Comparative Analysis of Lipid Profile Management in Ischaemic Heart Disease

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Maia Zarb

Department of Pharmacy

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I would like to dedicate this dissertation to my parents,

Charles and Jacqueline, my brother Matthew and Noelia

and my boyfriend Alex for their unwavering love and support

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Abstract

The European Society of Cardiology (ESC) guidelines for management of dyslipidaemias recommend a target low density lipoprotein cholesterol (LDL-C) goal of ≤1.4 mmol/L or ≥50% relative reduction. Patients with documented cardiovascular disease and elevated individual risk factors are candidates for early intervention with high-intensity statins.

The aim of this study was to compare effectiveness and safety of statins in patients with ischaemic heart disease (IHD).

Patients diagnosed with IHD and receiving statin therapy were recruited from the Cardiology Department at Mater Dei Hospital and matched for age, gender, hypertension and diabetes mellitus. LDL-C levels and side-effects at the time of recruitment (t1), 6 months (t2) and 12 months (t3) were documented. Mean LDL-C level and percentage LDL-C reduction achieved with different statins was analysed.

Eighty-one patients (62 male, 19 female, mean age 68 years, 42 with previous revascularisation) were recruited and followed-up for one year. Statin therapy prescribed included atorvastatin (n=39), simvastatin (n=34), and rosuvastatin (n=8). By t3, 17 patients were switched to a higher intensity statin (atorvastatin 80mg or rosuvastatin 20-40mg) and 4 patients underwent dose intensification. LDL-C reduction observed was similar for those with changed and unchanged statin status ($p>0.05$). The greatest mean LDL-C reduction was achieved with atorvastatin 80mg: LDL-C score 1.56 mmol/L and 32% reduction from t1. Patients on rosuvastatin achieved a greater percentage LDL-C reduction from t1 (24%)

compared to simvastatin (2%) ($p<0.001$). At t3, 24 patients achieved the 1.4 mmol/L target goal and 12 patients achieved ≥50% relative reduction with high-intensity statins. Eleven cases of myalgia were reported; simvastatin (n=9) and rosuvastatin (n=2). Renal dysfunction was recorded in patients on atorvastatin (n=7) and simvastatin (n=3). Three cases of deranged liver function tests were documented with simvastatin.

The high-intensity statins atorvastatin 80mg and rosuvastatin 20-40mg were associated with the greatest LDL-C reduction from baseline. The overall LDL-C levels achieved with statin therapy after 12 months were significantly higher than 1.4 mmol/L. A more intensive LDL-C lowering regime is required to attain targets recommended in ESC guidelines and to reduce cardiovascular risk.

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List of Abbreviations

4S	Scandinavian Simvastatin Survival Study
ACE	Angiotensin converting enzyme
ACS	Acute coronary syndrome
ADA	American Diabetes Association
AHA	American Heart Association
ALT	Alanine transaminase
ApoB	Apolipoprotein B
ARB	Angiotensin II receptor blocker
ASCVD	Atherosclerotic cardiovascular disease
AST	Aspartate transaminase
CABG	Coronary artery bypass grafting
CARDS	Collaborative Atorvastatin Diabetes Study
CCB	Calcium channel blocker
CK	Creatinine kinase
CKD	Chronic Kidney Disease
CRP	C-reactive protein
CTT	Cholesterol Treatment Trialists
CVD	Cardiovascular disease
CVIS	CardioVascular Information System

DH	Department of Health
DM	Diabetes mellitus
ESC	European Society of Cardiology
FREC	Faculty of Medicine and Surgery Research Ethics Committee
GFR	Glomerular filtration rate
HDL-C	High density lipoprotein cholesterol
HMG-CoA	3-hydroxy-3-methylglutaryl coenzyme A
IDL-C	Intermediate density lipoprotein cholesterol
IHD	Ischaemic heart disease
JUPITER	Justification for the Use of Statins in Primary Prevention
KDIGO	Kidney Disease: Improving Global Outcomes
LDL-C	Low density lipoprotein cholesterol
LFT	Liver function test
LIPS	Lescol Intervention Prevention Study
LUNAR	Limiting Under-treatment of Lipids in Acute Coronary Syndrome with Rosuvastatin
MACE	Major adverse cardiovascular events
MDH	Mater Dei Hospital
MI	Myocardial infarction
NHS	National Health System
NICE	National Institute for Health and Care Excellence
NSTEMI	Non-ST-elevation myocardial infarction

PATROL	Comparison of Pitavastatin, Atorvastatin, and Rosuvastatin for Safety and Efficacy
PCI	Percutaneous coronary intervention
PROVE-IT	Pravastatin or Atorvastatin Evaluation and Infection Therapy
REVERSAL	Reversal of Atherosclerosis With Aggressive Lipid Lowering
RNA	Ribonucleic acid
SATURN	Study of Coronary Atheroma by Intravascular Ultrasound: Effect of Rosuvastatin Versus Atorvastatin
SPACEROCKET	Secondary prevention of acute coronary events – reduction of cholesterol to key European targets trial
STELLAR	Comparison of the Efficacy and Safety of Rosuvastatin Versus Atorvastatin, Simvastatin, and Pravastatin Across Doses
TC	Total cholesterol
TRIUMPH	Translational Research Investigating Underlying Disparities in Acute Myocardial Infarction Patients' Health Status
TSH	Thyroid-stimulating hormone
VLDL-C	Very low density lipoprotein cholesterol
VYMET	Vytorin in Metabolic Syndrome
WHO	World Health Organization
WOSCOPS	West of Scotland Coronary Prevention Study

Chapter 1

Introduction

1.1 Cardiovascular disease

Cardiovascular diseases (CVD) are characterised by occlusion of blood vessels obstructing blood flow to the heart and brain. The occlusion is most commonly caused by accumulation of plaque on the endothelium of blood vessels.[1] Plaques first appear as fatty streaks, which later progress to larger and more serious atheromas which are a combination of platelets and cell debris covered by a fibrous plaque (Deanfield *et al*, 2007). The patient may be asymptomatic until the body mounts a great enough immune response to occlude most of the artery lumen. The patient then starts to experience angina which may later develop into chronic ischaemic heart disease (IHD) if left uncontrolled (Vanhoutte, 2009).

Dynamic acute changes in plaques may appear on any degree of stenosis, including moderate atheroma (Deanfield *et al*, 2007), rendering the condition unstable. Rupture and fissure of the atherosclerotic plaque results in superimposed thrombosis, which falls under the general term acute coronary syndrome (ACS) (Insull, 2009). The thrombus may proceed to block other small- to medium-sized arteries, including renal arterioles and coronary arteries, leading to complete occlusion of the vessel or myocardial infarction (MI), sudden death from arrhythmias, and renal abnormalities (Zeibig *et al*, 2011).

[1]World Health Organization (WHO). What are cardiovascular diseases? [Online]. Geneva: WHO; 2016 [cited 2019 Apr 20]. Available from: URL: http://www.who.int/en/

CVD persists as a foremost cause of morbidity and mortality worldwide despite major advances in medicine (Taylor *et al*, 2013; Nichols *et al*, 2014; Timmis *et al*, 2020). According to the 2019 European CVD statistics, 4.1 million deaths in Europe are caused by CVD, with IHD being the first most common cause of mortality, accounting for 44% of CVD deaths in males and 38% in females. Stroke is the second most common cause of mortality due to CVD (Timmis *et al*, 2020).

1.2 Prevention of cardiovascular disease

Lifestyle modification is the first line of action in the prevention of CVD, including salt and weight reduction, increase in physical activity, smoking cessation, decreased consumption of saturated fats and inclusion of plant sterols in the diet. Pharmacological treatment is added when non-pharmacological measures do not produce an adequate response (Bhatnager *et al*, 2008).

1.2.1 Diet recommendations

The 2014 National Institute for Health and Care Excellence (NICE) clinical guideline 181 on recommendations to prevent CVD at individual and population level was updated in 2016. This guideline recommends that fat intake should be 30% or less than the daily energy intake and the amount of saturated fats should not exceed 7% of the daily intake. Saturated fats should be replaced with monounsaturated and polyunsaturated fats. Physical activity is encouraged and routine check-ups of all cardiovascular risks are highly emphasised in the

guideline. Patients at high risk of or diagnosed with CVD are advised to allocate between 75 and 150 minutes of aerobic activity every week. [2]

The 2019 guideline on the primary prevention of cardiovascular disease issued by the American Heart Association (AHA) provides evidence-based recommendations on lifestyle management, including a reduction in total daily sodium intake of not more than 2000mg, decreasing saturated and trans-fats consumption and reducing total caloric intake. The guidelines recommend a Mediterranean or plant-based diet, including fish, nuts, fruits and legumes, which have been associated with a greater survival benefit than standard diets (Estruch *et al*, 2018; Arnett *et al*, 2019). Similar to the NICE guidelines, the AHA stresses the importance of engaging in 75 minutes of vigorous-intensity or 150 minutes of moderate-intensity physical activity per week (Arnett *et al*, 2019).

Lifestyle advice in the 2019 European Society of Cardiology (ESC) guideline on management of chronic coronary syndromes is comparable to the NICE and AHA guidelines and also focuses on a Mediterranean diet low in saturated fat (<10% of total caloric intake) and salt (<5-6g per day). Regular exercise should be included in a person's daily routine, irrelative of weight and the guideline recommends ≥30 minutes daily moderate-intensity exercise

[2]National Institute for Health and Care Excellence (NICE). Clinical guideline 181 [CG181]. Cardiovascular disease: Risk assessment and reduction, including lipid modification [Online]. UK: NICE; 2014 [cited 2020 Apr 20]. Available from: https://www.nice.org.uk/

(Knuuti *et al*, 2020). Restriction of alcohol consumption and complete smoking cessation is paramount in CVD prevention (Mach *et al*, 2020).

