13%) did not experience any differences in their cramp frequency with both CoQ10 and placebo.

Table 4.24 Group B- Significant Inter-Week Differences in the numbers of muscle cramps as Identified by Scheffè testing

(I) Week	(J) Week	Mean Difference (I-J)	SE	P value (a)	95% Confidence Interval for Difference(a)	
					Lower Bound	Upper Bound
1	2	1.261(*)	0.229	0.000	0.787	1.735
	3	1.304(*)	.0263	0.000	0.760	1.849
	4	0.174	.0249	0.492	-0.342	0.690
	5	1.348(*)	.0256	0.000	0.816	1.879
	6	1.478(*)	.0326	0.000	0.802	2.154
2	1	-1.261(*)	.0229	0.000	-1.735	-0.787
	3	0.043	.0194	0.824	-0.358	0.445
	4	-1.087(*)	.0198	0.000	-1.497	-0.676
	5	0.087	.0226	0.704	-0.382	0.555
	6	0.217	.0281	0.447	-0.365	0.800
3	1	-1.304(*)	.0263	0.000	-1.849	-0.760
	2	-0.043	.0194	0.824	-0.445	0.358
	4	-1.130(*)	.0202	0.000	-1.549	-0.712
	5	0.043	.0222	0.847	-0.417	0.504
	6	0.174	.0279	0.539	-0.404	0.752
4	1	-0.174	.0249	0.492	-0.690	0.342
	2	1.087(*)	.0198	0.000	0.676	1.497
	3	1.130(*)	.0202	0.000	0.712	1.549
	5	1.174(*)	.0174	0.000	0.813	1.535
	6	1.304(*)	.0263	0.000	0.760	1.849
5	1	-1.348(*)	.0256	0.000	-1.879	-0.816
	2	-0.087	.0226	0.704	-0.555	0.382
	3	-0.043	.0222	0.847	-0.504	0.417
	4	-1.174(*)	.0174	0.000	-1.535	-0.813
	6	0.130	.0283	0.650	-0.457	0.718
6	1	-1.478(*)	.0326	0.000	-2.154	-0.802
	2	-0.217	.0281	0.447	-0.800	0.365
	3	-0.174	.0279	0.539	-0.752	0.404
	4	-1.304(*)	.0263	0.000	-1.849	-0.760
	5	-0.130	.0283	0.650	-0.718	0.457
Based on estimated marginal means						
* The mean difference is significant at the .05 level.						
A Adjustment for multiple comparisons: Least Significant Difference (equivalent to no adjustments).						

Repeated measures ANOVA analysis was performed to determine whether or not there were any differences in the number of cramps in the Group B over the 6-week period of time. This identified that the number of cramps differed significantly over the 6 weeks of the study, with $F(5,110) = 14.273$, $p=0.000$.

Scheffè testing was then undertaken to determine where significant differences existed in the numbers of muscle cramps between the weeks of the study (Table 4.24). The Scheffè test showed that the number of cramps on the baseline period (Weeks 1) and the washout period (Week 4) was significantly different, and much higher than cramp numbers on COQ10 periods (Weeks 2 and 3) and placebo periods (Weeks 5 and 6), with $p<0.01$.

Further thorough testing using t-paired analysis was performed to determine whether there were any differences in the number of cramps between the two medication periods, namely the periods when participants were on CoQ10 **(Weeks 5 + 6)** and those when they were on placebo **(Weeks 2 + 3).** From t-paired analysis, on average, participants suffered more muscle cramps during the periods they were on placebo (Weeks 2 + 3; mean score= 10.04 ± 1.49), than on CoQ10 (Weeks 5 + 6; mean score= 9.78 ± 1.67). However, the differences were not statistically significant ($t(22) = 0.699$, 95% CI= -0.513 – 1.035; p= 0.492).

4.2.5.3. Average Pain Score Associated with Muscle Cramps

4.2.5.3.1 Group A - Statin Group

Table 4.25 below presents the mean of the average weekly pain scores associated with the muscle cramps from each statin user across the 6 weeks of the study.

Table 4.25 Group A – Mean of average pain scores per week

Patient No	*Mean of average pain score per week*					
	Week 1	**Week 2**	**Week 3**	**Week 4**	**Week 5**	**Week 6**
	Baseline	CoQ10		Washout	Placebo	
1	7.2	6.0	6.5	7.0	7.0	7.3
2	4.0	4.0	5.0	6.0	5.0	4.0
3	2.7	2.2	1.2	1.5	1.4	2.7
4	3.0	0.0	1.0	2.0	3.0	2.0
5	2.4	1.5	1.4	1.4	1.7	1.4
6	1.0	2.0	1.0	1.0	1.0	1.0
7	2.0	1.0	1.0	2.0	2.0	2.0
8	3.0	3.0	2.5	2.0	0	0
9	3.3	3.3	3.2	3.0	4.1	3.8
10	5.0	3.4	3.3	5.0	4.3	4.7
11	2.6	2.0	1.0	2.4	2.3	2.8
12	3.4	5.0	5.0	3.8	3.0	3.0
13	2.0	0.0	0	3.0	0	1.0
14	2.0	1.5	0	2.0	2.0	1.5
15	5.8	5.0	6.0	5.0	5.0	5.0
16	7.0	6.0	5.0	6.0	8.0	7.0
17	9.0	7.5	7.0	10	9.0	8.0
18	1.0	0.0	1.0	2.0	1.0	1.0
19	6.5	5.0	4.5	5.0	6.0	7.0
20	6.0	4.0	4.0	4.0	5.0	4.0
21	0	0	0	1.0	0.0	2.0
22	4.0	3.0	3.0	3.5	4.0	4.0
23	2.0	2.0	2.0	4.0	2.0	3.0
24	8.0	6.0	5.5	7.0	8.0	7.0
25	3.0	4.0	2.0	2.0	2.0	2.0
26	4.5	3.7	3.5	3.8	4.0	4.0
27	6.5	7.0	6.0	6.0	7.0	8.0
28	4.0	3.0	3.0	6.0	5.0	5.0
29	3.0	5.0	5.0	3.0	3.0	3.0
30	5.0	2.0	3.0	4.0	5.0	3.0
MEAN	**4.0**	**3.3**	**3.0**	**3.8**	**3.7**	**3.7**
SD	**2.2**	**2.1**	**2.1**	**2.1**	**2.5**	**2.3**

As an overall trend, the mean of the average daily pain score associated with the muscle cramps per week was lowest when participants were on CoQ10 100 mg daily (Weeks 2 and 3), and highest when they were on no medication, namely the baseline period (Week 1) and the wash out period (Week 4). On average, participants experienced a lower mean average daily pain score when they were on placebo (Weeks 5 and 6) than the baseline and the washout periods, but higher than when they were on CoQ10 therapy.

It is found while seven of the 30 people (23.3%) in the Group A noted their pain scores were lower when they were on placebo, 22 of them (73.3%) pointed out they had a minimal pain score with CoQ10. On the other hand, one person (3.3%) noted not experiencing any difference in the average pain score with both CoQ10 and placebo.

Repeated measures ANOVA analysis was performed to determine whether or not there were any differences in the average pain score associated with the muscle cramps in the Group A over the 6-week period of time. The data were found to have violated the sphericity assumption (the variances across the weeks were not equal), thus Greenhouse-Geisser correction was then used to provide a valid F-ratio[97]. The results show that the average pain score was significantly different over the weeks of treatment, $F(3.234, 93.784) = 5.191$, $p=0.002$ (using Greenhouse-Geisser correction).

Scheffè testing was then undertaken to determine where significant differences existed in the average pain score associated with the muscle cramps between the weeks of study (Table 4.26).

Table 4.26 Group A- Significant Inter-Week Differences in Average Pain Scores as Identified by Scheffè testing

(I) Week	(J) Week	Mean Difference (I-J)	SE	p value (a)	95% Confidence Interval for Difference (a)	
					Lower Bound	Upper Bound
1	2	0.693(*)	0.217	0.003	0.250	1.136
	3	0.877(*)	0.208	0.000	0.452	1.301
	4	0.150	0.192	0.440	-0.242	0.542
	5	0.270	0.155	0.091	-0.046	0.586
	6	0.290	0.188	0.133	-0.094	0.674
2	1	-0.693(*)	0.217	0.003	-1.136	-0.250
	3	0.183	0.138	0.194	-0.099	0.466
	4	-0.543(*)	0.253	0.040	-1.061	-0.026
	5	-0.423	0.259	0.113	-0.953	0.107
	6	-0.403	0.232	0.093	-0.879	0.072
3	1	-0.877(*)	0.208	0.000	-1.301	-0.452
	2	-0.183	0.138	0.194	-0.466	0.099
	4	-0.727(*)	0.217	0.002	-1.170	-0.283
	5	-.0607(*)	0.239	0.017	-1.096	-0.117
	6	-0.587(*)	0.233	0.018	-1.064	-0.109
4	1	-0.150	0.192	0.440	-0.542	0.242
	2	0.543(*)	0.253	0.040	0.026	1.061
	3	0.727(*)	0.217	0.002	0.283	1.170
	5	0.120	0.199	0.550	-0.286	0.526
	6	0.140	0.195	0.478	-0.258	0.538
5	1	-0.270	0.155	0.091	-0.586	0.046
	2	0.423	0.259	0.113	-0.107	0.953
	3	0.607(*)	0.239	0.017	0.117	1.096
	4	-0.120	0.199	0.550	-0.526	0.286
	6	0.020	0.154	0.898	-0.295	0.335
6	1	-0.290	0.188	0.133	-0.674	0.094
	2	0.403	0.232	0.093	-0.072	0.879
	3	0.587(*)	0.233	0.018	0.109	1.064
	4	-0.140	0.195	0.478	-0.538	0.258
	5	-0.020	0.154	0.898	-0.335	0.295

Based on estimated marginal means

* The mean difference is significant at the .05 level.

A Adjustment for multiple comparisons: Least Significant Difference (equivalent to no adjustments).

From the table above, it can be seen that there was a significant difference in the mean average daily pain score between the periods when participants were on no medication (Weeks 1 and 4) and those when they were on CoQ10 (Weeks 2 and 3); $p<0.05$. It is also noted that the mean average daily pain scores of the no medication periods (Weeks 1 and 4) and placebo period (Weeks 5 and 6) did not differ significantly, with $p>0.05$.

Further thorough testing using t-paired analysis performed to determine whether there were any differences in the average pain score associated with the muscle cramps between two medication periods, namely the periods when participants were on CoQ10 **(Weeks 2 + 3)** and those when they were on placebo **(Weeks 5 + 6).** From t-paired analysis, on average, participants experienced significantly lower average pain scores during the periods they were on CoQ10 (Weeks 2 + 3; mean score= 6.36 ± 0.75), than on placebo (Weeks 5 + 6; mean score= 7.37 ± 0.85), with t (29) = - 2.316; 95% CI= -1.902 – -0.118; p= 0.028.

4.2.5.3.2 Group B –non-statin users (Controls)

Table 4.27 below presents the mean of average pain scores associated with the muscle cramps from each patient in the Group B across the 6 weeks of the study.

Table 4.27 Group B – Mean of average pain scores per week

Patient No	Mean of average daily pain score per week					
	Week 1	**Week 2**	**Week 3**	**Week 4**	**Week 5**	**Week 6**
	Baseline	Placebo		Washout	CoQ10	
1	2.2	3.3	3.5	3.5	2.0	2.7
2	2.0	1.5	1.0	1.0	1.5	2.0
3	2.4	2.0	3.0	3.0	1.0	2.0
4	3.0	4.0	4.0	3.5	6.0	6.5
5	2.0	2.0	1.0	2.0	1.0	0
6	3.0	2.0	2.0	3.0	2.0	3.0
7	4.0	4.0	3.0	4.0	4.0	3.0
8	6.0	6.5	8.0	7.0	7.0	8.0
9	1.0	0	0	1.0	1.0	0
10	2.0	2.2	1.8	2.2	1.7	1.7
11	5.5	4.5	5.0	5.0	4.0	4.0
12	5.7	4.8	4.3	5.5	4.3	4.0
13	4.0	3.3	3.0	3.3	2.8	2.5
14	3.0	2.8	3.0	3.0	2.5	2.5
15	5.0	2.0	2.0	4.0	3.0	0
16	3.1	3.8	2.7	2.4	2.7	2.3
17	4.5	3.8	4.5	5.0	4.3	4.0
18	2.8	1.5	1.0	2.0	2.0	2.0
19	3.8	3.0	2.5	3.4	2.5	2.7
20	4.0	4.5	5.0	5.0	5.0	6.0
21	5.4	5.0	4.8	5.3	5.0	4.5
22	8.2	7.0	7.0	8.1	7.0	8.0
23	7.2	8.0	9.0	7.0	7.5	8.0
MEAN	**3.9**	**3.5**	**3.5**	**3.9**	**3.5**	**3.4**
SD	**1.8**	**1.9**	**2.2**	**1.9**	**2.0**	**2.4**

In general, the mean of the mean average daily pain scores per week was lowest when participants were on either placebo (Weeks 2 and 3) or CoQ10 100 mg daily (Weeks 5 and 6), and highest when they were on no medication, namely the baseline period (Week 1) and the wash out period (Week 4).

It is found while eight of 23 participants (34.8%) noted their pain scores were lower when they were on placebo, 14 of them (60.1%) pointed out they had minimal pain score with CoQ10. One participant (4.4%) was noted not experiencing any differences in their average pain score with both CoQ10 and placebo.

Repeated measures ANOVA analysis was performed to determine whether or not there were any differences in the average pain score associated with the muscle cramps in the Group B over the 6-week period of time. The data were found to have violated the sphericity assumption (the variances across the weeks were not equal), thus Greenhouse-Geisser correction was then used to provide a valid F-ratio. The results show that the average pain score was not significantly different over 6 weeks period of time, F (2.349, 51.681) = 1.909, p= 0.152 (using Greenhouse-Geisser correction). The interpretation of the results (Scheffè test) was discontinued because the main effects were non-significant.

Further t-paired analysis was undertaken to determine whether there were any differences in the mean average daily pain scores between the two medication periods, namely the periods when participants were on CoQ10 **(Weeks 5 + 6)** and those when they were on placebo **(Weeks 2 + 3).** It was found that, on average, participants experienced a higher average pain scores during the periods they were on placebo (**Weeks 2 + 3**; mean score= 7.07 ± 0.86), than on CoQ10 (**Weeks 5 + 6**; mean score= 6.92 ± 0.91). However, this difference was not statistically significant (t (22) = 0.463; (95% CI= -0.514 – 0.809; p= 0.648).

4.2.5.4. Maximum Pain Score Associated with the Muscle Cramps

4.2.5.4.1 Group A - Statin Group

Table 4.28 below shows the mean of maximum pain scores associated with the muscle cramps from each statin user over the 6 weeks of the study.