1.2.2 Pharmacotherapy in cardiovascular disease

Commonly prescribed pharmacotherapy in CVD includes angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), beta-blockers, calcium channel blockers (CCBs), aspirin, statins and diuretics, to control or decrease the risk of organ damage and CVD events. According to the ESC guidelines on CVD prevention in clinical practice, ACE inhibitors or ARBs, statins, metformin and aspirin should be included as first-line therapy in diabetic and hypertensive patients with clinically-established CVD since these patients are increasingly susceptible to thrombotic episodes (Mach *et al*, 2020).

Combination therapy is the mainstay treatment for hypertension with or without CVD, using an effective blood pressure-lowering agent. Beta-blockers are usually avoided in diabetic patients due to their dysmetabolic action. However, carvedilol and nebivolol continue to be used since evidence suggests a reduced incidence of adverse effects compared to conventional beta-blockers (Gerstein *et al,* 2014; Tsujimoto *et al*, 2017). ACE inhibitors and ARBs are reported to have superior nephroprotective effects, are generally well-tolerated and can be combined with a diuretic. CCBs are usually prescribed for asymptomatic atherosclerosis or when ACE inhibitors or ARBs are contraindicated (Mach *et al*, 2020). The role of aspirin in primary and secondary prevention of CVD remains unclear, with recent

studies finding no sufficient evidence to suggest survival benefit from low-dose aspirin (Gargiulo *et al,* 2016; Squizzato *et al,* 2017; McNeil *et al*, 2018; Knuuti *et al*, 2020).

1.3 Lipoproteins

Two-thirds of cholesterol in the body is synthesised by the liver and small intestine. Lipoproteins consist of unesterified and esterified cholesterol, phospholipids, triglycerides and apolipoproteins. In plasma, lipoproteins have a role in energy utilisation, lipid deposition, steroid hormone synthesis and bile acid formation. Different densities of lipoproteins are related to triglyceride content and the risks they evoke (Mach *et al*, 2020).

There are six types of lipoproteins; the largest and least dense are the chylomicrons. Very low density lipoprotein cholesterol (VLDL-C) extracts cholesterol to store it as fat and is a precursor of both low density lipoprotein cholesterol (LDL-C) and intermediate density lipoprotein cholesterol (IDL-C). Elevated lipid levels, especially LDL-C, have been implicated in plaque formation and major cardiovascular events. High density lipoprotein cholesterol (HDL-C) has the highest protein-to-lipid ratio and is essential for homeostasis, for the regulation of cholesterol levels in peripheral tissues and transportation back to the liver. HDL-C can also be increased via exercise, weight loss and high oestrogen levels. Lipoprotein A, like LDL-C, can be retained in the arterial wall (Hlaing and Park, 2013).

The concentration of apolipoprotein B (ApoB) within these lipoproteins determines their effect on atherosclerotic cardiovascular disease (ASCVD) since it favours entry and growth

of atherosclerotic plaques. LDL-C is the most abundant ApoB-containing lipoprotein (Mach *et al*, 2020).

1.4 Total cardiovascular risk

According to the ESC guidelines on the management of dyslipidaemias, estimating cardiovascular risk will determine the likelihood of a person developing an ASCVD event over a defined period of time. The total CVD risk is the combination of all cardiac risk factors presented by the patient (Mach *et al*, 2020).

The guidelines suggest target levels for the ideal LDL-C range in multiple risk patients, some of whom may require the appropriate pharmacotherapy. 'Very high-risk' patients are those with documented CVD, including a history of coronary revascularisation procedures such as percutaneous coronary intervention (PCI) and coronary artery bypass graft (CABG) surgery, ACS, stroke, transient ischaemic attack and peripheral artery disease. Persons with elevated individual risk factors, such as hypertension, type 1 or type 2 Diabetes Mellitus (DM) or chronic kidney disease (CKD), are generally at high total cardiovascular risk and risk estimation models are not required. All patients within this category are candidates for early pharmacological intervention (Mach *et al*, 2020) (Table 1.1).

A Systematic Coronary Risk Estimation (SCORE) chart is used to quantify risk in patients without overt CVD or elevated individual risk factors over a ten-year period. These patients are considered to be at moderate to low cardiovascular risk depending on their age, gender, systolic blood pressure, total cholesterol and smoking habits (Mach *et al*, 2020). Table 1.1 specifies LDL-C goals according to CVD risk estimation.

Table 1.1: LDL-C goals according to CVD risk

Adopted from: Mach F, Baigent C, Catapano AL, Koskinas KC, Casula M, Badimon L, et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. Eur Heart J. 2020;41(1):111-188.

CVD Risk	LDL-C goal
Very high	<1.4 mmol/L or 55 mg/dL
High	<1.8 mmol/L or 70 mg/dL
Moderate to low	2.6 to <3mmol/L or 100 to <116 mg/dL

Intervention strategies for CVD are included in the guidelines on CVD prevention in clinical practice. SCORE is a measure of total cardiovascular risk and is used to determine an appropriate treatment strategy to reduce risk factors, based on results of randomised clinical trials. The guidelines recommend lifestyle advice as first-line, followed by concomitant drug therapy if the calculated SCORE for 10-year risk of fatal CVD is high and LDL-C values are uncontrolled with lifestyle advice alone (Mach *et al*, 2020).

1.4.1 Hyperlipidaemia as a risk factor for cardiovascular disease

Cholesterol, particularly LDL-C, is a major determinant of CVD risk and is one of many targets in primary and secondary prevention strategies. In patients with no history of ASCVD, each 1 mmol/L reduction of LDL-C confers a 15% reduction in risk of vascular death (Silverman *et al*, 2016; Timmis *et al*, 2020). The prevalence of elevated total cholesterol is higher for developed countries including Europe, when compared to low to moderate-income countries in Africa and South East Asia.[3] Mendelian randomisation studies have shown that long-term exposure to raised LDL-C results in an increased risk of cardiovascular events when compared to short-term exposure, supporting the concept of a cumulative effect on ASCVD (Ference *et al,* 2012; Mach *et al,* 2020).

Hyperlipidaemia is divided into subtypes which include hypercholesterolaemia, hypertriglyceridaemia and mixed hyperlipidaemia. Hyperlipidaemia is a common biochemical disorder of primary and secondary causes. Primary hyperlipidaemia is associated with inherited susceptibility to raised lipid parameters and metabolic disorders such as diabetes mellitus. Secondary hyperlipidaemia is caused by external factors based on a person's lifestyle and pre-existing comorbidities, including obesity, hypothyroidism and nephrotic syndrome (Hlaing and Park, 2013).

[3]World Health Organisation (WHO). Global Health Observatory (GHO) data [Online]. WHO; 2019 [cited 2020 Jun 2]. Available from: http://www.who.int/gho/ncd/risk_factors/cholesterol_prevalence/en/.

1.4.2 The role of statins in hyperlipidaemia

Statins, 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, prevent hepatic cholesterol synthesis and lower the intracellular pool of sterol, which in turn stimulates upregulation of LDL-C receptors and increases the uptake of non-HDL-C particles from the systemic circulation (Mach *et al*, 2020). Statins are first-line agents for controlling total cholesterol and have led to significant reduction in cardiovascular morbidity and mortality (Deanfield *et* al, 2007; Khurana *et al,* 2015).

Mean reduction in serum LDL-C with statins ranges between 30% and 50% or more, according to their intensities (Foody *et* al, 2013; Mach *et al*, 2020). Statins have both a potent lipid-lowering effect as well as anti-inflammatory properties, which are beneficial for plaque stabilisation (Khurana *et al,* 2015).

1.5 The development of statins

In 1978, Alberts *et al* (1980) at Merck Research Laboratories identified a potent inhibitor of HMG-CoA reductase, originally named mevinolin, and which later became officially known as lovastatin. Lovastatin was the first major breakthrough in terms of lipid-lowering efficacy with very few side-effects compared to compactin despite similarity in structure. The maximal recommended dose of 80mg with once or twice daily dosing maximised patient compliance (Downs *et al*, 1998). The mechanism of action of statins interferes with the conversion of HMG-CoA into mevalonic acid in an irreversible reaction. Being an early step

in the pathway, inhibition of this enzyme avoids build-up of potentially toxic precursors, making it an attractive target in contrast to previous attempts on cholesterol biosynthesis (Cannon *et al*, 2004; Biasucci *et al*, 2010).

Simvastatin was the second statin to be discovered. It is a semi-synthetic derivative of lovastatin, with an additional methyl group side chain. It was initially approved for marketing in Sweden in 1988 and subsequently worldwide (Tobert *et al*, 2003). In 1994, the 'Scandinavian Simvastatin Survival Study (4S)' was conducted following controversies which challenged the therapeutic relevance of statins. The study observed lipid-lowering ability and occurrence of cardiovascular events in 4,444 patients receiving simvastatin treatment. The result was a net decrease in cardiovascular mortality of 35% with simvastatin therapy (Pedersen *et al*, 2000). Similar findings were obtained in a later 'Heart Protection Study' according to Wilmshurst (2003) using a larger sample population of 20,536 patients with IHD.

1.5.1 Second generation statins

The newer generation statins are all synthetic products, namely pravastatin developed in 1991, fluvastatin in 1994, atorvastatin in 1997, and rosuvastatin in 2003, the latter being the most potent. Cerivastatin was also discovered in 1998, however reports of severe myotoxicity and mortality led to its withdrawal (Tobert *et al*, 2003).

Fluvastatin acts directly on the walls of blood vessels to reduce inflammation caused by plaque formation (Aoki *et al*, 2010). Apart from its lipid-lowering effects, the 'Lescol Intervention Prevention Study (LIPS)' suggested that fluvastatin had cardioprotective properties following PCI (Serruys *et al*, 2002). Being the least potent of the newer generation statins, fluvastatin was indicated in patients with mildly to moderately elevated LDL-C, and was the statin of choice in diabetics and in patients with hepatic and renal impairment (Tomizawa *et al*, 2010).

In the 'Reversal of Atherosclerosis with Aggressive Lipid Lowering (REVERSAL)' and the 'Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE-IT)' studies, atorvastatin was found to be more potent than pravastatin with regards to reducing the risk of IHD, with a lower side-effect profile compared to high-dose simvastatin (Sever *et al,* 2003; Murrow *et al*, 2012; Naci *et al*, 2013).