Table 4.28 Group A – Mean of maximum pain score per week

Patient No	Mean of maximum pain score per week					
	Week 1	**Week 2**	**Week 3**	**Week 4**	**Week 5**	**Week 6**
	Baseline	CoQ10		Washout	Placebo	
1	7.2	6.8	7.0	7.0	7.3	7.3
2	5.0	5.0	7	7.0	6.0	5.0
3	2.7	2.3	1.2	1.5	1.4	2.7
4	3.0	0	1.0	2.0	3.0	2.0
5	2.9	1.6	2.6	2.2	2.4	1.9
6	1.0	2.0	1.0	1.0	1.0	1.0
7	2.0	1.0	1.0	2.0	2.0	2.0
8	3.0	3.0	2.5	2.0	0	0
9	3.5	3.3	3.2	3.0	4.1	3.8
10	5.0	4.0	4.0	5.0	5.7	6.0
11	3.6	2.8	2.5	3.3	3.4	2.9
12	4.0	6.0	6.0	4.0	3.0	3.0
13	2.0	0	0	3.0	0	1.0
14	2.0	1.5	0	2.0	2.0	1.5
15	6.5	6.0	6.0	6.0	5.0	5.0
16	7.0	6.0	5.0	6.0	8.0	7.0
17	9.0	8.0	8.0	10.0	9.0	9.0
18	1.0	0	1.0	2.0	1.0	1.0
19	7.0	5.0	4.5	5.0	6.0	7.0
20	6.0	4.0	4.0	5.0	4.0	5.0
21	0	0	0	1.0	0	2.0
22	4.0	3.0	3.0	4.0	4.0	4.0
23	2.0	2.0	2.0	4.0	3.0	3.0
24	8.5	6.0	5.5	7.5	8.0	7.0
25	3.0	4.0	3.0	4.0	3.0	2.0
26	5.0	4.0	4.0	4.2	4.0	5.2
27	7.0	7.0	6.0	8.0	8.0	8.0
28	4.0	3.0	3.0	6.0	5.0	5.0
29	4.0	5.0	5.0	3.0	3.0	3.0
30	5.5	3.0	3.0	4.5	5.0	5.3
MEAN	**4.2**	**3.5**	**3.4**	**4.2**	**3.9**	**4.0**
SD	**2.3**	**2.2**	**2.2**	**2.3**	**2.5**	**2.4**

As an overall trend, the mean of the maximum pain scores per week that was associated with the muscle cramps was highest when participants was on no medication, namely the baseline period (Week 1) and the wash out period (Week 4), and lowest when they were on CoQ10 100 mg (Weeks 2 and 3). On average, participants experienced a higher maximum pain score when they were on placebo (Weeks 5 and 6) than on CoQ10, but lower than when they were on the baseline and the washout periods.

Of the 30 participants in the Group A, 20 (66.7%) showed positive responses to CoQ10 (i.e. they had lower maximum pain score associated with the muscle cramps), while the rest of them (33.3%) showed positive responses to placebo.

Repeated measures ANOVA analysis was performed to determine whether or not there were any differences in the maximum pain scores associated with muscle cramps in the Group A over the 6-week period. The data were found to have violated the sphericity assumption (the variances across the weeks were not equal), thus Greenhouse-Geisser correction was then used to provide a valid F-ratio[97]. The results show that the maximum pain score was significantly different over the weeks of treatment, $F(2.767, 80.234) = 5.033$, $p = 0.004$ (using Greenhouse-Geisser correction).

Scheffè testing was then undertaken to determine where significant differences existed in the maximum pain score associated with the muscle cramps between the Weeks of study (Table 4.29).

Table 4.29 Group A- Significant Inter-Week Differences in Maximum Pain Score as Identified by Scheffè testing

(I) Week	(J) Week	Mean Difference (I-J)	SE	P value (a)	95% Confidence Interval for Difference(a)	
					Lower Bound	*Upper Bound*
1	2	0.703(*)	0.206	0.002	0.282	1.124
	3	0.813(*)	0.219	0.001	0.365	1.262
	4	0.040	0.192	0.837	-0.353	0.433
	5	0.303	0.182	0.106	-0.069	0.676
	6	0.260	0.177	0.154	-0.103	0.623
2	1	-0.703(*)	0.206	0.002	-1.124	-0.282
	3	0.110	0.131	0.409	-0.158	0.378
	4	-0.663(*)	0.232	0.008	-1.139	-0.188
	5	-0.400	0.261	0.136	-0.933	0.133
	6	-0.443	0.262	0.101	-0.979	0.092
3	1	-0.813(*)	0.219	0.001	-1.262	-0.365
	2	-0.110	0.131	0.409	-0.378	0.158
	4	-0.773(*)	0.216	0.001	-1.216	-0.331
	5	-0.510	0.262	0.061	-1.045	0.025
	6	-0.553	0.271	0.050	-1.108	0.001
4	1	-0.040	0.192	0.837	-0.433	0.353
	2	0.663(*)	0.232	0.008	0.188	1.139
	3	0.773(*)	0.216	0.001	0.331	1.216
	5	0.263	0.184	0.162	-0.112	0.639
	6	0.220	0.192	0.261	-0.173	0.613
5	1	-0.303	0.182	0.106	-0.676	0.069
	2	0.400	0.261	0.136	-0.133	0.933
	3	0.510	0.262	0.061	-0.025	1.045
	4	-0.263	0.184	0.162	-0.639	0.112
	6	-0.043	0.136	0.752	-0.322	0.235
6	1	-0.260	0.177	0.154	-0.623	0.103
	2	0.443	0.262	0.101	-0.092	0.979
	3	0.553	0.271	0.050	-0.001	1.108
	4	-0.220	0.192	0.261	-0.613	0.173
	5	0.043	0.136	0.752	-0.235	0.322

Based on estimated marginal means

* The mean difference is significant at the .05 level.

A Adjustment for multiple comparisons: Least Significant Difference (equivalent to no adjustments).

The Scheffè test showed there was a significant difference in the maximum pain score associated with muscle cramps during the time when participants were on no medication (Weeks 1 and 4) and on CoQ10 (Weeks 2 and 3), with $p<0.05$.

Further analysis using t-paired analysis was performed to determine whether there were any differences in the maximum pain score associated with the muscle cramps between two medication periods, namely the periods when participants were on CoQ10 (**Weeks 2 + 3**) and those when they were on placebo (**Weeks 5 + 6**). This revealed that on average, participants experienced a lower maximum pain score during the periods they were on CoQ10 (Weeks 2 + 3; mean score= 6.91 ± 0.81) than on placebo (Weeks 5 + 6; mean score= 7.86 ± 0.89). However, the difference was not significant ($t(29) = -1.935$; (95% CI= -1.961 – 0.054; p= 0.063).

4.2.5.4.2 Group B – non-statin users (Controls)

Table 4.30 below shows the mean of the maximum pain score associated with the muscle cramps from each patient in the Group B over the 6 weeks of the study.

Table 4.30 Group B – Mean of maximum pain score per week

Patient No	Mean of maximum pain score per week					
	Week 1	**Week 2**	**Week 3**	**Week 4**	**Week 5**	**Week 6**
	Baseline	Placebo		Washout	CoQ10	
1	2.5	3.3	3.5	3.5	2.0	3.0
2	2.3	1.5	1.0	1.0	1.5	2.0
3	2.4	2.0	3.0	3.0	1.0	2.0
4	4.0	3.0	2.0	3.3	4.0	5.0
5	2.0	2.0	1.0	2.0	1.0	0
6	3.0	2.0	2.0	3.0	2.0	3.0
7	5.0	4.0	4.0	5.0	4.0	4.0
8	7.0	7.5	8.5	8.0	8.0	8.5
9	1.0	0	0	1.0	1.0	0
10	2.8	2.5	2.0	2.5	2.0	2.0
11	5.5	4.5	5.0	5.0	4.0	4.0
12	6.8	6.0	5.0	5.0	5.3	4.8
13	4.5	4.3	4.0	4.3	4.0	3.3
14	3.5	2.8	3.3	3.0	2.5	2.5
15	5.0	3.0	2.0	5.0	3.0	0
16	3.7	4.1	3.5	2.8	3.3	2.8
17	4.8	4.3	4.5	5.3	4.5	4.0
18	2.8	1.5	1.5	2.0	2.0	1.8
19	4.0	3.0	4.0	5.0	3.0	3.0
20	4.0	5.5	6.0	6.0	6.0	7.0
21	7.1	7.0	6.0	7.0	6.0	5.5
22	8.5	7.5	7.0	8.4	8.5	9.0
23	7.8	8.0	9.0	7.5	8.0	8.5
MEAN	**4.4**	**3.9**	**3.8**	**4.3**	**3.8**	**3.7**
SD	**2.0**	**2.2**	**2.4**	**2.1**	**2.3**	**2.6**

As an overall trend, the mean of the maximum pain score per week associated with the muscle cramps was highest when participants were on no medication, namely the baseline period (Week 1) and the wash out period (Week 4), and lowest when they were

on CoQ10 100 mg daily (Weeks 5 and 6). On average, participants experienced slightly higher maximum pain scores when they were on placebo (Weeks 2 and 3) than on CoQ10, but lower than when they were on the baseline and the washout periods.

Of the 23 participants in the Group B, the majority of participants (52.2%; 12 of 23 participants) showed positive responses to CoQ10 (i.e. they had lower maximum pain score associated with the muscle cramps). In contrast, 10 of the participants (43.5%) had positive responses with placebo, and one person (4.4%) did not show positive responses with both CoQ10 and placebo.

Repeated measures ANOVA analysis was performed to determine whether or not there were any differences in the maximum pain score associated with the muscle cramps in the Group B over the 6-week period. The data were found to have violated the sphericity assumption (the variances across the weeks were not equal), thus Greenhouse-Geisser correction was then used to provide a valid F-ratio[97]. The results show that the maximum pain score was significantly different over the weeks of treatment, $F(2.719, 59.822) = 3.429$, $p = 0.026$ (using Greenhouse-Geisser correction).

Scheffè testing was then undertaken to determine where significant differences existed in the maximum pain score associated with the muscle cramps between the Weeks of study (Table 4.31).

Table 4.31 Group B- Significant Inter-Week Differences in Maximum Pain Score as Identified by Scheffè testing

(I) Week	(J) Week	Mean Difference (I-J)	SE	p value (a)	95% Confidence Interval for Difference(a)	
					Lower Bound	Upper Bound
1	2	0.465(*)	0.163	0.009	0.128	0.802
	3	0.530(*)	0.247	0.043	0.017	1.043
	4	0.061	0.173	0.728	-0.298	0.420
	5	0.583(*)	0.181	0.004	0.207	0.958
	6	0.622	0.317	0.063	-0.036	1.280
2	1	-0.465(*)	0.163	0.009	-0.802	-0.128
	3	0.065	0.147	0.662	-0.240	0.370
	4	-0.404(*)	0.169	0.026	-0.754	-0.054
	5	0.117	0.140	0.412	-0.174	0.409
	6	0.157	0.246	0.532	-0.354	0.667
3	1	-0.530(*)	0.247	0.043	-1.043	-0.017
	2	-0.065	0.147	0.662	-0.370	0.240
	4	-0.470(*)	0.188	0.020	-0.860	-0.080
	5	0.052	0.194	0.790	-0.349	0.454
	6	0.091	0.229	0.694	-0.384	0.566
4	1	-0.061	0.173	0.728	-0.420	0.298
	2	0.404(*)	0.169	0.026	0.054	0.754
	3	0.470(*)	0.188	0.020	0.080	0.860
	5	0.522(*)	0.175	0.007	0.158	0.885
	6	0.561	0.288	0.065	-0.037	1.159
5	1	-0.583(*)	0.181	0.004	-0.958	-0.207
	2	-0.117	0.140	0.412	-0.409	0.174
	3	-0.052	0.194	0.790	-0.454	0.349
	4	-0.522(*)	0.175	0.007	-0.885	-0.158
	6	0.039	0.191	0.840	-0.357	0.436
6	1	-0.622	0.317	0.063	-1.280	0.036
	2	-0.157	0.246	0.532	-0.667	0.354
	3	-0.091	0.229	0.694	-0.566	0.384
	4	-0.561	0.288	0.065	-1.159	0.037
	5	-0.039	0.191	0.840	-0.436	0.357

Based on estimated marginal means

* The mean difference is significant at the .05 level.

A Adjustment for multiple comparisons: Least Significant Difference (equivalent to no adjustments).

The Scheffè test showed there was a significant difference in the maximum pain score associated with muscle cramps during the time when participants were on no medication (Weeks 1 and 4) and on CoQ10 (Week 5), and on placebo (Weeks 2 and 3), with $p<0.05$

Further thorough test using t-paired analysis, was performed to determine whether there were any differences in the maximum pain score associated with the muscle cramps between the two medication periods, namely the periods when participants were on CoQ10 (**Weeks 5 + 6**) and those when they were on placebo (**Weeks 2 + 3)**. From t-paired analysis, on average, participants in the Group B had a higher maximum pain score during the periods they were on placebo (Weeks 2 + 3; mean score= 7.70 ± 0.93), than on CoQ10 (Weeks 5 + 6; mean score= 7.49 ± 1.00). However, the difference was not significant ($t(22) = 0.623$; 95% CI= -0.486 – 0.903; $p= 0.540$).

4.2.5.5 THE DURATION OF THE CRAMPS

4.2.5.5.1 Group A - Statin Group

Table 4.32 below shows the duration of the cramps per week suffered by each statin user over the 6 weeks of the study.

Table 4.32 Group A – Average of Cramp Duration per Week (minutes)

Patient No	Average of cramps duration per week (minutes)					
	Week 1	**Week 2**	**Week 3**	**Week 4**	**Week 5**	**Week 6**
	Baseline	CoQ10		Washout	Placebo	
1	0.8	0.9	0.9	1.0	1.2	0.9
2	3.6	3.8	4.8	5.0	5.0	4.5
3	2.3	1.7	1.3	2.0	2.0	2.1
4	2.0	0	1.5	1.5	1.5	1.3
5	7.5	7.0	6.5	5.0	5.0	5.5
6	2.0	1.0	1.0	1.0	1.0	1.0
7	2.0	1.0	1.0	3.0	3.0	3.0
8	1.1	1.5	1.3	1.7	0	0
9	0.4	0.2	0.1	0.1	0.2	0.3
10	10.0	9.5	9.0	10	10.0	10
11	1.0	1.3	1.0	1.2	2.3	1.5
12	0.8	0.6	0.5	0.8	0.8	1.0
13	0.5	0	0	0.3	0	0.3
14	0.5	0.5	0	0.5	0.3	0.3
15	3.5	2.9	2.7	3.2	3.4	3.5
16	5.3	3.8	3.8	4.0	3.8	4.3
17	5.7	4.3	4.5	5.0	5.5	5.3
18	2.3	0	1.8	1.7	2.1	2.0
19	4.5	4.2	3.8	4.0	3.5	3.7
20	2.2	2.0	1.8	2.0	2.2	2.0
21	0	0	0	1.0	0	1.5
22	2.2	1.8	1.5	2.7	2.4	2.1
23	1.8	1.0	0.8	2.0	1.7	1.4
24	9.0	7.5	8.0	7.5	8.0	8.0
25	2.0	1.5	1.0	2.0	2.5	2.7
26	3.5	2.2	2.0	2.8	3.7	3.5
27	5.0	3.8	4.5	4.5	5.2	6.0
28	2.8	3.3	2.9	4.0	2.9	3.5
29	2.2	2.8	2.0	3.5	3.0	3.2
30	4.3	3.3	3.1	4.8	4.5	4.0
MEAN	**3.0**	**2.4**	**2.4**	**2.9**	**2.9**	**2.9**
SD	**2.5**	**2.3**	**2.3**	**2.2**	**2.3**	**2.3**

In general, the average of cramp duration per week was longest when participants were on no medication, namely the baseline period (Week 1) and the wash out period (Week 4), and shortest when they were on CoQ10 100 mg daily (Weeks 2 and 3). On average, participants experienced longer cramp duration when they were on placebo (Weeks 5

and 6) than on CoQ10, but shorter than during the baseline (Week 1). There were no differences between the mean cramp duration during Week 4 (washout), and Weeks 5 and 6 (placebo).

Of the 30 participants in the Group A, the majority (26; 86.7%) of participants experienced shorter duration of cramps with CoQ10; whereas three participants (10%) had shorter cramp duration with placebo. The remaining participant did not experience any difference in the cramps duration with either CoQ10 or placebo.

Repeated measures ANOVA analysis was performed to determine whether or not there were any differences in the cramp duration of the Group A over the 6-week period of time. The data were found to have violated the sphericity assumption (the variances across the weeks were not equal), thus Greenhouse-Geisser correction was then used to provide a valid F-ratio[97]. The results show that the cramps duration was significantly different over the weeks of treatment, F (3.110, 90.188) = 8.131, p= 000 (using Greenhouse-Geisser correction).

Scheffè testing was then undertaken to determine where significant differences existed in the cramps duration between the Weeks of study (Table 4.33).

Table 4.33 Group A- Significant Inter-Week Differences in Cramp Duration as Identified by Scheffè testing

(I) Week	(J) Week	Mean Difference (I-J)	SE	p value (a)	95% Confidence Interval for Difference(a)	
					Lower Bound	Upper Bound
1	2	0.580(*)	0.133	0.000	0.308	0.852
	3	0.590(*)	.0106	0.000	0.374	0.806
	4	0.100	.0157	0.529	-0.221	0.421
	5	0.137	.0147	0.360	-0.164	0.437
	6	0.080	.0140	0.573	-0.207	0.367
2	1	-0.580(*)	.0133	0.000	-0.852	-0.308
	3	0.010	.0106	0.926	-0.207	0.227
	4	-0.480(*)	.0136	0.001	-0.757	-0.203
	5	-0.443(*)	.0167	0.013	-0.784	-0.103
	6	-0.500(*)	.0156	0.003	-0.819	-0.181
3	1	-0.590(*)	.0106	0.000	-0.806	-0.374
	2	-0.010	.0106	0.926	-0.227	0.207
	4	-0.490(*)	.0127	0.001	-0.749	-0.231
	5	-0.453(*)	.0141	0.003	-0.742	-0.165
	6	-0.510(*)	.0135	0.001	-0.787	-0.233
4	1	-0.100	.0157	0.529	-0.421	0.221
	2	0.480(*)	.0136	0.001	0.203	0.757
	3	0.490(*)	.0127	0.001	0.231	0.749
	5	0.037	.0105	0.729	-0.178	0.251
	6	-0.020	.0105	0.850	-0.234	0.194
5	1	-.0137	.0147	0.360	-0.437	0.164
	2	0.443(*)	.0167	0.013	0.103	0.784
	3	0.453(*)	.0141	0.003	0.165	0.742
	4	-0.037	.0105	0.729	-0.251	0.178
	6	-0.057	.0080	0.482	-0.219	0.106
6	1	-0.080	.0140	0.573	-0.367	0.207
	2	0.500(*)	.0156	0.003	0.181	0.819
	3	0.510(*)	.0135	0.001	0.233	0.787
	4	0.020	.0105	0.850	-0.194	0.234
	5	0.057	.0080	0.482	-0.106	0.219

Based on estimated marginal means

* The mean difference is significant at the .05 level.

A Adjustment for multiple comparisons: Least Significant Difference (equivalent to no adjustments).

The Scheffe analysis revealed that cramp duration whilst the participants were on CoQ10 (Week 2 and 3) was significantly shorter and than during any other period of the study, such as Weeks 1, 4, 5 and 6.

Further thorough testing using t-paired analysis was undertaken to determine whether there were any significant differences in the cramp durations between the two medication periods, namely the periods when participants were on CoQ10 **(Weeks 2 + 3)** and those when they were on placebo **(Weeks 5 + 6).** From t-paired analysis, on average, participants experienced significantly shorter cramps durations during the periods they were on CoQ10 (Weeks 2 + 3; mean score= 4.88 ± 0.84 minutes), than on placebo (Weeks 5 + 6; mean score= 5.84 ± 0.85 minutes) with t (29) = - 3.535; 95% CI= -1.505 – -0.402; p= 0.001.

4.2.5.5.2 Group B – non-statin users (Controls)

Table 4.34 below shows the duration of the cramps per week suffered by each participant in the Group B over the 6 weeks of the study.

Table 4.34 Group B – Average of Cramp Duration Per Week (minutes)

Patient No	Average of cramps duration per week (minutes)					
	Week 1	**Week 2**	**Week 3**	**Week 4**	**Week 5**	**Week 6**
	Baseline	Placebo		Washout	CoQ10	
1	2.2	2.0	3.5	4.0	3.8	2.5
2	0.5	0.3	0.3	0.3	0.3	0.2
3	2.3	2.3	1.7	1.5	1.5	1.0
4	2.2	3.3	2.0	3.8	3.0	3.0
5	0.2	0.2	0.1	0.1	0.1	0
6	3.0	2.0	2.0	3.0	2.0	1.0
7	3.0	3.0	2.5	3.0	2.8	2.3
8	1.7	1.6	1.5	1.3	1.5	1.4
9	1.3	0	0	1.3	1.0	0
10	1.3	1.0	0.8	1.2	0.5	0.5
11	7.0	6.0	7.5	6.0	5.0	5.0
12	2.8	1.8	2.0	2.3	2.0	2.0
13	4.3	3.8	3.5	4.5	4.0	4.0
14	2.7	2.5	2.3	3.0	2.0	2.8
15	1.0	0.5	0.8	1.0	0.5	0
16	2.0	1.3	1.0	2.0	1.4	1.0
17	4.2	3.7	4.0	4.5	3.7	4.0
18	2.3	1.5	2.3	2.3	2.0	1.5
19	10.0	9.3	9.5	11.0	10.0	8.0
20	5.0	4.3	3.5	4.5	4.0	5.0
21	5.8	4.9	5.0	5.3	5.1	4.7
22	9.5	8.8	8.3	8.0	7.5	8.8
23	9.4	9.2	8.8	8.5	7.5	8.7
MEAN	**3.6**	**3.2**	**3.2**	**3.6**	**3.1**	**2.9**
SD	**2.9**	**2.8**	**2.8**	**2.8**	**2.6**	**2.7**

In general, the average of cramp duration per week was longest when participants were on no medication, namely the baseline period (Week 1) and the wash out period (Week 4), and shortest when they were on CoQ10 100 mg daily (Weeks 5 and 6). On average, participants experienced shorter duration of cramps when they were on placebo (Weeks

2 and 3) than on the baseline and washout periods, but slightly longer than when they were on CoQ10.

Amongst the 23 participants in the Group B, more than half (13; 56.5%) experienced shorter cramp duration with CoQ10, while seven (30.4%) of the participants had shorter cramp duration with placebo. The remaining three participants did not experience any differences in the cramp duration with either CoQ10 or placebo.

Repeated measures ANOVA analysis was performed to determine whether or not there were any differences in cramp duration of the Group B over the 6-week period. The data were found to have violated the sphericity assumption (the variances across the weeks were not equal), thus Greenhouse-Geisser correction was then used to provide a valid F-ratio[97]. The results than show that the cramps duration was significantly different over the weeks of treatment, $F(3.279, 72.142) = 7.507$, $p = 0.000$ (using Greenhouse-Geisser correction).

Scheffè testing was then undertaken to determine where significant differences existed in the cramp duration between the Weeks of study (see table 4.35).

Table 4.35 Group B- Significant Inter-Week Differences in Cramp Duration as Identified by Scheffè testing

(I) Week	(J) Week	Mean Difference (I-J)	SE	p value (a)	95% Confidence Interval for Difference (a)	
					Lower Bound	Upper Bound
1	2	0.452(*)	0.105	0.000	0.234	0.671
	3	0.470(*)	0.126	0.001	0.209	0.730
	4	0.057	0.158	0.724	-0.271	0.384
	5	0.543(*)	0.167	0.004	0.196	0.891
	6	0.708(*)	0.151	0.000	0.395	1.021
2	1	-0.452(*)	0.105	0.000	-0.671	-0.234
	3	0.017	0.134	0.898	-0.260	0.294
	4	-0.396(*)	0.150	0.015	-0.706	-0.085
	5	0.091	0.153	0.557	-0.226	0.409
	6	0.256(*)	0.113	0.033	0.022	0.490
3	1	-0.470(*)	0.126	0.001	-0.730	-0.209
	2	-0.017	0.134	0.898	-0.294	0.260
	4	-0.413(*)	0.150	0.012	-0.724	-0.102
	5	0.074	0.154	0.637	-0.246	0.394
	6	0.239	0.173	0.183	-0.121	0.598
4	1	-0.057	0.158	0.724	-0.384	0.271
	2	0.396(*)	0.150	0.015	0.085	0.706
	3	0.413(*)	0.150	0.012	0.102	0.724
	5	0.487(*)	0.078	0.000	0.324	0.649
	6	0.652(*)	0.170	0.001	0.299	1.004
5	1	-0.543(*)	0.167	0.004	-0.891	-0.196
	2	-0.091	0.153	0.557	-0.409	0.226
	3	-0.074	0.154	0.637	-0.394	0.246
	4	-0.487(*)	0.078	0.000	-0.649	-0.324
	6	0.165	0.162	0.320	-0.171	0.501
6	1	-0.708(*)	0.151	0.000	-1.021	0-.395
	2	-0.256(*)	0.113	0.033	-0.490	0-.022
	3	-0.239	0.173	0.183	-0.5980	0.121
	4	-0.652(*)	0.170	0.001	-1.004	-0.299
	5	-0.165	0.162	0.320	-0.501	0.171

Based on estimated marginal means

* The mean difference is significant at the .05 level.

A Adjustment for multiple comparisons: Least Significant Difference (equivalent to no adjustments).

The Scheffe analysis demonstrated significant differences in the cramp duration during the periods when participants were on placebo (Weeks 2 and 3) and CoQ10 (Weeks 5 and 6) compared those when they were not receiving any medication (Week 1 and 4), with $p<0.05$. The analysis also revealed that the duration of cramps in Week 6 (the second week of CoQ10 period) was significantly shorter than during Week 2 (the first week of placebo period), with $p<0.05$.

Further testing using t-paired analysis, was undertaken to determine whether there were any differences in the cramp duration between the two medication periods, namely the periods when participants were on CoQ10 **(Weeks 5 + 6)** and those when they were on placebo **(Weeks 2 + 3).** From t-paired analysis, on average, participants experienced longer cramp duration during the periods they were on placebo (Weeks 2 + 3; mean score= 6.36 ± 1.16 minutes), than on CoQ10 (Weeks 5 + 6; mean score= 6.03 ± 1.09 minutes). However, the difference was not statistically significant, with $t(22) = 1.539$; 95% CI= -0.115 – 0.775; $p= 0.138$.

CHAPTER FIVE
DISCUSSION

5.1 MUSCLE ADVERSE EFFECT SURVEY

5.1.1 Patient Demographics

The Muscle Adverse Effects Survey was conducted from January 2006 to April 2006 in 45 community pharmacies throughout Western Australia. A follow up, which was done by a second mailing of the questionnaires as well as a reminder letter to the pharmacies, was issued to improve the response rate of the questionnaire. However, the response rate achieved was still quite low at 38.7% or 356 of a total 920 statin users who enrolled in the study. This low response rate might have resulted from the anonymity of participants in the survey, which led to difficulties in tracking down the respondents. Furthermore, pharmacists reported that many of the statin users had a perception that they did not need to return the questionnaire if they did not have muscle symptoms.

Of the 356 participants who returned the questionnaire, 205 of them (111 men and 94 women) suffered from muscle symptoms. It was found that the respondents who reported muscle symptoms (mean age 64.2 years) were significantly older than the rest of respondents who reported not having muscle symptoms (mean age 59.2 years). Contrary to general opinion[24], it was reported that women were not most likely to suffer from muscle symptoms. The survey revealed that there was no significant association between the sex of statin users and whether or not they had muscle symptoms.

It was also found that besides hypercholesterolaemia, participants suffered from a few other diseases. Hypertension was reported to be the most commonly suffered disease, comprising 39.93% of total participants, followed by diabetes mellitus (18.3%), ischaemic heart disease (11.5%), hypothyroidism (10.1%), and heart failure (3.9%). Kidney failure was reported as the least commonly suffered diseases, making up only 1.4% of total participants. It is worth noting that hypothyroidism can be associated directly with myopathy. Research has shown that 20%-50% of hypothyroid patients

complain of muscle pain or cramps[98]. The lack of thyroid hormone may result in decreased protein turnover and impaired carbohydrate metabolism, and leads to a shift in distribution of muscle fibers and the inhibition of the main oxidative pathways. All these factors can manifest as muscle weakness, muscle aching, cramps, fatigue and increased CK levels[13, 98].

Of the 356 participants, 220 (61.8%) took a few drugs that might be associated with myopathy when they were on statin therapy. Alcohol (more than 2 drinks daily) was reported as the most common drug taken, accounting for 95 cases or 26.7% of total respondents. The use of alcohol may be associated directly with myopathy. Alcoholic skeletal myopathy can be sub-divided into two different forms, acute and chronic conditions. Acute alcoholic myopathy is a rare condition affecting approximately 1% of alcoholics and is characterized by myalgia, muscle weakness, high levels of CK, renal impairment with myoglobinuria, and rhabdomyolysis. Chronic alcoholic myopathy (ingestion over 100 mg/day for more than 10 years) occurs in 45% to 70% of alcoholics, which leads to progressive proximal weakness and muscle atrophy involving legs and arms, and is characterized by reduced muscle strength, and normal or slightly increased levels of CK. The aetiology of alcoholic myopathy is multifactorial, including protein content disturbances related to the possible role of acetaldehyde, decreases in both amino acid availability and insulin-like growth factor concentrations, and free radical-induced protein membrane damage[52, 99-101].

5.1.2 Statin Therapy Used

The survey showed that most participants had been taking a statin for over 1 year (310; 84.6%), with atorvastatin being the most commonly prescribed statin (59.3%), followed by simvastatin (29.8%), then pravastatin and fluvastatin accounting for 10.4% and 0.6% respectively. These findings were similar to Mant et al's report[102], which revealed that atorvastatin was the most prescribed statin in Australia, followed by simvastatin, pravastatin and fluvastatin. Table 4.1 shows further details of statin therapy used in Australia between 1999 and 2004.

Table 5.1 Numbers of Statin Prescribed In Australia[102]. Australian community utilization of individual statins and all statins combined, DDDs/1000 population/day, yearly from 1999 to 2004.

Statin	Year					
	1999	**2000**	**2001**	**2002**	**2003**	**2004**
Atorvastatin	27.08	39.25	49.86	61.08	72.22	91.87
Simvastatin	24.18	29.73	35.36	40.88	46.98	55.29
Pravastatin	6.08	7.93	9.68	11.92	13.33	14.48
Fluvastatin	0.93	0.74	0.64	0.56	0.49	0.44
Cerivastatin	0.54	1.83	1.97	0	0	0
All statins	58.8	79.47	97.51	114.44	133.02	162.09

The high proportion of atorvastatin users may be due to the fact that atorvastatin may be more effective than other statins in treating hypercholesterolaemia[24, 103]. A study called ACCESS (the Atorvastatin Comparative Cholesterol Efficacy and Safety Study) involving 3916 patients conducted by Andrews et al[104], showed that atorvastatin produced a larger decrease in plasma LDL cholesterol than other statins in initial doses. In 2005, Australian Government accepted the recommendation of The Pharmaceutical Benefits Advisory Committee (PBAC) that Lipitor® (atorvastatin) is more effective at lowering cholesterol than other statins, and hence warrants a higher price for PBS subsidy. Consequently, Lipitor® was not affected by the 12.5% price reduction affecting other brands of cholesterol lowering medication[105].