Later in 2008, the 'Justification for the Use of Statins in Primary Prevention (JUPITER)' trial, researchers administered rosuvastatin to low and moderate-risk patients without established CVD and with normal-to-low cholesterol levels. The outcome was a 50% LDL-C reduction and a 50% decrease in MACE, confirming its superior potency to other statins (Bogaty *et al*, 2005; Ridker *et al*, 2008; Nicholls *et al*, 2010).

1.6 Benefits of statin therapy

Over the years, healthcare professionals have recognised the benefits of statin therapy in the prevention of fatal and non-fatal major cardiac events. Statins are established for use in primary and secondary prevention in patients of any age with manifest ASCVD or DM, with either normal or increased cholesterol levels. There have been notable reductions in stroke rates, PCI and CABG associated with statin use (Noto *et al*, 2014; Mortensen *et al,* 2019).

Statins are associated with approximately 30% reduction in major cardiovascular events and 15% reduction in all-cause mortality compared to placebo for both primary and secondary prevention patients, especially diabetics and the elderly (Brugts *et al*, 2009; Naci *et al*, 2013; Taylor *et al*, 2013). In the 'Cholesterol Treatment Trialists (CTT)' meta-analysis, both men and women achieved an LDL-C reduction of approximately 1.1 mmol/L on statin therapy versus placebo, and greater reduction was reported with more intensive LDL-C lowering therapy compared to low-intensity, regardless of baseline LDL-C level (Taylor *et al*, 2013; Fulcher *et al*, 2015).

The CTT meta-analysis was one of many studies to be incorporated in a systematic meta-analysis published in the Lancet in 2005, in which 14 randomised trials were included to identify clinical outcomes of statin therapy with regards to efficacy, benefits and risks. Previous meta-analyses failed to observe the long-term survival benefits of statins on major adverse coronary events (MACE), coronary revascularisation and stroke. A 10%

proportional reduction in MACE per mmol/L LDL-C reduction during the first year was reported. After one year of treatment, more frequent reductions of approximately 20% to 30% per mmol/L were reported, showing that absolute benefits increased with continued treatment. One limitation of this meta-analysis was that no high-dose statin regimens were included, hence no conclusions could be drawn regarding side-effects on liver enzymes and onset of rhabdomyolysis (Baigent *et al*, 2005).

The 'Study of Coronary Atheroma by Intravascular Ultrasound: Effect of Rosuvastatin Versus Atorvastatin (SATURN)' was the largest imaging trial comparing the anti-atherosclerotic efficacy of two potent statin regimens; atorvastatin 80mg and rosuvastatin 40mg. No significant difference in percentage atheroma volume, safety or risk of MACE was reported between both treatment groups at primary end-point (Nicholls *et al*, 2011). In 2014, a post hoc analysis of the SATURN trial was undertaken to ascertain the anti-atherosclerotic efficacy after 2 years of intensive statin therapy in patients presenting with or without ACS at recruitment. Rosuvastatin was associated with greater atheroma volume regression compared to atorvastatin. After 2 years of optimum statin therapy, 93% of patients without ACS and 91% of patients with ACS did not experience MACE (Puri *et al*, 2014).

From these findings, Puri *et al* (2014) concluded that the high-intensity statins serve a dual purpose of lowering LDL-C and possessing antioxidant and anti-inflammatory properties. Patients with ACS achieve greater atherosclerotic reduction with atorvastatin and rosuvastatin when compared to patients with chronic stable ischaemia, who accumulate

less modifiable fibrocalcific plaque. Physicians are encouraged to not only focus on attaining target LDL-C levels but to also consider the long-term survival benefits of potent statins (Sathyapalan *et al,* 2013; Puri *et al,* 2014; Khurana *et al,* 2015).

1.7 Statin-prescribing practices

The 'Translational Research Investigating Underlying Disparities in Acute Myocardial Infarction Patients' Health Status (TRIUMPH)' study investigated statin prescribing practices in United States hospitals in patients eligible for statin therapy with previous MI or symptoms of ischaemia. LDL-C levels and ST-segment elevations on admission were important drivers of prescribing higher-intensity statins, and their efficacy was independent of the type of MI and LDL-C levels at baseline (Arnold *et al*, 2014). However, rates of statin intensification were low, despite reports that higher-intensity statins are associated with improved outcomes (de Lemos *et al*, 2004; Murphy *et al*, 2007; Ribeiro *et al*, 2013).

The 2019 AHA guidelines on primary prevention of CVD were adopted from the 2018 guideline on the management of blood cholesterol by Grundy *et al* (2019), and focus on attaining between 30% and 50% relative LDL-C reduction, according to ASCVD risk estimation. Statin therapy is recommended in patients between 40 and 75 years with LDL-C ≥1.8 mmol/L and clinical ASCVD risk greater than 7.5% (Class of Recommendation I). Those with ASCVD risk enhancers, including diabetes, should be treated with high-intensity statins

and achieve at least a 50% reduction from baseline LDL-C, regardless of ASCVD risk. Statin intensities are categorised as high, moderate and low intensity (Arnett *et al,* 2019).

The ESC guidelines for the management of dyslipidaemias recommend a 'treat-to-target' strategy (Class I, level of evidence B recommendation), with a specified target LDL-C goal of <1.4 mmol/L and at least 50% reduction from baseline. These guidelines recommend that patients should be started on a high-intensity statin and that the choice of statin should be based on baseline LDL-C and on the expected percentage decrease in LDL-C. Unlike the American guidelines, the ESC guidelines do not categorise statins according to intensity (Table 1.2) (Mach *et al*, 2020).

NICE clinical guideline 181 advises that when a statin is indicated, a high-intensity statin with low acquisition cost should be recommended. All patients, including diabetics and CKD patients, who have a 10% or greater 10-year risk of developing CVD should be started on atorvastatin 20mg for primary prevention. For patients 85 years or older, atorvastatin 20mg is considered beneficial in reducing the risk of non-fatal myocardial infarction, taking into consideration general frailty, comorbidities and polypharmacy. High-intensity statins are currently more potent and cost-effective compared to the moderate-intensity statins atorvastatin 10mg and simvastatin 20mg in reducing cardiovascular outcomes. Patients with established CVD should be prescribed atorvastatin 80mg for secondary prevention. A lower starting dose is recommended in cases of potential drug interactions or a high risk of

adverse effects. Similarly to the AHA guidelines, no specific LDL-C level goal is set in the NICE guideline.[2]

Table 1.2: Comparison of practice guidelines for initiation of statin therapy

Guidelines (reference)	**Strategy and target LDL-C level**	**Statin intensity**
AHA (Grundy *et al,* 2019)	*≤75 years* **High-intensity statin therapy** which lowers LDL-C by ≥50% *>75 years or not candidates for high-intensity statins* **Moderate-intensity statin therapy** which lowers LDL-C by 30-49%	**High-intensity statins** atorvastatin 40-80 mg rosuvastatin 20-40 mg **Moderate-intensity statins** atorvastatin 10-20 mg rosuvastatin 5-10 mg simvastatin 20-40 mg
ESC (Mach *et al,* 2020)	**High-intensity statin therapy** <1.4 mmol/L and ≤50% reduction from baseline LDL-C	**Not specified**
NICE[2]	*<85 years* **High-intensity statin therapy** which lowers LDL-C by >40%	**High-intensity statins** atorvastatin 20-80 mg rosuvastatin 10-40 mg simvastatin 80 mg **Moderate-intensity statins** atorvastatin 10 mg simvastatin 20 mg

bd, twice daily; LDL-C, low-density lipoprotein cholesterol; ACC/AHA, American College of Cardiology/American Heart Association; ESC/EAS, European Society of Cardiology/European Atherosclerosis Society; NICE, National Institute for Health and Care Excellence

[2]National Institute for Health and Care Excellence (NICE). Clinical Guideline [CG181] Cardiovascular disease: risk assessment and reduction, including lipid modification [Online]. UK: NICE; 2014 [cited 2020 May 25]. Available from: www.nice.org.uk

1.8 Statin intensity

High-intensity statins have been reported to reduce MACE after ACS, however continue to be underused in clinical practice, particularly in women. Among males with CVD, 20% utilised high-intensity statins compared to 12% for females with CVD (Eisen *et al*, 2017; Rodriguez *et al,* 2017; Musich *et al,* 2018). This contrasts with the 2019 ESC guidelines which recommend high-intensity statins for all adults who can tolerate them (Mach *et al*, 2020), indicating that physicians are still hesitant to prescribe high-intensity statins, especially in community settings (Rodriguez *et al*, 2016; Rosenson *et al*, 2017; Musich *et al*, 2018).

Foody *et al* (2013) assessed the attainment of target LDL-C goals in patients on simvastatin, atorvastatin and rosuvastatin. A medium LDL-C lowering potency was observed in simvastatin patients with a maximum LDL-C reduction of 41%. A 50% to 60% LDL-C reduction was achieved in patients prescribed atorvastatin and rosuvastatin. Similarly, a 2017 study on the comparative lipid-lowering efficacy of atorvastatin and rosuvastatin carried out on 150 patients, concluded that these higher-intensity statins lowered LDL-C by 47% to 63% after 6 months of therapy (Prasanth *et al*, 2017).

A clinical trial in IHD patients 65 years or older was conducted to analyse whether higher-intensity statins are superior to other intensities in preventing MACE (O'Brien *et al,* 2016). The study identified the higher-intensity statins as atorvastatin >40mg, rosuvastatin >20mg and simvastatin 80mg. The 4,488 patients who were prescribed these higher-intensity statins were mostly young males with acute MI. Inverse propensity weighting showed that

statin intensity was not significantly associated with lower risk of morbidity and mortality. However more recently, Hwang *et al* (2018) suggested that risk of MACE was similar for all statin intensities once adequate LDL-C levels were attained, while Musich *et al* (2018) concluded that mortality hazard ratios indicated the most benefit from high-intensity statins.