Despite the high use of atorvastatin, the incidence rate of myopathy amongst atorvastatin individual users in the survey was found to be similar with fluvastatin, paravastatin and simvastatin (it might result from the low number of respondents in the survey). This finding is contrary to Rosenson's hypothesis[24], which suggests that statin's lipophilicity in penetrating into peripheral tissues may contribute to an increase in the potential of myopathy effects. Rosenson further points out that in vitro and in vivo studies support the idea that hydrophilic agents (such as pravastatin) are less likely to produce muscular effects than lipophilic agents (such as atorvastatin and simvastatin). However, this opinion is opposed by The National Lipid Association's Muscle Safety Expert Panel[49].

The panel argues that statins do vary in their myotoxicity, but there are no direct comparisons among statins as to their myotoxic potential.

In this study it was found that there was no association between the dose of statin used and myopathy. This might be due to the fact that there were small numbers of patients so the study was never powered to detect a genuine effect of the dose of statins used and their association to myopathy[97].

5.1.3 Prevalence and Nature of Statin-Induced Myopathy

By assuming that non-respondents did not suffer from muscle symptoms, it was estimated that the prevalence of myopathy from this survey was 22.3% (205/920). Amongst the respondents with muscle symptoms, 73 (35.6%) reported their muscle symptoms had been worsening on using statins. This reduced the overall incidence of statin-induced myopathy to 73/920 or 7.93%. This figure was quite close to the prevalence of statin-induced myopathy reported by Thompson et al[37]. They believed that the less serious adverse effects of statins are underreported, and may vary between 1% and 5%.

The survey identified that the most commonly experienced muscle symptom amongst statin users was night cramps (54.6% of total respondents); while the most commonly affected area of the body were the calves (61.9%). It was worth noting that on average patients on statins reported suffering 2.5 muscle symptoms.

5.1.4 Factors Increasing the Risk of Statin-Induced Myopathy

Statistical analysis with Multiple Logistic Regression was performed to determine factors increasing the risk of myopathy amongst statin users, with a series of explanatory variables including the respondent's age and sex, statin therapy (fluvastatin data were excluded from analysis due to low number of users), duration of statin therapy, other diseases suffered (heart failure, heart attack, hypertension, hypothyroid, diabetes

mellitus and kidney failure), and other medicines taken (cortisone, prednisone, sodium valproate, nifedipine, diltiazem, amiodarone, alcohol, labetolol, and chemotherapy).

It was found that increase in age, experiencing heart failure and taking cortisone-like drugs is associated with statin users becoming more susceptible to myopathy. For every 1-year increase in age, the odds of suffering from myopathy increased 1.039 (95% CI 1.019 – 1.061). Older people are more susceptible to myotoxicity due to normal muscle loss (atrophy) that begins in the mid-40s, and accelerates with inactivity[14].

Furthermore, taking cortisone-like medication increased the odds of suffering myopathy 16.4 times (95% CI 2.2 – 124.3), while patients with heart failure were 9.4 times (95% CI 1.2 – 73.2) more likely to develop muscle symptoms when prescribed statins.

Owczarek et al[52] in their review mentions that high doses of corticosteroids may result in "Corticosteroid Myopathy", a condition with loss of the thick myofilament from the muscle that manifests in proximal weakness, atrophy, myalgia, increased CK levels and rhabdomyolysis. These conditions result from the impaired regulation of the activity factors involved in peptide initiation by corticosteroid, which leads to the inhibition of protein synthesis (primarily in type II muscle fibers). Moreover, corticosteroid also increases the cyctoplasmic protease activity in muscles, leading to myofibrillar destruction. Glutamine synthetase is an enzyme needed to catalyze the formation of glutamine from glutamate and ammonia. The excess of corticosteroid results in the decrease of muscle protein synthesis with the reduced intramuscular glutamine levels. This leads to the increased glutamine synthetase activity in skeletal muscles that releases high levels of glutamine, resulting from the intensified proteolysis process[39, 52].

Another risk factor identified was heart failure. Myopathy and heart failure can be associated with reduced CoQ10 levels. Jeejeebhoy et al[73] point out that the degree of CoQ10 reduction is related to the severity of heart failure. CoQ10 content is also decreased in aged myocardium, which may contribute to the reduced recovery of contractile function in aged myocardium observed after cardiac surgery[106]. CoQ10

functions as an antioxidant and a transmembrane proton conductor and an electron carrier between NADH and succinate dehydrogenases and the cytochrome system, which is needed for the phosphorylation of ADP into ATP[66-71]. In patients with heart failure, CoQ10 is believed to be able to improve the efficiency of cardiac mitochondrial energy production, increase myocardial tolerance to hypoxic stress, and reduce intraoperative myocardial damage[107]. A decline in the CoQ10 levels may contribute to impaired muscle function, including myocardium[106, 107]. As statins inhibit the formation of mevalonate, a precursor of CoQ10, statin users with heart failure might become more susceptible to myotoxicity.

5.2 COENZYME Q10 FOR MUSCLE CRAMPS STUDY

5.2.1 Patients Demographics

A total of 53 participants were included in the statistical analysis, 30 people in the Group A (stain users) and 23 people in the Group B (non-statin users). It was found that participants in the Group A were significantly older than those in the Group B, with Mean Difference of 6.17 years (95% CI: 1.02-11.83). More than half of the participants (41; 77.4%) had cramps at least once a week, and most of them (38; 71.7%) had been suffering from cramps for over 5 years. Furthermore, it was also reported that only 11 of 53 participants (20.8%) had family history associated with muscle cramps.

In the Group A, alcohol became the most commonly consumed drug besides the statin, accounting for 11 cases (22.9%), while in the Group B, magnesium was noted to be the most frequently used drug, making up 13 cases (26%). In contrast with participants in the Group A, it was reported that none of the participants in the Group B suffered from hypercholesterolaemia. The most common disease suffered by participants in both groups was hypertension, making up 11 cases (20.8% of total participants).

5.2.2 Part of the Body Affected by Cramps

Participants were given a diary to record the following data across the 6 weeks of the study: days on which cramps were experienced, number of cramps suffered per day,

average and maximum pain score (on a scale of 0 to 10), duration of the cramps (in minutes), part(s) of body affected by the cramps, and any adverse reactions suffered over the duration of the study.

During the study, it was found that the majority of participants reported their calves as the most affected area of the body (34; 64.2% of total participants), followed by legs (20; 37.7%), thighs and buttocks (18; 34%) and feet (16; 30.2%). Fingers, on the other hand, were reported as the least affected area of the body, only accounting for 1 case (1.9% of total participants). This finding is similar to few literatures which mention the calf is the most commonly affected area [2, 4, 9]

5.2.3 CoQ10 Efficacy

The efficacy of CoQ10 was assessed on the basis of changes in the following: the average number of days per week participants suffered from muscle cramps, the average number of muscle cramps suffered per day, the intensity of the pain associated with muscle cramps (measured with average and maximum pain score), and the average of cramp duration per day.

As an overall trend, most participants in both groups experienced the highest improvements (the highest changes) on all assessed variables when they received CoQ10 100 mg, and experienced the lowest improvements (the smallest changes) when they were not on medication, namely the baseline period (Week 1) and the wash out period (Week 4). It was worth noting, on average, participants showed higher improvements on the assessed variables when they were on placebo than during the baseline and washout periods (Weeks 1 and 4), but less than when they were on CoQ10.

“The placebo effects” occurring in this study were considered primarily and fundamentally as a psychological phenomenon[108-110]. There were two main factors that might account for the placebo effects; namely anxiety and the expectancy-mediated attributes of the therapist-patient relationship[108, 111]. The placebo effects are often attributed to anxiety reduction. Administering of placebo may lead to a decline of

anxiety, which may in turn be accompanied by a decrease in the perception of suffering. Besides anxiety, the placebo effects may also be mediated by expectancies generated within the context of the therapist-patient relationship. The mediation of belief systems about the plausibility of treatment and anticipated clinical change were shown in a review of double-studies evaluating the effectiveness of a placebo in reducing pain compared to other standard analgesic medications[108]. Placebo has been found to be 56% as effective as a standard dose of morphine in reducing clinical postoperative pain in a few double-blind studies. Thus, positive response to placebo in this study did not only indicate that, for the patients, expectancy and hope for further success in therapy was realistic; for the therapist, it indicated that the patients, at some cognitive level, had the resources to be able to influence, modulate, and control their pain[112, 113].

5.2.3.1 Group A- Statin Users

In the Group A, more participants experienced higher improvements on all assessed variables when they were assigned to CoQ10 100 mg (Weeks 2 and 3) than those who showed positive responses with placebo (Weeks 5 and 6), and those who did not experience any differences in all assessed variables on either CoQ10 or placebo. It was revealed that 63.3% of participants in the Group A experienced fewer days with muscle cramps when they were on CoQ10. Furthermore, the proportion of participants in the Group A who had a reduction in cramp frequency, average and maximum pain scores associated with cramps, and cramp duration when they were on CoQ10 were 66.7%, 73.3%, 66.7%, and 86.7% respectively. On the other hand, the proportion of participants in the Group A who experienced a decrease in days with muscle cramps, cramp frequency, average and maximum pain score, and cramp duration during the period on placebo were 26.7%, 26.7%, 23.3%, and 33.3%, and 10% respectively.

T-paired test was performed to determine whether or not there were any differences in days with muscle cramps, cramp frequency, average and maximum pain score, and cramp duration between the two medication periods, namely the periods when they were on CoQ10 (Weeks 2 + 3) and those when they were on placebo (Weeks 5 + 6). Despite the CoQ10 periods producing higher improvements in all assessed variables than the

placebo periods, t-paired test analysis revealed only two data, namely average pain score and pain duration, which showed the mean difference between CoQ10 and placebo periods were large enough not to be a result of chance chance. On average, participants experienced significantly lower average pain score associated with cramps during the CoQ10 period (mean score= 6.36± 0.75) than the placebo period (mean score= 7.37 ± 0.85; p=0.028). Furthermore, patients also experienced shorter cramp duration during periods when they were on CoQ10 (mean score= 4.88 ± 0.84) than those when they were on placebo (mean score= 5.84 ± 0.85; p=0.001).

Therefore, even though therapy with CoQ10 100 mg per day over two weeks did not necessarily reduce cramps frequency, exogenous CoQ10 supplementation was shown to be effective in reducing pain severity and cramps duration. The supplementation of CoQ10 100 mg per day may successfully increase the CoQ10 blood levels, which can be reduced due to increased age[35, 55, 114], ischaemic heart disease[107, 115, 116] and medications such as statins.

In terms of age, it was reported that, on average, participants in the Group A were much older (64.5±8.4 years) than those in the Group B (58.0±11.3 years). This difference was significant, with t(51) = 2.386, p= 0.021. According to Kaikkonen et al[114], after 20 years of age, CoQ10 levels decline as age increases. Hence, participants in Group A (statin users) might have had lower levels of CoQ10 than the controls (Group B), and this might make them more susceptible to muscle problems, including muscle cramps. Furthermore, CoQ10 levels in the myocardium are also decreased during ischaemia reperfusion. Thus, two participants (6.7%) from the Group A might experience CoQ10 deficiency since they suffered from ischaemia heart disease.

Besides the elderly and people with ischaemia heart disease, low levels of CoQ10 are also found in people taking statins. A number of studies have shown that statins reduced CoQ10 blood levels[54, 57-62]. Since CoQ10 and cholesterol have the same biochemical pathway, the inhibition of HMG-CoA reductase by statins does not only reduce cholesterol levels but also CoQ10 blood levels[38]. Moreover, CoQ10 is carried by serum

lipoproteins in the circulation, and the reduction of cholesterol and triglycerides by statins can also lead to reduced concentrations of serum CoQ10[55].

These findings support the hypothesis arguing statin-induced myopathy may result from the low level of CoQ10[38, 48, 52-54]. Besides being an essential antioxidant, CoQ10 also functions as a transmembrane proton conductor and an electron carrier between NADH and succinate dehydrogenases and the cytochrome system which is essential for the phosphorylation of ADP into ATP[35, 67-69]. As muscles need ATP to meet energy demands, a decline in the CoQ10 tissues levels may contribute to muscle impairment, such as muscle cramps[38, 48, 52-54].

Consequently, the consumption of CoQ10 100 mg per day in this trial might have prevented the decline and/or increased the CoQ10 levels amongst the statin users; thus, reducing the statin-induced muscle adverse effects manifested in muscle cramps.

5.2.3.2 Group B- Non Statin Users (Controls)

In the Group B (non-statin users), more participants experienced higher improvements in all assessed variables when they received CoQ10 100 mg daily (Weeks 5 and 6) than those who showed positive responses with placebo (Weeks 2 and 3), and those who did not experience any differences in all assessed variables on either CoQ10 or placebo.

However, the percentages of participants who showed positive responses to CoQ10 in the Group B were slightly lower than those in the Group A. It was revealed 47.8% of participants in the Group B experienced fewer days with muscle cramps when they were on CoQ10, while 43.5% of them experienced fewer days with muscle cramps when they were given placebo. Furthermore, the percentages of participants in the Group B that had a reduction in cramp frequency, average and maximum pain score, and the duration of the cramps when they were on CoQ10 were 47.8%, 60.1%, 52.2%, and 56.5% respectively. In contrast, it was reported that the percentages of participants in the Group

B who experienced a decrease in the four the same variables when they were on placebo were 39.1%, 34.8%, 43.5%, and 30.4% respectively.

Despite the majority of participants having greater improvements in their muscle cramps when they took CoQ10, t-paired analysis confirmed that there were no significant differences between CoQ10 and placebo efficacy amongst all assessed variables. This may be due to a number of reasons. Firstly, muscle cramps suffered by participants in the Group B might not result from CoQ10 deficiency. Ikematsu et al[75] argue that exogenous CoQ10 supplementation may not affect CoQ10 plasma levels in people who do not experience reduced CoQ10 levels. They reported that there were no significant differences in CoQ10 plasma concentrations for the 84 volunteers (who did not experienced CoQ10 deficiency) after taking CoQ10 at doses 300, 600 and 900 mg/day for 4 weeks. Given that participants in the Group B might not take any substance (such as statins) or condition that might lower their CoQ10 levels, the administration of exogenous CoQ10 supplementation might not affect their CoQ10 levels, and not improve the condition of their cramps.

Another factor that might contribute to the lesser efficacy of CoQ10 in Group B was the nature of cramps suffered by participants. It was confirmed that a third of participants in the Group B (9 of 23 participants or 39.13%) had a family history of muscle cramps, while only two of 30 participants (6.67%) had this in the Group A. Two participants in the Group B are siblings, and they might suffer from a condition described as autosomal-dominant inherited generalized muscle cramps. Both of them admitted that the cramping was first recognized and most severe during adolescence. For these reasons above, hypothetically, muscle cramps suffered by participants in the Group B might not be fully associated with reduced CoQ10 levels. This may explain why CoQ10 in the Group B was not as effective as in the Group A in reducing muscle cramps. Therefore, exogenous CoQ10 supplementation may be only effective in reducing muscle cramps associated with CoQ10 deficiency, such as in the elderly, ischaemia heart disease patient and also statin users.

5.2.4 Adverse Events Associated with CoQ10 and Placebo

The adverse effects of CoQ10 were probably subjective, since there were no significant differences in adverse events frequency between CoQ10 and placebo in both Group A and Group B. The symptoms were mild and ceased without requiring any treatment; they included nausea, stomach upset, insomnia, and flu-like symptoms.

Furthermore, in terms of placebo, it was reported that one participant from the Group B experienced a skin rash while taking placebo (on day 5 of the 2nd week of the study), and decided to withdraw from the trial. A doctor gave the participant an antihistamine, and the Investigator was later informed that since the participant commenced the trial in spring, the allergy was most probably caused by pollen, not the medicine (placebo).

5.3 LIMITATIONS OF THE STUDY

There are several limitations to this study that are important to acknowledge:

1. The low number of respondents in the Muscle Adverse Effects Survey might have resulted in the prevalence of muscle symptoms associated with statin being over-estimated. On the other hand, the assumption that non-respondents did not suffer from muscle symptoms might have resulted in muscle symptoms associated with statin being under-estimated.
2. The low number of respondents in the Muscle Adverse Effects Survey might have resulted in no association between the dose of statin used and myopathy, and in incidence rate of myopathy amongst individual atorvastatin users to be found similar with other statins.
3. Not all of the data used in the study was retrieved from objective evidence, such as the prevalence of respondents reporting their muscle symptoms had worsened on using statins. In this case, where data was unavailable from the patient's medical records (such as laboratory test results); patient data was retrieved solely from the patient's questionnaire that may not have been a reliable source.
4. The study design of the trial conducted was a single-blind study. A double blind study is considered as the gold standard for providing a high level of scientific validity and reliability. In a single-blind study, there may be some biases that occur

due to the fact that the investigator is aware of which treatment (either medicine or placebo) has been given to the patients.

CHAPTER SIX
CONCLUSION

The study was comprised of two phases: Phase 1 the "Muscle Adverse Effect Survey", and Phase 2 the "CoQ10 for Muscle Cramps Study". The first phase of the study, the Muscle Adverse Effect Survey, was conducted at 45 community pharmacies in WA. From the 920 participants enrolled into the survey, 356 (38.7%) returned the questionnaire. Two hundred and five of the 356 (57.6%) respondents, 111 men and 94 women, reported muscle symptoms. Amongst the respondents with muscle symptoms, 73 (35.6%) reported their muscle symptoms had worsened on using statins. Assuming non-respondents did not suffer from muscle problem reduced the overall incidence of potential statin-induced myopathy to 73/920 or 7.93%. It was reported that atorvastatin was the most commonly prescribed statin (59.3%), followed by simvastatin (29.8%), then pravastatin (10.4%) and fluvastatin (0.6%). Despite the high use of atorvastatin, the incidence rate of myopathy by atorvastatin users was found to be similar with other statins. The most common muscle symptoms were night cramps (54.6%), muscle aching (52.7%), and fatigue (49.3%), while the most commonly affected area of the body was the calves (62%).

Statistical analysis with Multiple Logistic Regression showed increase in age, heart failure and the use of cortisone-like drugs increased the risk of myopathy among statin users. It was found that for every 1-year increase in age, the odds of suffering from myopathy increased 1.039 (95% CI 1.019 – 1.061). Furthermore, taking cortisone-like medication increased the odds of suffering myopathy 16.4 times (95% CI; 2.2 – 124.3), while participants with heart failure were 9.3 times (95% CI 1.2 – 73.2) more likely to develop muscle symptoms when prescribed statins.

The second phase of the study, Coenzyme Q10 for Muscle Cramps Study, was a single blind, placebo-controlled, cross over, 6-week evaluation of the benefits CoQ10 in reducing muscle cramps amongst statin and non-statin users.

It was found that on average, that statin users experienced a significant reduction in the severity of their muscle cramps, as indicated by lower average pain scores, during the period they were on CoQ10 (mean score = 6.36 ± 0.75) compared with placebo (7.37 ± 0.85; p = 0.028). Furthermore, patients also experienced significantly shorter cramp duration when they were on CoQ10 (4.88 ± 0.84) than on placebo (5.84 ± 0.84; p = 0.001). In contrast, amongst non-statin users (who were used as controls), there were no significant differences between CoQ10 and placebo efficacy in all assessed variables.

This study revealed that muscle symptoms were common among statin users, particularly those suffering from heart failure, taking corticosteroids, and increasing in age. Furthermore, the administration of CoQ10 100 mg per day was safe and effective in reducing severity and duration of muscle cramps amongst statin users. However, these later findings need to be confirmed by larger, double blind, placebo controlled studies.

REFERENCES

1. Miller T, Layzer R. Muscle Cramps. Muscle and Nerve [serial online]. 2005 [cited 2007 April 14];32:431-442. Available from: Curtin University Library and Information Service E-Reserve.
2. Butler J, Mulkerin E, O'Keeffe S. Nocturnal leg cramps in older people. Postgraduate Medical Journal [serial on the internet]. 2002 [cited 2007 April 14];78:596-598. Available from: http://pmj.bmj.com/cgi/content/full/78/924/596.
3. Roeleveld K, Van Engelen B, Stegeman S. Possible mechanism of muscle cramps from temporal and spatial surface EMG characteristics. Journal of Applied Physiology [serial on the internet]. 2000 [cited 2007 April 14];88:1698-1706. Available from: http://jap.physiology.org/cgi/content/full/88/5/1698#BIBL.
4. Marotta P, Graziadei I, Ghent C. Muscle cramps: A 'complication' of cirrhosis. Journal Gastroentology [serial on the internet]. 2000 [cited 2007 April 14];14:21D-25D. Available from: www.pulsus.com/Gastro/14-SD/Pdf/maro-ed.pdf.
5. Pryse-Phillips W, Valenstein E. Involuntary muscle activity. Patient Care [serial online]. 2004 [cited 2007 April 14];15(5):52-61. Available from: ProQuest.
6. Layzer R. Muscle pain, cramps, and fatigue. In: Engel A, Franzini-Armstrong C, editors. Myology. Basic and Clinical. New York: McGraw-Hill Inc; 1994. p. 1754-1768.
7. Mense S, Simons D, Russel I. Muscle pain. Understanding its nature, diagnosis, and treatment. Baltimore, Philadelphia: Lippincott Williams and Wilkins; 2001.
8. Layzer R, Rowland L. Muscle cramps and stiffness. In: Houston H, Rowland L, Rowland R, editors. Merritt's neurology. 10 ed. New York: Lippincott Williams and Wilkins; 2000.
9. Nixon J. The lower leg, ankle and foot. In: Gates S, Mooar P, editors. Musculoskeletal primary care. Philadelphia, New York, Baltimore: Lippincott Williams and Wilkins; 1999. p. 250-287.
10. Abdulla A, Jones P, Pearce V. Leg cramps in elderly: prevalence, drug and disease associations. International Journal of Clinical Practice [serial online]. 1999 [cited 2005 November 18];53:494-496. Available from: Science Direct.
11. Jensen P, Veenhuizen K, Wesseling A, de Boo T, Verbeek A. Estimation of the frequency of muscle cramps in the adult population of the Netherlands; a neuro-epidemic survey. In: Layzer R, G S, Piccolo G, Martinelli P, editors. Motor unit hyperactive states. New York: Raven; 1993. p. 125-131.
12. Layzer R. The origin of muscle fasciculations and cramps. Muscle and Nerve [serial online]. 2004 [cited 2007 April 14];17(11):1243-1249. Available from: Curtin University Library and Information Service E-Reserve.
13. Modi G. Cores in hypothyroid myopathy: a clinical, histological and immunofluorescence study. Journal of the Neurological Sciences [serial online]. 2000 [cited 2005 August 16];175(1):28-32. Available from: Science Direct.
14. MedicineNet. Muscle cramps (of skeletal muscle) [homepage on the internet]. No date [cited 2005 September 6]. Available from: http://www.medicinenet.com/muscle_cramps/article.html.

15. Petty N. Principles of neuromusculoskletal treatment and management. A guide for therapist. Edinburgh, London, New York, Oxford, Philadelphia, St Louis, Sydney, Toronto: Churchill Livingstone; 2004.
16. Gonzalez-Alonso J, Heaps C, Coyle E. Rehydration after exercise with common beverages and water. International Journal Sports Medicine [serial online]. 1992 [cited 2005 December 11];13:399-406. Available from: Science Direct.
17. Ray M, Bryan M, Rudem T, Baier S, Sharp R, King D. Effect of sodium in a rehydration beverage when consumed as a fluid or meal. Journal Applied Physiology [serial online]. 1998 [cited 2005 December 22];85:1329-1336. Available from: Science Direct.
18. Jansen P, Veenhuizen K, Wesseling A, de Boo T, Verbeek A. Randomised controlled trial of hydroquinine in muscle cramps. The Lancet [serial online]. 1997 [cited 2005 August 31];349(9051):528-532. Available from: Science Direct.
19. Fung M, holbrook J. Placebo-controlled trial of quinine therapy for nocturnal leg cramps. The Western Journal of Medicine [serial online]. 1989 [cited 2007 April 14];151:42-22. Available from: PubMed.
20. Mackie M, Davidson J. Prescribing of quinine and cramp inducing drugs in general practice. BMJ [serial on the internet]. 1995 [cited 2007 April 14];311:1541. Available from: http://www.bmj.com/cgi/contentfull/311/7019/1541.
21. Handbook BotAM. Australian medicines handbook 2003. Adelaide: Australian Medicines Handbook Pty Ltd; 2003.
22. Endo A. The discovery and development of the statins. In: Gaw A, Packard CJ, Sheperd J, editors. Statins. The HMG-CoA reductase inhibitors in perspective. 2 ed. London, New York: Martin Dunitz; 2004. p. 32-44.
23. Shitara Y, Sugiyama Y. Pharmacokinetic and pharmacodynamic alterations of HMG-CoA reductase inhibitors: Drug-drug interactions and interindividual in transporter and metabolic enzyme functions. Pharmacology and Therapy [serial online]. 2006 [cited 2006 March 9];112:71-105. Available from: Science Direct.
24. Rosenson RS. Current overview of statin-induced myopathy. The American Journal of Medicine [serial online]. 2004 [cited 2006 March 10];116(6):408-416. Available from: Science Direct.
25. McKenney J. Dyslipidemias. In: Young L, Koda-Kimble M, editors. Applied therapeutics: The clinical use of drugs. 6 ed. Vancouver: Applied Therapeutics Inc; 1992. p. 9-15.
26. Walker R. Dyslipidemia. In: Walker R, Edward C, editors. Clinical pharmacy and therapeutics. 3 ed. Edinburgh, London, New York, Oxford, Philadephia, St Louis, Sydney, Toronto: Churchill Livingstone; 2003. p. 353-373.
27. Hughes J, James-Chatgilaou G, Donnely R. Hyperlipidemia. In: Hughes J, James-Chatgilaou G, Donnely R, editors. Clinical pharmacy: a practical approach. 2 ed. South Yarra, Victoria: Macmillan Education Australia; 2001. p. 275-277.
28. Scheig R. Antihyperlipidemic agents. In: Smith C, Reynard A, editors. Essential of pharmacology. Philadelphia, London, Toronto, Montreal, Sydney, Tokyo: W.B. Saunders Company; 1995. p. 304-308.
29. Rodondi K. Hyperlipidemia. In: Herfindal E, Gourley D, Hart L, editors. Clinical pharmacy and therapeutics. 5 ed. Baltimore: Wiiliam and Walkins; 1992. p. 333-345.

30. Sexton J, Nickless G, Green C. Pharmaceutical care made easy: Essentials of medicines management in the individual patient. London, Chicago: Pharmaceutical Press; 2006.
31. Gowan J, Roller L. Practical disease state management for pharmacists. Balmain, New South Walles: Australian Pharmaceutical Publication; 2004.
32. Malloy M, Kane J. Agents used in hyperlipidemia. In: Katzung B, editor. Basic and clinical pharmacology. 9 ed. New York, Chicago: Lange Medical Books/McGraw-Hill; 2001. p. 561-585.
33. Clark LT. Treating dyslipidemia with statins: The risk-benefit profile. American Heart Journal [serial online]. 2003 [cited 2006 March 10];145(3):387-396. Available from: Science Direct.
34. Schwinghammer T. Hyperlipidemia. In: Wells B, Dipiro J, Scwinghammer T, Hamilton C, editors. Pharmacotherapy handbook. 5 ed. New York, Chicago: McGraw-Hill; 2003. p. 71-82.
35. Bliznakov E. Coenzyme Q10, lipid-lowering drugs (statins) and cholesterol: A present day pandora's box. The Journal of the American Nutraceutical Association [serial on the internet]. 2002 [cited 2005 October 11];5(3):32-38. Available from: http://www.americanutra.com/reprints/CoQ10reprint.pdf.
36. McDonald R. Lipid lowering drugs and atherosclerosis. In: Broody T, Larner J, Minneman K, Neu H, editors. Human pharmacology. Molecular to clinical. 2 ed. St Louis, Baltimore, Berlin, Boston, Chicago: Mosby; 1994. p. 257-274.
37. Thompson PD, Clarkson P, Karas RH. Statin-associated myopathy. Journal of American Myopathy Association [serial on the internet]. 2003 [cited 2005 August 10];289(13):1681. Available from: http://jama.ama-assn.org/cgi/content/abstract/289/13/1681.
38. Tomlinson SS, Mangione KK. Potensial adverse effects of statin on muscle. Physical Therapy [serial on the internet]. 2005 [cited 2005 August 10];85(5):459-465. Available from: http://ptjournal.org/PTJournal/May2005/v85n5p459.cfm.
39. Guis S, Mattei J, Liote F. Drug-induced and toxic myopathies. Best Practice and Research Clinical Rheumatology [serial online]. 2003 [cited 2007 April 5];17(6):877-907. Available from: Science Direct.
40. Ballantyne CM, Corsini A, Davidson MH, Holdaas H, Jacobson TA, Leitersdorf E, et al. Risk for myopathy with statin therapy in high-risk patients. Archives of Internal Medicine [serial online]. 2003 [cited 2005 August 17];163(5):553-564. Available from: ISI.
41. Bellosta S, Paoletti R, Corsini A. Safety of Statins. Focus on clinical pharmacokinetics and drug interactions. Circulation [serial online]. 2004 [cited 2005 August 10];109 (suppl III):III-50 - III-57. Available from: PubMed.
42. Bliznakov E. Lipid-lowering drugs (statins), cholesterol, and coenzyme Q10. The Baycol case- a modern Pandora's box. Biomedicine & Pharmacotherapy [serial online]. 2001 [cited 2006 October 11];56:56-59. Available from: Science Direct.
43. Hodel C. Myopathy and rhabdomyolysis with lipid-lowering drugs. Toxicology Letters [serial online]. 2002 [cited 2006 March 10];128(1-3):159-168. Available from: Science Direct.
44. Law M, Rudnicka A. Statin safety: A systematic review. The American Journal of Cardiology [serial online]. 2006 [cited 2006 August 8];97:52C-60C. Available from: Science Direct.