1.8.1 Simvastatin versus Atorvastatin

The 'Vytorin in Metabolic Syndrome (VYMET)' study compared efficacy and safety of treatment with ezetimibe/simvastatin to atorvastatin monotherapy. Inclusion criteria were patients diagnosed with hypercholesterolaemia and metabolic syndrome who were moderately-high to high-risk patients for IHD. After 6 weeks of treatment, a reduction in mean LDL-C of 2.75 mmol/L with ezetimibe/simvastatin 20mg compared to a 2.02 and 2.18 mmol/L reduction with atorvastatin 10mg and 20mg respectively, was observed from baseline value. Similarly, the ezetimibe/simvastatin 40mg combination maintained better control of LDL-C levels than atorvastatin 40mg (2.99 > 2.55 mmol/L LDL-C reduction). The improved control on lipid profile was consistent with the combination therapy at all doses studied, however safety end-points were similar for both treatment groups (Robinson *et al*, 2009).

In a post-hoc analysis of the VYMET study, three predictive factors were identified for attaining target LDL-C goals. Increasing age (≥65 years), obesity and low C-reactive protein (CRP) levels at baseline were all significantly associated with enhanced LDL-C lowering in

moderately high to high-risk patients on ezetimibe/simvastatin and atorvastatin treatments, with greater evidence favouring combination therapy. Simvastatin therefore requires additional lipid-lowering agents to achieve better overall efficacy, which may not be acceptable by all patients. A limitation of this study is that only medium-intensity statins were used for comparison (Robinson *et al*, 2013). The ESC guidelines limit the use of ezetimibe with statins to selected patients when target goals are not attained despite optimal statin therapy (Mach *et al,* 2020).

In another study, patients with elevated alanine aminotransferase (ALT) levels were recruited to investigate the effects of monotherapy simvastatin 20–40 mg/day and atorvastatin 80 mg/day on cardiovascular risk. Atorvastatin significantly improved total cholesterol (TC), LDL-C, triglycerides and ApoB levels, while simvastatin improved HDL-C and ApoA1 levels. The risk of occurrence of a MACE with simvastatin and atorvastatin were 11.5% and 6.5% respectively, indicating a greater survival benefit with atorvastatin therapy (Pederson *et al*, 2010).

The pleiotropic effects of simvastatin and atorvastatin were studied by Sathyapalan *et al* (2013), who observed a correlation between the inflammatory marker CRP and vitamin D levels in patients with type 2 DM. The authors concluded that vitamin D acts as an inhibitor of the inflammatory response and hence reduces concentrations of CRP, which is the cornerstone of atherosclerosis. Vitamin D levels were higher in the atorvastatin group, indicating greater exposure to pleiotropic benefits. Moreover, treatment with simvastatin

and atorvastatin at any dose for a duration of more than one year had a positive effect on bone mineral density (Thabit *et al*, 2014).

1.8.2 Simvastatin versus Rosuvastatin

The main trial comparing simvastatin 40mg with rosuvastatin 10mg was the 'Comparison of the Efficacy and Safety of Rosuvastatin Versus Atorvastatin, Simvastatin, and Pravastatin Across Doses (STELLAR)' trial. A superior cholesterol-lowering effect was reported for rosuvastatin 10mg over the six-week trial, with 79% of patients attaining target LDL-C goals with rosuvastatin 10mg and 63% of patients with simvastatin 40mg (Jones *et al*, 2003).

In the 'Secondary Prevention of Acute Coronary Events – Reduction of Cholesterol to Key European Targets (SPACEROCKET)' trial, recent acute MI patients were selected to undergo treatment with simvastatin 40mg or rosuvastatin 10mg. After 3 months of therapy, the attained lipid profile parameters showed no significant differences between the two treatment arms (Hall *et* al, 2009). This lies in contrast to the STELLAR trial (Jones *et al*, 2003), which included patients with stable hyperlipidaemia, and hence would have excluded all participants in the SPACEROCKET trial. Side-effect profiles were similar in both patient groups, making both agents equally effective as first-line agents for secondary prevention. However, by the time the study was finalised, rosuvastatin patients had attained target LDL-C goals according to ESC guidelines more effectively than the simvastatin group (Hall *et al*, 2009).

A post-hoc analysis of the genetic component linked to lipid-lowering efficacy showed that one in three patients with CYP3A5 and/or breast cancer resistant protein variant genotypes had a greater tendency of achieving target LDL-C goals when receiving rosuvastatin 10mg compared to simvastatin 40mg (Bailey *et al*, 2010). This evidence suggests a greater push towards rosuvastatin prescribing and highlights the importance of more individualised regimens based on genomics (Aggarwal and Showkathali, 2013).

1.8.3 Atorvastatin versus Rosuvastatin

The 'Comparison of Pitavastatin, Atorvastatin and Rosuvastatin for Safety and Efficacy (PATROL)' trial investigated the efficacy and safety of three statins in lowering LDL-C. A constant 40% reduction was reported in all study groups. The proportion of patients who experienced adverse effects of therapy amounted to 18% for atorvastatin and 12% for rosuvastatin. Atorvastatin particularly had a slight tendency of raising ALT, HbA1c and creatinine kinase (CK) levels, while rosuvastatin was associated with a non-significant increase in HbA1c. Side-effects reported by patients related to ALT elevation were more predominant with atorvastatin (9.6%) than rosuvastatin (4.5%). However, elevation of CK is considered a class effect with varying degrees of adverse reactions occurring through different mechanisms (Saku *et al*, 2011).

Inflammatory markers were investigated by Khurana *et al* (2015) as predictors of ACS due to their progressive effect on atherosclerosis. The study focused on the anti-inflammatory effects of atorvastatin and rosuvastatin on CRP in 100 patients with ACS. After 4 weeks of

treatment, a significantly greater CRP regression from baseline was observed with rosuvastatin 20mg compared to atorvastatin 40mg. Lipid profiles of both statin groups were controlled with similar efficacies. All 100 patients adhered to statin therapy throughout the study, with no reports of MACE or adverse effects related to treatment (Khurana *et al*, 2015).

In the 'Limiting Under-treatment of Lipids in Acute Coronary Syndrome with Rosuvastatin' (LUNAR) study, three patient groups were prescribed high-intensity statin regimens namely atorvastatin 80mg, rosuvastatin 20mg or rosuvastatin 40mg to analyse their efficacy in ACS. Mean LDL-C reduction from baseline during follow-up at 6 and 12 weeks was significantly greater with rosuvastatin 40mg (47%) than with atorvastatin 80mg (43%). Rosuvastatin 40mg also improved TC, triglycerides and non-HDL-C when compared to high-dose atorvastatin. The adverse effects reported at these doses were considerably high in all treatment groups, however only a few were attributed to statin therapy (Pitt *et al,* 2012; Aggarwal and Showkathali, 2013).

1.8.4 Simvastatin versus Atorvastatin versus Rosuvastatin

In a research study on the comparison of statins for secondary prevention in patients with ischaemia, Tramcere *et al* (2019) studied the relative efficacy and safety of simvastatin, atorvastatin and rosuvastatin at different doses. The authors consulted various randomised controlled trials which compared any single statin at any dose with another statin or placebo, for secondary prevention in adults ≥18 years diagnosed with IHD. The primary end-

point was the reduction in MACE. High-intensity statins proved to have the best outcome in reducing morbidity and mortality, with high-quality evidence indicating the most benefit with atorvastatin 80mg and to a lesser extent with simvastatin 40mg. From the safety data retrieved, no conclusions could be drawn to ascertain the safety of one statin over another.

In a similar study, long-term outcomes of hydrophilic versus hydrophobic statins for secondary prevention in diabetic patients were evaluated. Patients with previous MI and prescribed statin therapy were followed-up over a period of 1,059 days. Propensity score matching was carried out to determine the level of interaction between statin treatment and cardiac risk factors. No significant difference was reported in the prevention of all-cause mortality or MACE between the groups, both before and after propensity score matching. In contrast, a significantly lower incidence of HF admission was observed in patients receiving hydrophilic statins, namely rosuvastatin, compared to the lipophilic statins simvastatin and atorvastatin (Shutta *et al,* 2020).

1.9 Adverse effects and monitoring with statins

Despite the popularity of statins and their lipid-lowering efficacy, 10 to 15% of patients on statin therapy present with side-effects. One of the most threatening side-effects is rhabdomyolysis. Oxidative stress from statin use is the probable cause of rhabdomyolysis in skeletal muscle (Rasmussen *et al*, 2016). A reduction in mitochondrial respiration in skeletal muscle was primarily associated with the inhibition of production of coenzyme Q10.

As a result, CK levels tend to rise and patients affected are at an increased risk of heart failure (Sigala *et al*, 2017). A simple urine test is able to predict the oxidative stress to ribonucleic acid from the presence of ribonucleoside 8-oxoGuo. This is of particularly high clinical significance in patients suffering from DM and may prove fatal if left untreated (Rasmussen *et al*, 2016).

Hepatic effects are also a major concern with statins, especially in alcoholics and the elderly. Patients are required to undergo periodic liver function tests (LFTs) prior to starting statin therapy and as clinically indicated thereafter to monitor serum transaminase levels, which may be elevated in patients taking statins. If these levels exceed three times the upper limit of normal, treatment is recommended to be withdrawn (Desai *et al*, 2014).

1.9.1 Drug-statin interactions

The main adverse effects linked to drug-statin interactions are the onset of myalgia, and consequently rhabdomyolysis, and the effect on liver metabolism. Potent inhibitors of CYP3A4, such as ketoconazole and ritonavir, increase the risk of myopathy, while potent inducers of CYP3A4 such as carbamazepine, greatly decrease plasma concentrations of statins, lowering response to therapy. Table 1.3 highlights potential interactions with the different statins, according to the British National Formulary (Joint Formulary Committee, 2020). Rosuvastatin has the least documented interactions.