45. Maron D, Fazio S, Linton M. Current Perspectives on Statins. Journal of the American Heart Association [serial on the internet]. 2000 [cited 2006 September 14]:207-213. Available from: http://circ.ahajournals.org/cgi/content/full/101/2/207.
46. Ucar M, Mjorndal T, Dahqvist R. HMG-CoA reductase inhibitors and myotoxicity. Drug Safety [serial on the internet]. 2000 [cited 2005 September 6];22(6):441-457. Available from: http://www.ingentaconnect.com/content/adis/dsf/2000/00000022/00000006/art00003.
47. Yan L, Lan F, Wang Z-G, Li Y-P. Statins and myotoxicity. Trends in Pharmacological Sciences [serial online]. 2003 [cited 2006 March 10];24(3):113-114. Available from: Science Direct.
48. Jamal S, Eisenberg M, Christopoulos S. Rhabdomyolysis associated with hydroxymethylglutaryl-coenzyme-a reductase inhibitors. ACC Current Journal Review [serial online]. 2004 [cited 2005 Agust 16];13(9):11. Available from: Science Direct.
49. Thompson P, Clarkson P, Rosenson RS. An assessment of statin safety by muscle experts. The American Journal of Cardiology [serial online]. 2006 [cited 2006 September 2];2006(97):69C-76C. Available from: Science Direct.
50. Sinzinger H, O'Grady J. Professional athletes suffering from familial hypercholesterolaemia rarely tolerate statin treatment becasue of muscular problems. British Journal of Clinical Pharmacology [serial on the internet]. 2004 [cited 2005 September 7];57(4):525-528.
51. Gaist D, Rodriguez LAG, Huerta C, Hallas J, Sindrup SH. Lipid-lowering drugs and risk of myopathy: A population based follow-up study. Epidemiology [serial online]. 2001 [cited 2005 August 17];12(5):565-569. Available from: ISI.
52. Owczarex J, Jasinka M, Orszulak-Michalak D. Drug-induced myopathies. An overview of the possible mechanism. Pharmacological Reports [serial online]. 2005 [cited 2005 August 10];57:23-34. Available from: PubMed.
53. Baker S. Molecular clues into pathogenesis of statin-mediated muscle toxicity. Muscle Nerve [serial on the internet]. 2004 [cited 2005 July 5];31:572-580. Available from: http://www.medscitalk.com/ftopic6336.html.
54. Rundek T, Naini A, Sacco R, Coates K, Dimauro S. Atorvastatin decreases the coenzyme Q10 level in the blood of patients at risk for cardiovascular disease and stroke. Archieves of Neurology [serial online]. 2004 [cited 2005 July 4];61(6):889-892. Available from: Medline.
55. Levy H, Kohlhaas K. Considerations for supplementing with Coenzyme Q10 during statin therapy. Annals Pharmacotherapy [serial online]. 2006 [cited 2007 January 11];40:290-294. Available from: Science Direct.
56. Bargosis A, Grossis G, Fiorellas PL, Gaddi A, Di Giullot R, Battino M. Exogenous CoQ10 supplementation prevents plasma ubiquinone reduction induced by HMG-CoA reductase inhibitors. Molec Aspec Med [serial online]. 1994 [cited 2006 July 11];145:s187-s193. Available from: Science Direct.
57. Human JA, Ubbink JB, Jerling JJ, Delport R, Vermaak WJH, Vorster HH, et al. The effect of simvastatin on the plasma antioxidants concentrations in patients with hypercholesterolaemia. Clinica Chimica Acta [serial online]. 1997 [cited 2005 July 3];263(1):67-77. Available from: Medline.
58. Colquhoun M, Jackson R, Walters M, Hicks B, Goldsmith J, Young P, et al. Effects of simvastatin on blood lipids, vitamin E, coenzyme Q10 levels and left

ventricular function in humans. European Journal of Clinical Investigation [serial online]. 2005 [cited 2005, July 4];35(4):251-258. Available from: InfoTrac.
59. Strey CH, Young JM, Molyneux SL, George PM, Florkowski CM, Scott RS, et al. Endothelium-ameliorating effects of statin therapy and coenzyme Q(10) reductions in chronic heart failure. Atherosclerosis [serial online]. 2005 [cited 2005 July 4];179(1):201-206. Available from: Science Direct.
60. Mabuchi H, Higashikata T, Kawashiri M, Katsuda S, Mizuno M, Nohara A, et al. Reduction of serum ubiquinol -10 and ubiquinone-10 levels by atorvastatin in hypercholesterolemic patients. Journal of Atherosclerosis and Thrombosis [serial on the internet]. 2004 [cited 2005 October 11];12(2):111-119. Available from: http://www.jstage.jst.go.jp/article/jat/12/2/111_pdf.
61. Mortensen SA, Leth A, Agner E, Rohde M. Dose-related decrease of serum coenzyme Q10 during treatment with HMG-CoA reductase inhibitors. Molecular Aspects of Medicine
Biomedical and Clinical Aspects of Coenzyme Q [serial online]. 1997 [cited 2006 May 11];18(Supplement 1):137-144. Available from: Science Direct.
62. Littarru GP, Langsjoen P. Coenzyme Q10 and statins; biochemical and clinical implications. Mitochondrion [serial online]. 2007 [cited 2007 April 16];Accepted manuscript:1-10. Available from: Science Direct.
63. Boitier E, Degoul F, Desguerre I, Charpentier C, Francois D, Ponsot G, et al. A case of mitochondrial encephalomyopathy associated with a muscle coenzyme Q10 deficiency. Journal of the Neurological Sciences [serial online]. 1998 [cited 2005 August 16];156(1):41-46. Available from: Science Direct.
64. Kontush A, Reich A, Baum K, Spranger T, Finckh B, Kohlschutter A, et al. Plasma ubiquinol-10 is decreased in patients with hyperlipidaemia. Atherosclerosis [serial online]. 1997 [cited 2005 August 23];129(1):119-126. Available from: Science Direct.
65. Laaksonen R, Ojala JP, Tikkanen MJ, Himberg JJ. Serum Ubiquinone Concentrations after Short-Term and Long-Term Treatment with Hmg-Coa Reductase Inhibitors. European Journal of Clinical Pharmacology [serial online]. 1994 [cited 2005 July 27];46(4):313-317. Available from: ISI.
66. Weber C, Bysted A, Holmer G. Coenzyme Q10 in the diet-daily intake and relative bioavailability. Molecular Aspects of Medicine [serial online]. 1997 [cited 2005 August 31];18(Supplement 1):251-254. Available from: Science Direct.
67. Kagan V, Nohl H, Quinn P. Coenzyme Q: Its role in scavenging and generation of radicals in membranes. In: Cadenas E, Packer L, editors. Handbook of antioxidants. New York, Basel, Hongkong: Marcell Dekker Inc; 1996. p. 157-201.
68. Ernster L, Dallner G. Biochemical, physiological and medical aspects of ubiquinone function. Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease [serial online]. 1995 [cited 2005 August 19];1271(1):195-204. Available from: Science Direct.
69. Miles MV, Horn P, Miles L, Tang P, Steele P, DeGrauw T. Bioequivalence of coenzyme Q10 from over-the-counter supplements. Nutrition Research [serial online]. 2002 [cited 2005 August 31];22(8):919-929. Available from: Science Direct.
70. Chow C. Dietary coenzyme Q10 and mitochondrial status. In: Abelson J, Simon M, editors. Methods in enzimology Vol.382. California: Elsevier Inc; 2004. p. 105-112.

71. Chan T, Wilson J, O'Brien P. Coenzyme Q10 cytoprotective mechanism. In: Abelson J, Simon M, editors. Methods in enzymology vol. 382. California: Elsevier Inc; 2004. p. 89-104.
72. Rustin P, Munnich A, Rotig A. Mitochondrial respiratory chain dysfunction caused by CoQ10 defficiency. In: Abelson J, Simon M, editors. Methods in enzymology Vol. 382. California: Elsevier Inc; 2004. p. 81-104.
73. Jeejeebhoy F, Sole MJ. Nutrition and The Heart. Clinical Nutrition [serial online]. 2001 [cited 2006 October 30];20:181-186. Available from: Science Direct.
74. Littarru GP, Battino M, Folkers K. Clinical aspects of Coenzyme Q: Improvement of cellular bioenergetics of antioxidant protection? In: Cadenas E, Packer L, editors. Handbook of Antioxidants. New York, Basel, Hongkong: Marcel Dekker Inc; 1996. p. 203-239.
75. Ikematsu H, Nakamura K, Harashima S-i, Fujii K, Fukutomi N. Safety assessment of coenzyme Q10 (Kaneka Q10) in healthy subjects: A double-blind, randomized, placebo-controlled trial. Regulatory Toxicology and Pharmacology [serial online]. 2006 [cited 2006 May 11];44(3):212-218. Available from: Science Direct.
76. Szkopinska A. Ubiquinone. Biosynthesis of quinone ring and its isoprenoid side chain. In tracellular localization. Acta Biochimica Polinica [serial on the internet]. 2000 [cited 2007 April 12];47(2):469-480. Available from: www.actabp.pl/pdf/12-2000/469-480s.pdf.
77. Hathcock J, Shao A. Risk assessment for coenzyme Q10 (ubiquinone). Regulatory Toxicology and Pharmacology [serial online]. 2006 [cited 2007 April 16];45:282-288. Available from: Science Direct.
78. Weiss D. CoQ10-Heart disease [homepage on the internet]. No date [cited 2005 September 1]. Available from: http://www.atdonline.org/atd/CoQ10-Heart%20Disease.pdf.
79. Center MAC. Review of therapies. Bologic/organic/pharmacologic therapies: Coenzyme Q10 [homepage on the internet]. c2004 [cited 2005 September 1]. Available from: http://md.anderson.org/department/cimer/.
80. Center MAC. Review of therapies. Bologic/organic/pharmacologic therapies: Coenzyme Q10 [webpage on the internet]. 2004 [cited 2005, September 1]. Available from: http://md.anderson.org/department/cimer/.
81. Bonakdar RA, Guarneri E. Coenzyme Q10. American Family Physician [serial on the internet]. 2005 [cited 2006 August 11];72(6):1065-1070. Available from: http://www.aafp.org/afp/20050915/1065.html.
82. Singh RB, Rastogi S, Mechirova V. Significance of coenzyme Q10 in statin intoxication. International Journal of Cardiology [serial online]. 2004 [cited 2007 January 11];97:S1-S75. Available from: ScienceDirect.
83. Caso G, Kelly P, McNurlan M, Lawson W. Effect of coenzyme Q10 on myopathic symproms in patients treated with statins. The American Journal of Cardiology [serial online]. 2007 [cited 2007 April 16];Article in press:1-2. Available from: Science Direct.
84. Whitaker J. Citizen petition to change the labeling for all statin drugs (Mevacor, Lescol, Pravachol, Zocor, Lipitor and Advicor) recommending use of 100-200 mg per day of supplemental co-enzyme Q10 to reduce the risk of statin-induced myopathies (including cardiomyopathy and congestive heart failure) [homepage on the internet]. c2002 [cited 2005 October 11]. Available from:

http://www.fda.gov/ohrms/dockets/dailys/02/May02/052902/02p-0244-cp00001-01-vol1.pdf.
85. Office USPaT. United States Patent No. 4,933,165 [homepage on the internet]. c1990 [cited 2005 October 11]. Available from: http://www.neto.com/rcr/patent.html.
86. Philips P. Is myopathy part of statin therapy? The Imposter trial [homepage on the internet]. No date [cited 2005 August 30]. Available from: http://www.impostertrial.com.
87. Cantrill J, Wood J. Diabetes mellitus. In: Walker R, Edward C, editors. Clinical pharmacy and therapeutics. 3 ed. Edinburgh, London, New York: Churchill Livingstone; 2003. p. 657-677.
88. Thomas S. Hypertension. In: Walker R, Edward C, editors. Clinical pharmacy and therapeutics. 3 ed. Edinburgh, London, New YOrk: Churchill Livingstone; 2003. p. 265-278.
89. Scott D. Coronary heart disease. In: Walker R, Edward C, editors. Clinical pharmacy and therapeutics. 3 ed. Edinburgh, London, New York: Churchill Livingstone; 2003. p. 279-297.
90. Hudson S, McAnaw J, Reid F. Congestive heart failure. In: Walker R, Edward C, editors. Clinical pharmacy and therapeutics. 3 ed. Edinburgh, London, New York: Churchill Livingstone; 2003. p. 299-319.
91. Cantrill J, Wood J. Thyroid and parathyroid disorders. In: Walker R, Edward C, editors. Clinical pharmacy and therapeutics. 3 ed. Edinburgh, London, New York: Churchill Livingstone; 2003. p. 639-655.
92. Marriot J, Smith S. Acute renal failure. In: Walker R, Edward C, editors. Clinical pharmacy and therapeutics. 3 ed. Edinburgh, London, New York: Churchill Livingstone; 2003. p. 229-245.
93. Affiliations OoA, Affairs UDoV. The pain screening process [homepage on the internet]. No date [cited 2005 September 4]. Available from: http://www.va.gov/oaa/pocketcard/section4.asp.
94. Epps C, Herr K, Packard A. Evaluation of the revised faces pain scale, verbal descriptor scale, numeric rating scale, and Iowa pain thermometer in olser minority adults. Pain Management Nursing [serial online]. 2006 [cited 2007 April 4];7(3):117-125. Available from: Science Direct.
95. Ferraz M, Quaresema M, Aquino L, Atra E, Tugwell P, Goldsmith C. Reliability of pain scale in the assessment of literate and illiterate patients with rheumatoid arthritis. J Rheumatol [serial online]. 1991 [cited 2007 April 4];18(8):1269-1270. Available from: Medline.
96. de Rond M, de Wit R, van Dam F, van Campen B, den Hartog Y, Klievink R, et al. Daily pain assessment: value for nurses and patients. Journal of Advanced Nursing [serial online]. 1999 [cited 2007 April 4];29(2):436-444. Available from: Curtin University and Information Service E-Reserve.
97. Field A. Discovering stastistics using SPSS. 2 ed. London, Thousand Oaks, New Delhi: Sage Publications; 2005. p. 779.
98. Cakir M, Samanci N, Balci N, Balci M. Musculoskletal manifestations in patients with thyroid disease. Clinical Endocrinology [serial on the internet]. 2003 [cited 2007 April 25];59:162-167. Available from: htpp://www.blackwell-synergy.com/doi/abs/10.1046/j.1365-2265.2003.01786.x.

99. Lang C, Frost R, Summer A, Vary T. Molecular mechanisms responsible for alcohol-induced myopathy in skeletal muscle and heart. The International Journal of Biochemistry and Cell Biology [serial online]. 2005 [cited 2007 April 25];37:2180-2195. Available from: Science Direct.
100. Fernandez-Sola J, Nicolas J, Fatjo F, Garcia G, Sacanella E, Estruch R, et al. Evidence of apoptosis in chronic alcoholic skelatal myopathy. Human Pathology [serial online]. 2003 [cited 2007 April 25];34(12):1247-1252. Available from: Science Direct.
101. Preedy V, Paice A, Mantle D, Dhillon A, Palmer T, Peters T. Alcaholic myopathy: biochemical mechanisms. Drug and Alcohol Dependence [serial online]. 2001 [cited 2007 April 25];63:199-205. Available from: Science Direct.
102. Mant A, Lowinger J, Hall W, Whicker S, Ringland C, Stark H. Letters to the editors. Statin down under. British Journal of Clinical Pharmacology [serial on the internet]. 2006 [cited 2006 September 14];63(1):125-127. Available from: http://blackwell-synergy.com/doi/pdf/10.1111/j.1365-2125.2006.02735.x.
103. Brown AS, Bakker-Arkema R, Yellen L, Henley R, Guthrie M, Campbell C, et al. Treating Patients With Documented Atherosclerosis to National Cholesterol Education Program-Recommended Low-Density-Lipoprotein Cholesterol Goals With Atorvastatin, Fluvastatin, Lovastatin and Simvastatin. Journal of the American College of Cardiology [serial on the internet]. 1998 [cited 2006 September 14];32(3):1-10. Available from: http://content.onlinejacc.org/cgi/content/full/32/3/665.
104. Andrews T, Christie B, Hsia J, Kramer J. Achieving and Maintaining National Cholesterol Education Program Low-density Lipoprotein Cholesterol Goals with Five Statins. The American Journal of Medicine [serial online]. 2001 [cited 2006 September 14];111:185-191. Available from: Science Direct.
105. Australian Government DoHaA. Questions and Answers - Price change for atorvastatin (Lipitor) in the 1 August issue of the Schedule of Pharmaceutical Benefits [homepage on the internet]. c2005 [cited 2006 September 14]. Available from: http://www.health.gov.au/internet/wcms/publishing.nsf/Content/health-pbs-atrovastatinqa.
106. Hadj A, Pepe S, Marasco S, Rosenfeld F. The principles of methabolic therapy for heart disease. Heart, Lung and Circulation [serial online]. 2003 [cited 2006 February 17];12(12):S55-S62. Available from: Science Direct.
107. Pepe S, Marasco S, Haas S, Sheeran F, Krum H, Rosenfeldt F. Coenzyme Q10 in cardiovascular disease. Mitochondrion [serial online]. 2007 [cited 2007 April 14];Accepted manuscript:1-41. Available from: Science Direct.
108. Evans F. Expectancy, therapeutic instructions, and the placebo response. In: White L, Tursky B, Schwartz G, editors. Placebo. Theory, research, and mechanisms. New York, London: The Guildford Press; 1985. p. 215-228.
109. Bakan D. The apprehension of the placebo phenomenon. In: White L, Tursky B, Schwartz G, editors. Placebo. Theory, research, and mechanisms. New York, London: The Guildford Press; 1985. p. 211-214.
110. Eaton M. Ethics and business of bioscience. Stanford, California: Stanford University Press; 2004. p. 195-234.
111. Plotkin W. A psychological approach to placebo: The role of faith in therapy and tratment. In: White L, Tursky B, Schwartz G, editors. Placebo. Theory, research, and mechanisms. New York, London: The Guildford Press; 1985. p. 237-254.

112. Miller N. Placebo factors in treatment: Views of a psychologist. In: Shepherd M, Sartorius N, editors. Non-specific Aspects of Treatment. Toronto, Lewiston, New York, Bern, Stuttgart: Hans Huber Publication; 1989. p. 39-56.
113. Joyce C. Non-specific aspects of treatment from the point of view of a clinical pharmacologist. In: Sheperd M, Sartorius N, editors. Non-specific aspects of treatment. Toronto, Lewiston, New York, Bern, Stuttgart: Hans Huber Publication; 1989. p. 57-94.
114. Kaikkonen J, Nyyssonen K, Toumainen T, Ristonmaa U, Salonen U. Determinants of plasma CoQ10 in humans. FEBS letters [serial online]. 1999 [cited 2007 January 11];443:163-166. Available from: Science Direct.
115. Crestanello J, Doliba N, Doliba N, Babsky A, Niborii K, Osbakken M, et al. Effect of Coenzyme Q10 supplementation on mitochondrial function after myocardial ischemia reperfusion. Journal of Surgical Research [serial online]. 2001 [cited 2007 April 25];102:221-228. Available from: Science Direct.
116. Langsjoen H, Langsjoen P, Willis R, Folkers K. Usefulness of Coenzyme Q10 in clinical cardiology: A long-term study. Molec Aspec Med [serial online]. 1994 [cited 2007 April 25];15:s165-s175. Available from: Science Direct.

APPENDICES

Appendix A

ETHICS APPROVAL

memorandum

Curtin University of Technology

To	Dede Indra Kurniwan Curtin Guild House, Flat G1 Room 6 63 Jackson Road KARAWARA WA 6152
From	Dr Stephan Millett, Executive Officer, Human Research Ethics Committee
Subject	Revised Protocol Approval **HR 148/2005**
Date	13 December 2005
Copy	Jeff Hughes, Pharmacy

Office of Research and Development

Human Research Ethics Committee

TELEPHONE 9266 2784
FACSIMILE 9266 3793
EMAIL s.darley@curtin.edu.au

Thank you for addressing the concerns raised by the Human Research Ethics Committee (HREC) for the project titled *"Statins-induced myopathy and the benefit of oral administration of coenzyme Q10"*.

Your response has been reviewed by members of the HREC reviewing panel who have recommended that your application be **APPROVED**.

- You are authorised to commence your research as stated in your proposal subject to you using the revised version of the documents, as attached to this letter.
- The approval number for your project is **HR 148/2005**. *Please quote this number in any future correspondence.*
- Approval of this project is for a period of twelve months **13/12/2005** to **12/12/2006**.

If you are a Higher Degree by Research student, data collection must not begin before your Application for Candidacy is approved by your Divisional Graduate Studies Committee.

Applicants should note the following:

- It is the policy of the HREC to conduct random audits on a percentage of approved projects. These audits may be conducted at any time after the project starts. In cases where the HREC considers that there may be a risk of adverse events, or where participants may be especially vulnerable, the HREC may request the chief investigator to provide an outcomes report, including information on follow-up of participants.
- All recommendations for approval are referred to the next meeting of the HREC for ratification. In the event the Committee does not ratify the recommendation, or would like further information, you will be notified. **The next meeting of the HREC is on 7/02/2006.**

The attached **FORM B** is to be completed and returned as soon as possible to the Secretary, HREC, C/- Office of Research & Development:

- When the project has finished, or
- If at any time during the twelve months changes/amendments occur, or
- If a serious or unexpected adverse event occurs.

Please find attached your protocol details together with the application form/cover sheet.

SDarley.

Dr Stephan Millett
Executive Officer
Human Research Ethics Committee

Please Note: The following standard statement must be included in the information sheet to participants:
This study has been approved by the Curtin University Human Research Ethics Committee. If needed, verification of approval can be obtained either by writing to the Curtin University Human Research Ethics Committee, c/- Office of Research and Development, Curtin University of Technology, GPO Box U1987, Perth, 6845 or by telephoning 08 9266 2784.

Appendix B

EXTENSION OF ETHICS APPROVAL

memorandum

Curtin University of Technology

To	Dede Indra Kurniawan, Pharmacy
From	Dr Stephan Millett, Executive Officer, Human Reseach Ethics Committee
Subject	PROTOCOL APPROVAL – EXTENSION 148/2005
Date	29 November 2006
Copy	Jeff Hughes, Pharmacy

Office of Research and Development
Human Research Ethics Committee
TELEPHONE 9266 2784
FACSIMILE 9266 3793
EMAIL hrec@curtin.edu.au

Thank you for keeping us informed of the progress of your research. The Human Research Ethics Committee acknowledges receipt of your Form B progress report for the project *Statins-induced myopathy and the benefit of oral administration of coenzyme Q10*.

Approval for this project is extended for the year to **12/12/2007.**

Your approval number remains **148/2005.** Please quote this number in any further correspondence regarding this project.

Thank you.

Dr Stephan Millett
Executive Officer
Human Research Ethics Committee

Appendix C

PARTICIPANT INFORMATION SHEET

Title: Coenzyme Q10 for Muscle Cramp Study

School of Pharmacy
Curtin University of Technology
GPO Box U1987
PERTH WA 6845

Participation in this study is entirely voluntary and you are under no obligation to do so. Please take your time to make your decision. Discuss it with your family and friends. Be sure to ask questions about anything you don't understand.

WHO IS DOING THE STUDY?

Investigator : Mr. Dede Indra Kurniawan
Supervisor : Mr. Jeff Hughes

The Investigator and Supervisor are from School of Pharmacy, Curtin University of Technology.

WHY IS THIS STUDY BEING DONE?

The purpose of the study is to investigate the efficacy of coenzyme Q10 in reducing muscle cramp amongst statin and non-statin users. It is known that cholesterol-lowering medications that are called statins (the generic names are atrovastatin, fluvastatin, pravastatin and simvastatin) reduce coenzyme Q10 blood levels, which may influence energy production. Since muscles need coenzyme Q10 to meet energy demands, a decline in the coenzyme Q10 levels may contribute to impaired muscle function.

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY?

Seventy (70) people with muscle cramps will take part in this study; thirty-five (35) statin users (Group A) and thirty-five (35) non-statin users (Group B).

HOW LONG WILL I BE IN THIS STUDY?

You will be in the study for 6 weeks, and you can stop participating at any time. If you want your information removed from the study this will be done.

WHAT IS INVOLVED IN THE STUDY?

If you take part in this study, you will be required to:

a) Sign the Consent Form after you have read the Patient Information Sheet and send it together with Muscle Adverse Effects Survey questionnaire to the Investigator using the pre-paid envelope provided. The Investigator will contact you within 72 hours of receiving your Consent Form.
b) You will be required to come to the research centre at the School of Pharmacy, Curtin University of Technology, to meet the Investigator. He will explain to

you in detail the study design and answer any questions that you may have at that time. As part of the study you will receive a diary to record any muscle cramps you experience during the study.

c) The first week of the study will be a lead-in period, during which time you will not be given any medication for your muscle cramps and you will be asked to record all muscle cramps experienced, including the time they occurred, their duration, severity and location.
d) During the second and third weeks you will be assigned to receive either a daily treatment of coenzyme Q10 100 mg or a placebo (inactive substance). You are asked to take the medicine once daily at night. Again you will be asked to record all muscle cramps experienced during the trial, including the time they occurred, their duration, severity and location. You will also be asked to record any other symptoms, which you experience during the study.
e) The fourth week will be a washout period during which time you will not be given any medicine for your cramps, and as in the previous week, you are asked to record the history of your muscle cramp in your diary.
f) During the fifth and six weeks, you will be given by the Investigator either co-enzyme Q10 or a placebo to take daily. You will, once again, be asked to record the history of your muscle cramps and to record any other symptoms during this period.
g) At the end of the study, the Investigator will collect your diary. You will be interviewed about any possible side effects that you may suffer from the trial. You will be given the opportunity to receive a copy of the results of the study.

WHAT ARE THE POSSIBLE SIDE EFFECTS, RISKS AND DISCOMFORT OF THE STUDY?

Coenzyme Q10, known as ubiquinone, is a naturally occurring enzyme in the human body. The safety of coenzyme Q10 has been evaluated, and there is no serious toxicity associated with the doses in the range of 100 mg to 1,200 mg per day (this study will use the minimal dose, 100 mg per day). The side effects of coenzyme Q10 are commonly mild, and may include nausea, stomach upset, heartburn, loss of appetite, rash and fatigue. These side effects are usually resolved without the need of any treatment.

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?

Taking part in this study may help in reducing your muscle cramp problem, and your participation may also lead to knowledge that will help others.

WHAT ABOUT CONFIDENTIALITY?

All data collected during the study will be treated strictly confidentially. On the completion of the study, all participants' data will be de-identified, preventing anyone from identifying those people who participated in it. All results of the study will be grouped, and no reference will be made to any individual patient. Data from the study will be kept in a locked cupboard in the office of the Investigator at the School of Pharmacy, Curtin University of Technology. Only the Investigator and his Supervisor will have access to the data.

WHAT ARE THE COSTS?
There will be no cost incurred in participating in the study.

WHAT ARE MY RIGHTS AS A RESEARCH PARTICIPANT?
Taking part in this study is voluntary. You may choose not to take part or may leave the study at any time without penalty.

For the protection of the rights of participants in this study, the Human Research Ethics Committee of Curtin University of Technology has reviewed this research project.
The Investigator will tell you about any new information that may affect your health, welfare, or willingness to stay in this study.

WHO DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?
If you have any questions about the study, you should contact:

DEDE INDRA KURNIAWAN AT THE SCHOOL OF PHARMACY, CURTIN UNIVERSITY OF TECHNOLOGY ON 0421378098

WILL I FIND OUT THE RESULTS OF THE STUDY?
You will be offered the opportunity to receive a copy of the results of the study.

Any person with complaints about the conduct of a research study can contact the secretary of the Human Ethics Committee, Curtin University of Technology, on (08) 92662784

Appendix D

CONSENT FORM

Coenzyme Q10 for Muscle Cramp Study
School of Pharmacy
Curtin University of Technology
GPO Box U1987
PERTH WA 6845

I, _____hereby voluntarily consent to participate in the study entitled "Coenzyme Q10 for Muscle Cramp Study". This study is being conducted by Mr. Dede Indra Kurniawan from the School of Pharmacy, Curtin University of Technology.

I understand that any of the data collected for the purpose of this study will remain strictly confidential and not be used to identify any participant. I have been informed that the information obtained from this research may be used in future research or published.

I have read the information sheet explaining this research in which details of the study have been clearly explained by the researcher. I am aware of the purpose of this project and what my involvement entails. My participation is entirely voluntary.

I have been informed of my right to question any part of the procedure or withdraw from the project at any time.

Name_____
Address_____
_____
_____
_____
Phone_____

Signature_____
Date_____

Any person with complaints about the conduct of a research study can contact the secretary of the Human Ethics Committee, Curtin University of Technology, on (08) 92662784

Appendix E

MUSCLE ADVERSE EFFECTS SURVEY

INTRODUCTION

Dear Patient,

Muscle aches and pain are common and may be associated with many conditions. They may also be associated with the use of a range of medications. This survey is being undertaken to assess types and severity of muscle complaints which may be related to cholesterol lowering therapy. Statins are a group of cholesterol-lowering medications [for example atrovastatin (Lipitor®), fluvastatin (Lescol®, Vastin®), pravastatin (Pravachol®) and simvastatin (Zocor®, Lipex®)]. These are known to cause muscle complaints, such as muscle pain, weakness and cramps. However, how common these problems are amongst patients in general use is unknown. With this background, would you consider taking a few minutes to complete a questionnaire about your experience with statins and any muscle symptoms you may have? After completing the questionnaire, please return it to your pharmacist or via post to the Investigator using the return paid envelope provided. Dependent on your responses to the survey questions, you may be eligible to participate in the **COENZYME Q10 FOR MUSCLE CRAMP STUDY** (further details are provided at the end of the survey questionnaire). The information obtained from this survey will be analyzed to determine the nature and frequency of statin-related muscle problems, and to identify any factors (age, sex, other diseases, etc) which may make statin users more prone too them. If you think of questions or you would like to talk to the Investigator after filling out this survey, please feel free to contact me or my Supervisor, Mr. Jeff Hughes at the School of Pharmacy, Curtin University of Technology.

Sincerely yours,

Investigator : Mr. Dede Indra Kurniawan Contact number: 0421378098.
Supervisor : Mr. Jeff Hughes Contact number: 9266 7367

QUESTIONNAIRE

1) Please TICK which of the following cholesterol-lowering medications that you take.