Table 1.3: Drug-statin interactions

	Simvastatin	Atorvastatin	Rosuvastatin
Antifungals (azoles)	X	X	X
Amiodarone	X	X	X
Colchicine, allopurinol	X	X	X
Ezetimibe and fibrates	X	X	X
CCBs	X	X	
Cephalosporins	X	X	X
Grapefruit juice	X	X	
HIV protease inhibitors	X	X	X
Macrolides	X	X	
Antiepileptics	X	X	X
St John's Wort	X	X	X
Ranolazine	X	X	

1.9.2 Monitoring with statin therapy

According to ESC guidelines, patients who are candidates for statin therapy should be monitored regularly, especially those with established ASCVD who present with other comorbidities such as diabetes and CKD. Potential drug interactions must be considered before initiating therapy, particularly in the elderly. Subsequent follow-ups are recommended every six to twelve months. The ESC guidelines recommend a full lipid

profile, including triglycerides and HDL-C prior to starting and throughout statin therapy. In diabetic patients, HbA1c monitoring is essential to ensure long-term control, particularly in high-risk patients receiving high-intensity statin therapy. A blood panel which focuses on CK and ALT levels can be performed whenever there are symptoms suggestive of muscle and liver damage respectively, however do not form part of routine follow-ups. Throughout therapy, patient adherence and lifestyle modifications should also be assessed as these may affect response to treatment (Mach *et al*, 2020).

1.10 Statin use in diabetes mellitus

A few clinical trials identified the correlation between statin use and T2DM (Maki *et al*, 2015). The 'West of Scotland Coronary Prevention Study (WOSCOPS)' concluded that pravastatin therapy posed a low risk for development of T2DM (Freeman *et al*, 2001). Conversely, the JUPITER trial showed a significant increase in reports of DM in high-risk patients receiving rosuvastatin therapy. High-risk patients included those with impaired fasting glucose, high body mass index (BMI), raised HbA1c and metabolic syndrome (Ridker *et al*, 2012; Hennekens *et al*, 2017). However, two recent reports have suggested that the cardiovascular benefits of statins in reducing cardiac events still outweigh the risk of DM (Erqou *et al*, 2014; Maki *et al*, 2015).

The 2018 American Diabetes Association (ADA) guidelines do not specify an LDL-C goal but recommend high-dose statin therapy to all diabetic patients with clinical ASCVD or with at

least one additional cardiac risk factor. Patients younger than 40 years or older than 75 years should be started on medium-intensity statins according to these guidelines (Kianoush and Mirbolouk, 2017). According to the ESC guidelines, the target HbA1c level for prevention of CVD and microvascular complications in type 1 or type 2 diabetic patients on statin therapy should be less than 7% (Mach *et al*, 2020).

A 'Collaborative Atorvastatin Diabetes Study (CARDS)' provided robust support for statin benefit. Study groups were divided into atorvastatin 10mg and placebo. It was concluded that higher-intensity statins provided a greater CVD risk reduction, and that adding ezetimibe to the regimen resulted in an even greater benefit for DM patients, regardless of their baseline and post-therapy LDL-C levels (Colhoun *et al,* 2004; Mach *et al*, 2020).

1.11 Statin use in chronic kidney disease

Patients with CKD are increasingly susceptible to cardiovascular events compared to patients with normal kidney function. In patients who do not require dialysis, raised LDL-C levels may lead to MI that persists while kidney function continues to decline (Baber and Muntner, 2014). The 'Kidney Disease: Improving Global Outcomes (KDIGO)' guideline states that all CKD patients over 50 years of age should be prescribed statin therapy owing to their increased risk of a cardiovascular event (Schneider *et al*, 2015). Patients younger than 50 years of age are eligible for treatment only if they have persisting comorbidities (Wanner *et al*, 2014; Schneider *et al*, 2015).

Despite higher potency statins lowering plasma lipid concentrations to a greater extent, the renal effects seem to increase in proportion to the dose administered (Nikolic *et al*, 2013; Verdoodt *et al,* 2018). Comparison of rosuvastatin and atorvastatin showed that atorvastatin has more renoprotective effects for patients suffering from CKD (de Zeeuw *et al*, 2015). A meta-analysis of 24,194 patients tested the theory of proteinuria associated with dose-dependent rosuvastatin therapy. The authors concluded that the effects on glomerular filtration rate (GFR) of both atorvastatin and rosuvastatin were similar, however atorvastatin reduced proteinuria more efficiently (Wu *et al*, 2012). According to Dormuth *et al* (2013), patients on high-intensity statins were 34% more likely to be hospitalised with acute renal injury within 4 months of treatment initiation and dose adjustments or switching to a less potent drug was recommended in these situations.

1.12 The situation with statin therapy in Malta

In 2017, Malta had 1,574 per 100,000 inhabitants who were discharged with diseases of the circulatory system, where the hospitalisation period was considered long compared to other EU member states.[3] The long hospitalisation period and the number of patients reflect the gravity of some of these conditions, with a significant impact on the national

[3] European Statistics (Eurostat). Statistics Explained: Cardiovascular diseases Statistics [Online]. Eurostat; 2019 [cited 2020 July 3]. Available from: https://ec.europa.eu/eurostat/statistics-explained/index.php?title=Cardiovascular_diseases_statistics

healthcare system (NHS) and the economy. Regular screening and increased prevention of non-communicable diseases is important for the improvement of quality of life and prevention of premature death. Malta has recorded an alarming rise in CVD mortality in both males and females, which does not match the 25% reduction goal by 2025 set by WHO[4] (Wilkins *et al,* 2017; Timmis *et al*, 2020).

In the Maltese NHS, protocols are issued to all health care professionals as indications for each statin, taking into consideration the patient's comorbidities, appropriate monitoring and multiple drug therapy. As of July 2018, both simvastatin and atorvastatin are first-line agents prescribed in CVD, following the elimination of fluvastatin from the Government Formulary due to international shortage.[5] A statin conversion guide for healthcare professionals was issued, representing equivalent doses of statins available in comparison to fluvastatin (Table 1.4).

[4]World Health Organisation (WHO). Fact Sheets: Cardiovascular Diseases (CVDs) [Online]. WHO; 2017 [cited 2020 July 3]. Available from: https://www.who.int/news-room/fact-sheets/detail/cardiovascular-diseases-(cvds)

[5]Directorate for Pharmaceutical Affairs (DPA). Deletion of fluvastatin and changes in statin entitlement. DH no. 54/2018 [Online]. Malta: DPA; 2018 [cited 2020 May 25]. Available from: https://health.gov.mt/

Table 1.4: Statin conversion guide

(Reproduced from: Directorate for Pharmaceutical Affairs (DPA). Deletion of fluvastatin and changes in statin entitlement. DH no. 54/2018 [Online]. Malta: DPA; 2018 [cited 2020 May 25]. Available from: https://health.gov.mt/

%LDL reduction	Fluvastatin	Simvastatin	Atorvastatin	Rosuvastatin
<24%				
25-32%	40 mg	10 mg		
31-39%	80 mg	20 mg	10 mg	
37-45%		40 mg	20 mg	
48-52%			40 mg	
55-60%			80 mg	20 mg
60-63%				40 mg

Patients who were previously prescribed fluvastatin due to intolerance or a contraindication to simvastatin, were now entitled to atorvastatin. Protocols were updated to recommend rosuvastatin as a second-line agent in CVD (Table 1.5).

Table 1.5: Statin protocol for rosuvastatin

Statin	Indications	Conditions for use
Rosuvastatin	Low-moderate risk (LDL>3 mmol/L); hypertension, genetic dyslipidaemia High risk (LDL>1.8 mmol/L); cerebrovascular disease, CKD, T1DM, T2DM, IHD, peripheral vascular disease[6]	Target level not achieved with maximum dose of atorvastatin after 3-month treatment period[6]

Two recent audits on statin prescribing practices have been carried out locally to investigate whether patients are achieving target LDL-C levels according to NHS protocols[7] (Curtolo *et al,* 2018). A small prospective cohort study of 82 patients to assess achievement of lipid targets after admission with ACS demonstrated that only 38 patients reached target LDL-C level (<1.8mmol/L or at least 50% relative reduction) in the 20-month audit period, and only 5 of these patients achieved the target within 3 months. The authors concluded that a more intense statin regime to ensure rapid achievement of target LDL-C is recommended.[7] Similarly, a retrospective cohort study assessed LDL-C control and statin prescribing in 200

[6]Directorate for Pharmaceutical Affairs. Rosuvastatin 20 mg and 40 mg tablets. Protocol No. 177 [Online]. Malta: DPA; 2018 [cited 2020 May 25]. Available from: https://health.gov.mt/

[7]Gialanze' E, Axiaq MC, Yamagata K, Borg A. Lipid control after acute coronary syndrome in cardiology outpatients. Poster presentation, Maltese Cardiac Society Conference, 20-23 October 2016.

patients with IHD. Only 40% of patients achieved target LDL-C at 19-24 months from baseline and the change from simvastatin to atorvastatin resulted in a significantly larger mean LDL-C reduction (Curtolo *et al*, 2018).

1.13 Aims of this study

The aims of the study were to:

- Compare the effectiveness of simvastatin, atorvastatin and rosuvastatin in patients with IHD by assessing attainment of target LDL-C goals according to ESC guidelines
- Analyse side-effects reported for all statins

Chapter 2

Methodology

2.1 Overview

Following ethics approval, patients diagnosed with IHD and prescribed statin therapy were identified from the Department of Cardiology at Mater Dei Hospital (MDH). A data collection form was developed, validated and completed by the researcher for each patient recruited after obtaining informed written consent (t1). Patients were matched for age, gender and comorbidities. A prospective approach was adopted whereby LDL-C control was assessed after six (t2) and twelve months (t3). Effectiveness and safety of the low and high-intensity statin therapy were assessed during scheduled outpatient visits at the Department of Cardiology and via telephone contact. Results from t2 and t3 were compared to t1 to evaluate the LDL-C lowering effect and side-effects experienced with the different statins.

2.2 Literature review

A literature search on the secondary prevention of CVD, the benefits of statin therapy in CVD patients, and the efficacy and safety of different statins, particularly simvastatin, atorvastatin and rosuvastatin, was undertaken using HyDi, PubMed, Google Scholar and ScienceDirect. Current statin protocols in Malta for IHD were reviewed and the most recent ESC guidelines on dyslipidaemia were consulted to identify LDL-C target levels to reduce cardiovascular risk in IHD patients (Mach et al, 2020).

2.3 Study approvals

Prior to commencing the study, approvals from the Chairman of the Department of Cardiology, Consultant Cardiologists, Chief Executive Officer and Data Protection Officer at MDH were obtained. An ethics proposal form was completed together with the required approvals and was submitted for review by the Faculty of Medicine and Surgery Research Ethics Committee (FREC). An interview with the FREC to discuss the dissertation proposal was attended by the researcher (MZ), and FREC approval (Protocol 07/2018) was granted (Appendix 1).

2.4 Design of the data collection form

A data collection form to compile patient data was developed using Microsoft® Office Word 2016. The form was divided into 8 sections (Table 2.1).

Table 2.1: Sections of the data collection form

Section number	Title
1	Patient demographic information
2	Cardiac risk factors
3	Comorbidities
4	Procedure at time of recruitment
5	Investigations
6	Medications at time of recruitment
7	Problems related to statin therapy
8	Changes to statin therapy during follow-up

Information about patient age, gender and hospital status (inpatient or outpatient) was recorded in section 1. In section 2, smoking and alcohol habits, body mass index, waist circumference and family history of hypercholesterolaemia were documented. Section 3 included 10 comorbidities and an 'Others' option to be ticked as required. During patient recruitment, particular focus was made on 'Hypertension' and 'Diabetes mellitus' for patient matching. These comorbidities are considered cardiac risk factors. In section 4 details of the procedure carried out based on reason for admission and diagnosis at recruitment (t1) were recorded.

The most recent relevant laboratory investigations at baseline (t1) and follow-up (t2 and t3) were documented in section 5 from patient hospital records. The parameters considered were lipid profile, liver function tests, renal function, glycaemic control, skeletal muscle markers and thyroid function. The medications at t1 were listed in section 6, including class of drug, generic name, dose, dosage regimen and start date. Section 7 included information obtained from the patient during follow-up regarding occurrence of side-effects. Drug interactions were identified by the researcher in the same section. Section 8 was dedicated to changes in statin therapy, including dose, during follow-up. The date and reason for change were documented as applicable.

2.5 Validation of the data collection form

Face and content validation of the data collection form was carried out by two academic pharmacists at the Department of Pharmacy at the University of Malta and the Chairman of the Department of Cardiology at MDH. These persons were assigned the task of validating the data collection form for content, layout, clarity and comprehensiveness. A final version after validation was developed (Appendix 2).

2.6 Study setting

This study was undertaken at the Cardiac Catheterisation Suite, Cardiac Medical Ward and Critical Cardiac Care Unit within the Department of Cardiology at MDH. Follow-up sessions were carried out at Cardiology Outpatients MOP4.

2.7 Study criteria

The inclusion criteria were patients diagnosed with IHD and on simvastatin, atorvastatin or rosuvastatin therapy. Patients were inpatients or outpatients, of any gender and aged ≥18 years. The patients were matched for gender, age and comorbidities (hypertension and diabetes). The exclusion criteria were foreigners on holiday in Malta, severe renal impairment (eGFR <30 mL/min/1.73m^2) and liver disease.

2.8 Patient recruitment

Patients were recruited by convenience sampling. A patient information sheet in English and Maltese language was given to each patient explaining the purpose of the study and what participation in the study entails (Appendix 3). Patients who accepted to participate were asked to complete a consent form in English or Maltese language so as to provide informed written consent (Appendix 3). The patient information sheet and consent form state that participation is completely voluntary, that the patient can withdraw from the study at any time and that routine treatment received at MDH is not affected. The data

collection form was completed by the researcher using Philips CardioVascular Information System (CVIS), iSoft Clinical Manager, hospital records, outpatient visits and telephone contact.

2.9 Pilot study

A pilot study was carried out on 28 patients to test the applicability and practicality of the data collection form and the established methodology between July 2018 and July 2019. The patients (13 simvastatin, 14 atorvastatin, 1 rosuvastatin) were matched for age, gender and comorbidities. No changes were made and these 28 patients were included in the study group.

2.10 Data analysis

Statistical analysis was carried out using IBM® SPSS® Statistics version 23 after inputting and encoding all relevant data into the database. Descriptive statistics, including mean, standard deviation, range, frequencies and percentages were applied throughout the study and statistical outputs were copied onto Microsoft® Office Word 2016 for editing. Graphical representations were created using Microsoft® Office Excel 2016.

The Shapiro-Wilk test was applied to determine whether LDL-C values at t1, t2 and t3 are normally distributed or skewed. The null hypothesis specifies that mean LDL-C distribution is normally distributed and the alternative hypothesis states that LDL-C distribution is skewed. The resultant p-value was smaller than the 0.05 level of significance (p=0.001) and the alternative hypothesis was accepted, hence non-parametric tests were used to analyse the data.

The Friedman test is used to verify whether there is a significant difference between means of several related samples. TC, HDL-C, triglycerides and LDL-C values were analysed to determine whether the change in mean was significant between t1, t2 and t3. This test was also used to determine whether mean LDL-C reduction was significant after patients were grouped according to statin taken at the three time points. The null hypothesis specifies that mean lipid parameters differ marginally between time points and is accepted if the p-value exceeds 0.05. The alternative hypothesis specifies that mean lipid parameters vary significantly between time points and is accepted if the p-value is less than the 0.05 criterion.

The Kruskal-Wallis test is a non-parametric method to determine the equality of independent population means. This test was used to determine whether patients who changed statin or underwent statin dose intensification attained greater mean LDL-C reduction than those who were maintained on the same treatment throughout the research period. The null hypothesis specifies that mean LDL-C reduction is unaffected by a change

in statin or dose and is accepted if the p-value exceeds 0.05. The alternative hypothesis states that statin changes result in a significantly greater mean LDL-C reduction and is accepted if the p-value is less than the 0.05 criterion.

The binomial test is used to compare the sample mean to a known value. LDL-C values achieved at t2 and t3 were compared to the LDL-C target reference range ≤1.4 mmol/L to see how many patients achieved target goal and whether LDL-C values were comparable or significantly different from 1.4 target goal. The null hypothesis specifies that mean LDL-C is comparable to the 1.4 mmol/L target goal and is accepted if p-value exceeds 0.05. The alternative hypothesis specifies that mean LDL-C is significantly different from the 1.4 mmol/L target goal and is accepted if the p-value is less than the 0.05 criterion.

Analysis of variance was carried out to observe whether the fixed factors age, gender and statin affected response to therapy in terms of LDL-C outcomes. Each patient was categorised based on statin type, age group and gender and their main effects on statin efficacy was analysed. The null hypotheses are accepted if p-values exceed the 0.05 level of significance, whilst the alternative hypotheses are accepted if p-values are less than the 0.05 criterion.

2.11 Dissemination of results

An abstract entitled ‘Comparative Analysis of Lipid Profile Management in Ischaemic Heart Disease’ was accepted and a poster was developed for presentation at FIP Virtual, 4-25 September 2020 (List of Publications and Abstracts).

Chapter 3

Results

In this chapter, patient characteristics, cardiac risk factors, comorbidities, diagnosis and cardiac procedure at time of recruitment, laboratory investigations, efficacy of statin therapy analysis, drug interactions and side-effects are presented.

3.1 Patient characteristics

A total of eighty-four patients were recruited at baseline (t1) and followed up after 6 months (t2) and 12 months (t3). Three patients passed away at t2, hence data analysis was conducted on eighty-one patients. Of these eighty-one patients, sixty-two were male and nineteen were female. Their mean age was 68 years, ranging from 45 to 85 years.

3.2 Cardiac risk factors

The cardiac risk factors taken into consideration for this study were smoking habits, alcohol consumption, BMI and waist circumference and family history of hypercholesterolaemia. Data was gathered at t1, hence information was available for all patients.

3.2.1 Smoking habits

Fifty-one patients (63%) were non-smokers, accounting for the majority of the study population. Thirty patients (37%) were either active or past smokers (Figure 3.1). Of the past smokers, 4 patients recalled smoking more than two packets of cigarettes a day, while

the rest smoked one packet or less a day. Ten active smokers reduced their smoking habits, based on medical recommendation.

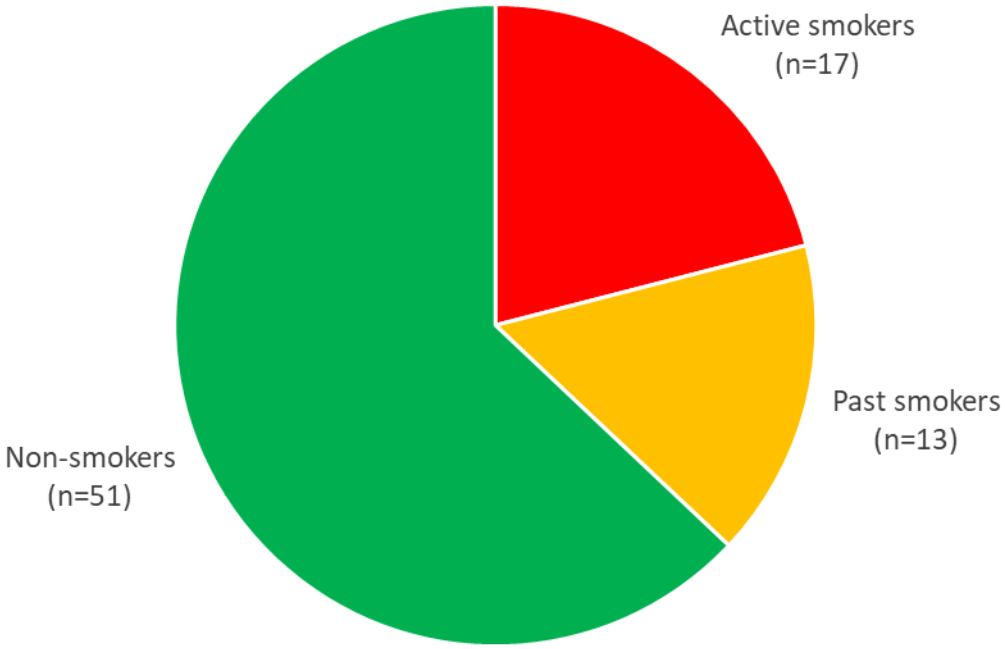


Figure 3.1: Smoking habits (N=81)

3.2.2 Alcohol consumption

Forty-five patients (56%) stated that they do not consume alcohol and 36 patients (44%) consume alcohol on a daily, weekly or occasional basis (Figure 3.2). Out of the patients who consume alcohol, 29 patients consume between 1 and 5 units. Five patients said they consume 10 units or more only on a special occasion and 2 patients said they consume between 6 and 10 units per week.