Drug Name	Strength	Dose	Duration
❑ Atorvastatin *(Lipitor®)*		___tablet(s) per day	❑ Less than 6 months ❑ 6-12 months ❑ More than 1 year
❑ Fluvastatin *(Lescol®,Vastin®)*		___ capsule(s) per day	❑ Less than 6 months ❑ 6-12 months ❑ More than 1 year
❑ Pravastatin *(Pravachol®)*		___tablet(s) per day	❑ Less than 6 months ❑ 6-12 months ❑ More than 1 year
❑ Simvastatin *(Lipex®, Zocor®)*		___tablet(s) per day	❑ Less than 6 months ❑ 6-12 months ❑ More than 1 year
❑ Cholestyramine *(Questran Lite®)*		___ sachet(s) per day	❑ Less than 6 months ❑ 6-12 months ❑ More than 1 year
❑ Colestipol *(Colestid®)*		___ sachet(s) per day	❑ Less than 6 months ❑ 6-12 months ❑ >1 year
❑ Fenofibrate *(Lipidil®)*		___tablet(s) per day	❑ Less than 6 months ❑ 6-12 months ❑ More than 1 year
❑ Gemfibrozil *(Ausgem®, Gemhexal®, Jezil®, Lipazil®, Lopid®)*		___tablet (s) per day	❑ Less than 6 months ❑ 6-12 months ❑ More than 1 year
❑ Ezetimibe *(Ezetrol®)*		___tablet(s) per day	❑ Less than 6 months ❑ 6-12 months ❑ More than 1 year
❑ Nicotinic Acid		___tablet(s) per day	❑ Less than 6 months ❑ 6-12 months ❑ More than 1 year

❑ Another lipid-lowering medicine, please mention it _____ _____		___tablet(s)/capsule(s) /sachet(s) per day	❑ Less than 6 months ❑ 6-12 months ❑ More than 1 year

2) Do you suffer from any following diseases? ☐ Yes ☐ No
If yes, please TICK the conditions you suffer from.
- ❑ Diabetes mellitus
- ❑ Hypertension
- ❑ Heart attack
- ❑ Heart failure
- ❑ Hypothyroidism
- ❑ Kidney failure

3) Do you take any of the following medications? ☐ Yes ☐ No
If yes TICK which one in the table below, and complete the other details

Drug Name	Strength	Dose	Duration
❑ Diltiazem *(Cardiazem®, Coras®, Diltahexal®, Dilzem®, Vasocardol®)*		___tablet(s)/capsule(s) per day	❑ Less than 6 months ❑ 6-12 months ❑ More than 1 year
❑ Nifedipine *(Adalat®, Adefin®, Adefin XL®, Nifecard®, Nifehexal®, Nyefax®)*		___tablet(s)/capsule(s) per day	❑ Less than 6 months ❑ 6-12 months ❑ More than 1 year
❑ Verapamil (*Anpec®, Isoptin®, Verahexal®, Cordilox®, Veracaps®)*		___tablet(s)/capsule(s) per day	❑ Less than 6 months ❑ 6-12 months ❑ More than 1 year

4) Do you currently take or have you taken in the past any of the following? (You may TICK more than one)

- ❑ Alcohol (more than 2 drinks daily)
- ❑ Amiodarone
- ❑ Antimalarial drugs
- ❑ Carnitine
- ❑ Chemotherapy for cancer
- ❑ Colchicine
- ❑ Coenzyme Q10 / Ubiquinone
- ❑ Cyclosporin
- ❑ Cortisone
- ❑ Labetolol
- ❑ Prednisone/steroids
- ❑ Protease Inhibitors for AIDS
- ❑ Thyroid preparations
- ❑ Sodium valproate
- ❑ Vitamin D
- ❑ Vitamin E
- ❑ Warfarin

5) Please TICK any of the following muscle symptoms that you suffer from (or add your own).
   - ❑ None → **Please go to Question 19**
   - ❑ Cramp at night
   - ❑ Cramp after exercise
   - ❑ Muscle aching or soreness
   - ❑ Fatigue or tiredness
   - ❑ Muscle weakness (like trouble rising from a chair or mounting stairs)
   - ❑ Breathlessness with exercise
   - ❑ Another muscle symptom, please list _____

6) Which muscle(s) hurt most?
   - ❑ Calves
   - ❑ Thighs and buttocks
   - ❑ Back
   - ❑ Arms
   - ❑ All muscles hurt equally
   - ❑ Another part of body, please list _____

7) How would you describe the frequency of you muscle symptoms?
   - ❑ Constant throughout the day
   - ❑ Comes and goes throughout the day
   - ❑ Appears at particular times of the day (Please state when _____)

8) If you suffer from leg-cramps, how often to these occur?
   - ❑ Every day
   - ❑ At least once a week
   - ❑ At least once a month
   - ❑ Other (Please state frequency _____)

9) How long have you had your muscle symptoms?
   - ❑ Less than 1 month
   - ❑ 1-12 months
   - ❑ 1 – 5 years
   - ❑ More than 5 years

10) Since commencing this therapy how would you describe you muscle symptoms (consider both the frequency and severity of your symptoms)?

   - ❑ No change **Please go to Question 12**
   - ❑ Better **Please go to Question 11**
   - ❑ Worse **Please go to Question 11**

11) If your muscle symptoms have got better or worse, what has changed?
   - ❑ Frequency
   - ❑ Severity
   - ❑ Frequency and severity
   - ❑ Other, please list _____

12) Do your symptoms improve off statin therapy?
   - ❑ Yes
   - ❑ No
   - ❑ Do not know

13) Have you ever had any following laboratory tests?
Please TICK the appropriate answer for each test.

Test	**Yes**	**No**	**Do not know**
Liver function test			
Creatine kinase			
Myoglobinuria			

14) Are you currently taking either of the following minerals alone or as part of a mixed mineral supplement?

   - ❑ Calcium
   - ❑ Magnesium

15) Is there any family history of muscle disorders?
   - ❑ Yes
   - ❑ No

16) Does your urine appear dark or tea colored after exercise or fasting?
   - ❑ Yes
   - ❑ No

17) Have you discussed your muscle symptoms with your general practitioner or specialist?
   - ❑ Yes
   - ❑ No

18) Does your general practitioner or specialist believe that your symptoms are related to your statin therapy?
   - ❑ Yes
   - ❑ No

19) Please enter the following demographic information:

Age : _____ years

Sex : ❑ Male
❑ Female

Thank you very much for your cooperation.

Appendix F

THE LIST OF PHARMACIES PARTICIPATED IN MUSCLE ADVERSE EFFECT SURVEY

No	Name of Pharmacies	No	Name of Pharmacies
1.	Stirling Village	24.	Bayley St
2.	Pemberton	25.	Inglewood Amcal Chemist and News
3.	Albany Amcal Chemist	26.	Beverley
4.	Chemmart Central	27.	Helena State
5.	Kingsley Village	28.	Warnbro Fair Chemist
6.	Thomas & Co Chemist	29.	Pharmacy 149
7.	Augusta	30.	Wellness on Walcott
8.	Lynwood	31.	Pharmacy 777 Bayswater
9.	Higa Wyombe	32.	Pharmacy 777 Mt Hawthorn
10	Guardian Pharmacy Craigie	33.	Pharmacy 777 Cottesloe
11.	Victoria Park	34.	Pharmacy 777 Spearwood
12.	Toodyay	35.	Pharmacy 777 Whitford City
13.	Forrestfield Amcal Chemist	36.	Pharmacy 777 Glendalough
14	Gnowangerup	37.	Pharmacy 777 Maylands
15.	Northam	38.	Pharmacy 777 Applecross
16.	Murdoch	39.	Pharmacy 777 Hilton Centre
17.	Usher	40.	Pharmacy 777 Karratha
18.	Friendlies Chemist Subiaco	41.	Pharmacy 777 Midland
19.	Emslie's Floreat	42.	Pharmacy Help Cottesloe
20.	Ashburton Village Chemist	43.	Laurie Keys
21.	Friendlies Chemist Leederville	44.	West Busselton Pharmacy
22.	Centrepoint Amcal Chemist	45.	East Victoria Park
23.	Thornlie Square		

Appendix G

SAMPLE DIARY OF A PARTICIPANT FROM COENZYME Q10 FOR MUSCLE CRAMPS STUDY

Week 1 (PLEASE COMPLETE DIARY DAILY)

Day	Day 1 (Date)	Day 2 (Date)	Day 3 (Date)	Day 4 (Date)	Day 5 (Date)	Day 6 (Date)	Day 7 (Date)
Study Medication to be taken	Nil	Nil	Nil	Nil	Nil	Nil	Nil
Number of cramps suffered today (if zero put **NONE**)							
Time you suffered from cramp today							
Trigger of your cramp today							
Average duration of your cramps **(minutes)**							
Average pain score for all the cramps suffered today **(0 – 10)**							
Pain score for the **worst** cramp experienced today **(0 – 10)**							
Muscle(s) were affected by cramp today							
Any other symptoms beside cramp you suffered today (please list)							

Appendix H

POSTER PRESENTATION

This study was presented at the following conference:
The Annual Conference of Australasian Pharmaceutical Science Association (APSA) in Adelaide, on 3rd December 2006.

TITLE: HOW COMMMONLY DO STATIN-USERS SUFFER FROM MUSCLE SYMPTOMS?

Dede Indra Kurniawan, Dr. Jeff Hughes, Prof. Moyez Jiwa
School of Pharmacy, Curtin University of Technology, Bentley Western Australia, 6102.

Background: Muscle aches and pain are common and may be associated with many conditions including the use of drugs. Statins are a group of cholesterol-lowering medications known to cause muscle complaints, such as muscle pain, weakness and cramps.

Aims: The aims of this study were to assess the frequency and nature of muscle symptoms amongst statin users and factors, which may influence them. Methods: The study was undertaken in 46 community pharmacies in WA. Patients taking statins were asked to complete a questionnaire, which had been adopted from a myopathy survey of IMPOSTER (Is Myopathy Part of Statin Therapy?). Statistical analysis of data was performed using the SPSS statistical software package for Windows, version 13.0.

Results: Of the 920 patients enrolled into the study, 356 (38.7%) returned their questionnaire. Of these 205 (111 men and 94 women; 57.6%) had muscle symptoms. Assuming, non-responders did not suffered from muscle symptoms then the overall incidence was (22.3%; 205/920). Amongst respondents with muscle symptoms 73 (35.6%) reported worsening on using statins. Atorvastatin was the most commonly prescribed statin (59.3%), followed by simvastatin (29.8%), pravastatin (10.4%) and fluvastatin 0.6%. Despite the higher use of atorvastatin, the incidence rate of myopathy by atorvastatin users was found to be similar with other statins. The most commonly

reported muscle symptoms were night cramps (54.6%), muscle aching (52.7%) and fatigue/tiredness (49.3%), while the most commonly affect area of the body was the calves (62%). Apart from statin use, age and other drugs being taken (e.g. cortisone and prednisone) were associated with increased risk of myopathy.

Conclusion: Muscle symptoms were common amongst statin users, and appeared more common in those taking corticosteroids and in the elderly.

Appendix I

ORAL PRESENTATION

This paper was presented at the following conference:
The Australian Society for Medical Research (ASMR) Week Symposium in Perth, on 7th June 2007, and was awarded The Invitrogen™ Award for the Best Presenter.

TITLE: COENZYME Q10 FOR MUSCLE CRAMPS STUDY

Dede Indra Kurniawan, Dr. Jeff Hughes, Prof. Moyez Jiwa
School of Pharmacy, Curtin University of Technology, Bentley Western Australia, 6102.

Background: Muscle cramps are one of the adverse affects suffered by hypercholesterolemia patients who are treated with statin. Besides reducing cholesterol levels, statins also reduce coenzyme Q10 blood levels. One of several hypotheses of pathophysiology for statins- inducing muscle cramps are reduced level of coenzyme Q10. Besides being a very important antioxidant, coenzyme Q10 also functions as a transmembrane proton conductor and an electron carrier between NADH and succinate dehydrogenases and the cytochrome system, which is needed for phosphorylation of ADP into ATP. Therefore, a decrease in the coenzyme Q10 tissue levels, as reflected in its reduced blood levels, may contribute to the muscle function impairment.

Aims: The aims of this study were to investigate the efficacy of oral coenzyme Q10 supplements in reducing muscle cramps in statin users and non-users.

Methods: Coenzyme Q10 for Muscle Cramps Study was a single blind, placebo-controlled, cross over trial of CoQ10. Participants were separated into two groups: Group A was those who suffered from muscle cramps who were taking statins; and Group B was those who suffered from muscle cramps but not taking statins. The trial consisted of four phases: a 1-week assessment period, during which the baseline frequency of muscle cramps was assessed; a 2-week treatment period, during which participants of Group A were allocated coenzyme Q10 100 mg per day, and Group B were allocated placebo; a 1-week wash out period, during which participants did not

take either coenzyme Q10 or placebo; and then a second 2-week of the second treatment during which participants of Group A took placebo, and Group B took CoQ10 100 mg per day. Patients were given a diary to record days on which cramps were experienced, the number of cramps suffered per day, the average and maximum pain scores associated with cramps, the duration of the cramps, the part(s) of body affected by the cramps, and any adverse reactions suffered over the duration of the study for the entire 6 weeks. Statistical analysis of data was performed using the SPSS statistical software package for Windows, version 13.0.

Results: It was found that on average, participants on Group A (statin users) experienced significant lower average pain scores associated with cramps during the periods they were on CoQ10 (mean score = 6.36 ± 0.75) than on placebo (7.37 ± 0.85), with $t(29)= -2.316$, $p=0.028$. Furthermore, patients also experienced significant shorter cramp duration when they were on CoQ10 (4.88 ± 0.84) than on placebo (4.88 ± 0.84), with $t(29)= -3.535$, $p=0.001$. On the contrary, in Group B (non-statin users or controls), there were no significant differences between CoQ10 and placebo efficacy in all assessed variables.

Conclusion: the administration of CoQ10 100 mg per day was safe and effective in reducing severity and duration of muscle cramps amongst statin users

Appendix J

BRIEF EXPLANATION: REPEATED MEASURES ANOVA FOR THE UNINITIATED

Repeated Measures Analysis of variance (ANOVA) is an approach to help us deal with individual differences. These differences usually are part of the error term. Since they increase the error term, they decrease the likelihood of finding a significant result. While individual differences reflect actual differences among individuals, they also reflect the individual's state when the instrument was administrated, environmental factors, and response style. With repeated measures ANOVA, we may be able to measure, thus control, some of this variation.

There are two main types of repeated measures designs (also called within-subjects designs). One type involves taking repeated measures of the same variable(s) over time on a group or groups of subjects. For example, if we were studying hypertension, we would probably want more than one blood pressure reading on our subjects.

The other main type of repeated measures designs involves exposing the same subjects to all levels of the treatments. This often called using subjects as their own controls. For example, we wanted to test medications to reduce nausea during chemotherapy. We could randomly assign individuals to one of the following three conditions: medication one, medication two, or control.

However, if our participants varied widely in the amount of nausea they experienced, the within-subject variability would be larger because *F* statistic is based on the ratio of between-group variance to within-group variance, there would have to be a very large between-group difference to attain a significant result; that is, the large variability among the subjects could obscure any real differences between groups. One way to remove these individual differences would be to assign each subject to all treatments. Each participant would be exposed to medication one, medication two, and the control

condition in random order. Each participant would serve as his or her own control, and the within or error variance would be decreased. This would result in a more powerful test and would decrease the number of subjects needed for the study.

The basic assumption for independent ANOVA and repeated measures ANOVA also are almost the same. The dependent variable should be normally distributed, and the homogeneity of variance requirement should be met. However, there is one major difference where with independent ANOVA; the observations are independent of each other, which are achieved by randomly assigning participants to mutually exclusive groups. With repeated measures ANOVA, however, there is correlation between the measures because they are from the same people. Therefore, the assumption of compound symmetry (also known as ***sphericity***) must be met.

There are two part of the assumption. The first part is the assumption that the correlations across the measurements are the same. The second part of the assumption is that the variances should be equal across the measurements. With three measurements (medication one, medication two, and control), the variance of 1 = variance of 2 = variance of control. If data violate the sphericity of the assumption, there are several corrections that can be applied to produce a valid F-ratio, such as *the Greenhouse-Geisser correction* and *the Huynh-Feldt correction*.

Source: Munro, B. *Statistical Methods for Health Care Research*. 3ed. Philadelphia, New York: Lippincott; 1997.