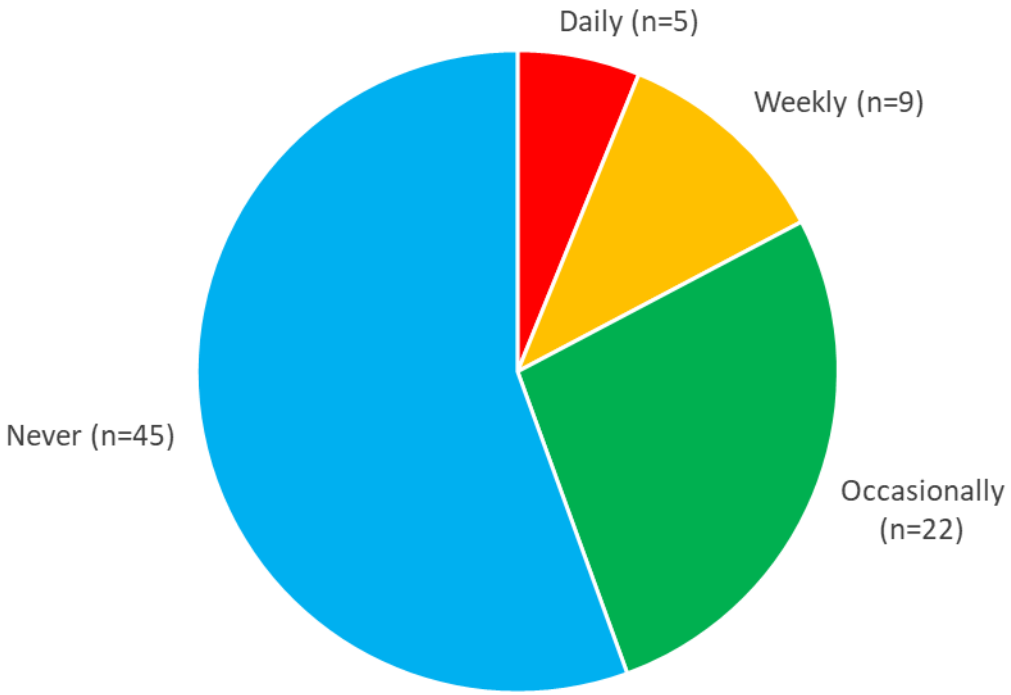


Figure 3.2: Alcohol consumption (N=81)

3.2.3 BMI and waist circumference

Mean BMI was 31.6 kg/m^2 (Obesity Class I) for 62 (77%) patients, ranging from 29.31 to 44.75 kg/m^2. Nineteen patients (23%) had no weight or height measurements recorded; 8 patients were either immobile, obese or too frail for waist circumference to be measured. Waist circumference was measured at t1 and the study population was divided according to those who exceeded the recommended circumference for each gender and those who did not (Mach *et al,* 2020). Twenty-eight males measured ≥94 cm and 26 measured <94 cm. Eleven females exceeded 80cm and 8 did not.

3.2.4 Family history of hypercholesterolaemia

Twenty-four patients (30%) had a family history of CVD in at least one parent and sibling, of whom 15 patients recalled at least one revascularisation procedure in their family. Twenty-one patients (26%) said that one or both their parents were diagnosed with dyslipidaemia and suffered from ACS. Twelve patients (15%) had at least one sibling with a history of CVD; 3 of whom recalled a major cardiovascular event happening before the age of 55 years. Thirteen patients (16%) were not sure about their family history and 11 (13%) patients had no family history of hypercholesterolaemia (Figure 3.3).

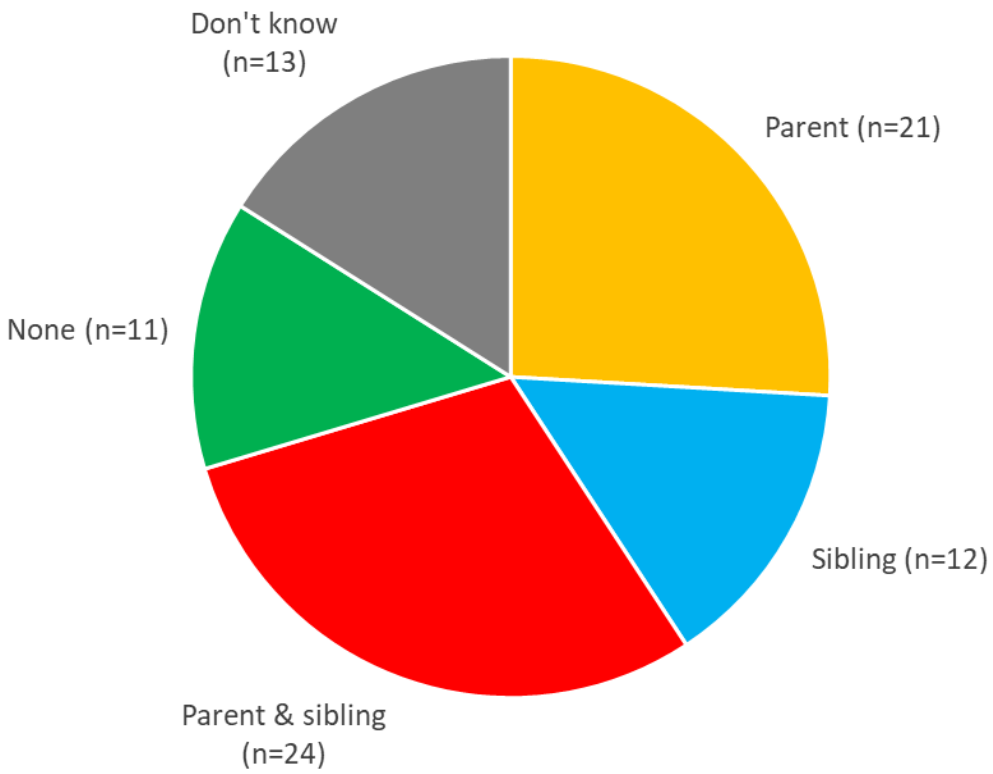
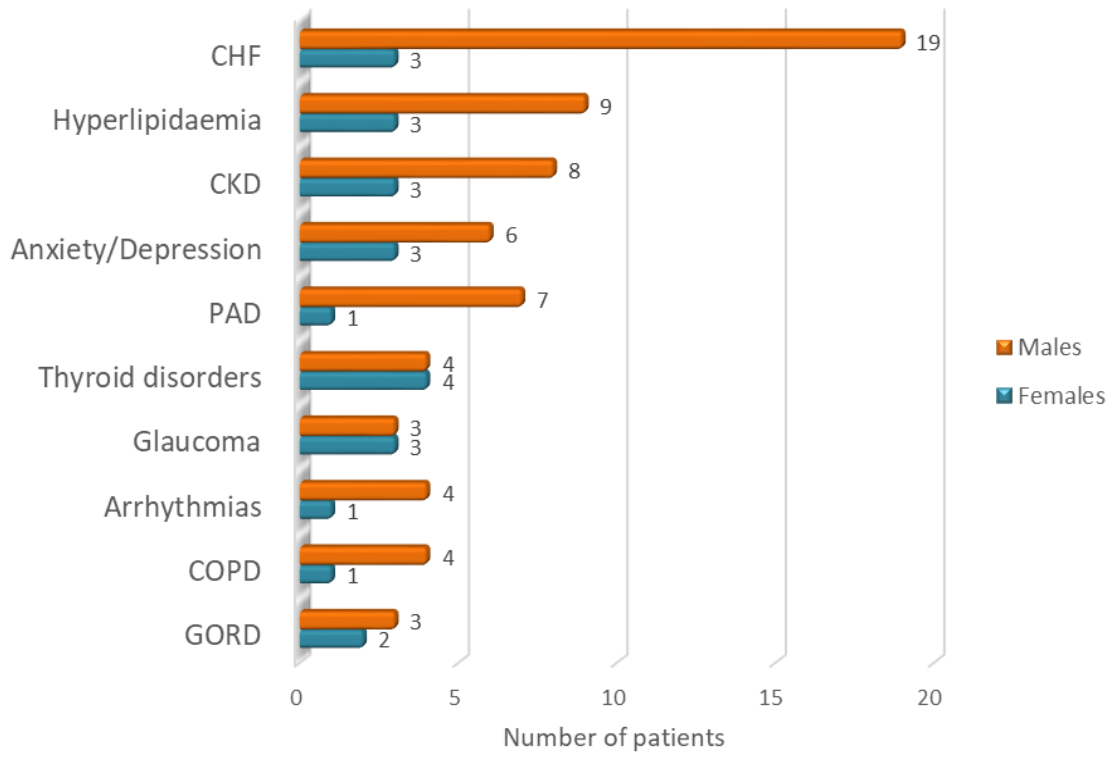


Figure 3.3: Family history of hypercholesterolaemia (N=81)

3.3 Comorbidities

All 81 patients recruited were diagnosed with IHD, diabetes and hypertension. Sixty-two of these patients had other comorbidities. Thirty-three patients (41%) had two or more comorbidities and 29 (36%) patients had one other comorbidity. Nineteen patients (23%) had no other comorbidities. The prevalence of comorbidities for each gender are shown in Figure 3.4. The most common comorbidity was heart failure (n=22), followed by hyperlipidaemia (n=12) and CKD (n=11).



CHF – congestive heart failure; CKD – chronic kidney disease; COPD – chronic obstructive airway disease; GORD – gastro-oesophageal reflux disease; PAD – peripheral artery disease

Figure 3.4: Comorbidities (n=62)

Other comorbidities (n=17, 21%) were benign prostatic hyperplasia, cerebrovascular disease, gout (all n=3), anaemia, cancer, diabetic neuropathy (all n=2), hepatitis B and psoriasis (both n=1).

3.4 Diagnosis and cardiac procedure at time of recruitment

The most common reason for admission was symptoms of angina (n=53), followed by a positive stress test (n=12). A troponin rise was documented in 6 patients. Table 3.1 represents the diagnosis at t1 in the 81 patients. Fifty patients (62%) were diagnosed with ACS without specifying unstable angina, NSTEMI or STEMI.

Table 3.1: Diagnosis at t1 (N=81)

Diagnosis at time or recruitment	Number of patients	Percentage (%)
ACS (not specified)	**50**	**61.7**
NSTEMI	17	21.0
STEMI	12	14.8
Stable angina	2	2.5

Forty-two patients (52%) underwent revascularisation procedures at t1, with 37 patients referred for PCI and 5 referred for CABG. Four out of the 37 patients were referred for a second PCI at t2 and 1 patient was referred for CABG at t3. The remaining 39 patients (48%) were referred for medical treatment after angiogram.

3.5 Laboratory investigations

The laboratory investigations undertaken concerned lipid profile monitoring at t1, t2 and t3 and assessment of liver function, skeletal muscle markers, glycaemic control, renal parameters and thyroid function for each patient recruited.

3.5.1 Lipid profile monitoring results

Documented lipid parameters, including total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C) and triglycerides (TG) were assessed at the three time points. Lipid profile values were available for all 81 patients at t1, which decreased to 76 patients (94%) at t2 and 75 patients (93%) at t3.

3.5.1.1 Total cholesterol

Mean TC was 3.96 mmol/L at t1, which decreased significantly ($p<0.001$) at all time points studied to 3.23 mmol/L at t3 (Table 3.2). All mean values were within the reference range (2.0-5.0 mmol/L).

Table 3.2: Total cholesterol

Time point	Mean TC (mmol/L)	Standard deviation	Minimum	Maximum
t1 (n=81)	3.96	1.09	2.27	7.04
t2 (n=76)	3.49	0.71	2.26	5.46
t3 (n=75)	3.23	0.81	1.2	5.70

TC – total cholesterol p<0.001

3.5.1.2 High-density lipoprotein cholesterol

Mean HDL-C was 1.20 mmol/L at t1 which remained constant throughout the study period (p>0.05) (Table 3.3). All mean values were within the reference range (1.15-1.68 mmol/L).

Table 3.3: High-density lipoprotein cholesterol

Time point	Mean HDL-C (mmol/L)	Standard deviation	Minimum	Maximum
t1 (n=81)	1.20	0.31	0.69	2.57
t2 (n=76)	1.19	0.26	0.53	1.93
t3 (n=75)	1.21	0.27	0.38	1.83

HDL-C – high-density lipoprotein cholesterol p=0.205

3.5.1.3 Triglycerides

Mean TG was 1.76 mmol/L at t1 which decreased significantly ($p<0.001$) to 1.50 mmol/L at t3 (Table 3.4). All mean TG values recorded were within the reference range (0.1-2.26 mmol/L).

Table 3.4: Triglycerides

Time point	Mean TG (mmol/L)	Standard deviation	Minimum	Maximum
t1 (n=81)	1.76	0.91	0.54	4.58
t2 (n=76)	1.59	0.83	0.52	4.62
t3 (n=75)	1.50	0.87	0.58	4.83

TG – triglycerides $p<0.001$

3.5.1.4 Low-density lipoprotein cholesterol

Mean LDL-C was 2.13 mmol/L at t1 which decreased significantly ($p<0.001$) to 1.70 mmol/L at t2 and further to 1.67 mmol/L at t3 (Table 3.5). Despite this reduction, neither mean value was within the reference range (<1.4 mmol/L) at all time points studied.

Table 3.5: Low-density lipoprotein cholesterol

Time point	Mean LDL-C (mmol/L)	Standard deviation	Minimum	Maximum
t1 (n=81)	2.13	0.95	0.66	5.04
t2 (n=76)	1.70	0.53	0.63	3.15
t3 (n=75)	1.67	0.60	0.38	3.35

LDL-C – low-density lipoprotein cholesterol $p<0.001$

3.5.2 Other laboratory investigations

Liver function (AP, ALT, GGT, bilirubin, albumin), skeletal muscle markers (CK), glycaemic control (HbA1c), renal parameters (eGFR, Cr, urea) and thyroid function (T4, TSH) were assessed for mean, standard deviation, minimum, maximum and compliance to reference range.

Results indicate that mean CK was nearly three times the upper limit of the reference range for the 14 patients who had these values documented. Mean GGT, HbA1c and urea were slightly higher than the reference range for each parameter (Table 3.6).

Table 3.6: Other laboratory investigations

Parameter (reference range)	Mean	Standard deviation	Minimum	Maximum
AP (n=77) (40-104 U/L)	87.15	39.52	32	285
ALT (n=77) (5-33 U/L)	23.97	12.73	6	69
GGT (n=77) (5-36 U/L)	**43.64**	**52.87**	**10**	**415**
Bilirubin (n=77) (0-21 µmol/L)	10.64	6.74	3.3	46.9
Albumin (n=51) (32-52 g/L)	41.74	7.07	4.7	49.3
CK (n=14) (26-192 U/L)	**539.79**	**819.46**	**37**	**3121**
HbA1c (n=77) (4.7-6.4%)	**7.44**	**1.37**	**5.1**	**11.8**
eGFR (n=80) (>60ml/min/1.73m^2)	75.44	25.46	33	141
Cr (n=80) (59-104 µmol/L)	99.95	41.52	52	311
Urea (n=80) (1.7-8.3 mmol/L)	**8.77**	**4.04**	**3.3**	**26.4**
Free T4 (n=72) (11-18 pmol/L)	16.02	2.26	9.41	21.74
TSH (n=72) (0.3-3 mIU/L)	1.53	1.21	0.088	6.976

ALT – alanine aminotransferase; AP – alkaline phosphatase; CK – creatinine kinase; Cr – creatinine; eGFR – glomerular filtration rate; GGT – gamma glutamyl transferase; HbA1c – glycated haemoglobin; T4 – thyroxine; TSH – thyroid stimulating hormone. **Bold text denotes parameters exceeding reference range.**

3.6 Statin therapy

At t1, 34 patients were on simvastatin (42%), 39 patients were on atorvastatin (48%) and 8 patients were on rosuvastatin therapy (10%). At t2, 1 patient stopped simvastatin treatment due to side-effects, therefore the number of patients who could be assessed at t2 and t3 was 80. Statin name and dose for patients at the different time points are specified in Table 3.7.

Table 3.7: Statin therapy

Statin and Dose	Number of patients		
	t1 (n=81)	t2 (n=80)	t3 (n=80)
Simvastatin 20mg	8	5	5
Simvastatin 40mg	**26**	**16**	**14**
Atorvastatin 20mg	1	1	1
Atorvastatin 40mg	8	10	7
Atorvastatin 80mg	**30**	**40**	**39**
Rosuvastatin 5mg	2	2	2
Rosuvastatin 10mg	1	1	2
Rosuvastatin 20mg	1	1	4
Rosuvastatin 40mg	4	4	6

At t1, most patients were on atorvastatin 80mg (n=30) and simvastatin 40mg (n=26). By t3, atorvastatin 80mg was the most prescribed statin and dose in 39 patients (48%).

3.6.1 Change to a higher intensity statin

At t2 and t3, a change in statin was recorded in 17 patients (21%); simvastatin to atorvastatin (n=12), atorvastatin to rosuvastatin (n=2); simvastatin to atorvastatin to rosuvastatin (n=3). All changes made were towards a higher intensity statin. Mean LDL-C reduction achieved by those who changed statin was similar ($p>0.05$) to that achieved by the majority of the study population who did not change statin (Table 3.8).

Table 3.8: Change to a higher intensity statin

Change to a higher intensity statin	Number of patients	Mean LDL-C reduction (mmol/L)	Standard deviation	p-value
Yes	17	0.10	0.47	0.712
No	63	0.12	0.42	

3.6.2 Statin dose intensification

Four patients (5%) had their statin dose intensified from t2 to t3; atorvastatin 40mg to atorvastatin 80mg (n=2), rosuvastatin 10mg to rosuvastatin 20mg (n=1), rosuvastatin 20mg to rosuvastatin 40mg (n=1). Despite achieving a greater mean LDL-C reduction with dose intensification, patients who were kept on the same dose of atorvastatin and rosuvastatin throughout the study achieved a similar LDL-C reduction ($p>0.05$) (Table 3.9).

Table 3.9: Statin dose intensification

Statin dose intensification	Number of patients	Mean LDL-C reduction (mmol/L)	Standard deviation	p-value
Yes	4	0.25	0.03	0.200
No	76	0.16	0.44	

3.7 Statin efficacy

Statin efficacy was analysed based on achievement of target LDL-C and relative percentage reduction from t1. The influence of age, gender and comorbidities on statin efficacy is also analysed in this section.

At t1, LDL-C values were available for all 81 patients recruited. At t2, 1 patient stopped simvastatin therapy and was therefore excluded from statin efficacy analysis at the subsequent time points. Five patients had no LDL-C value recorded at t2 (n=75) and 6 patients had no LDL-C value recorded at t3 (n=74).

At t3, the lowest calculated mean LDL-C was with atorvastatin (1.56 mmol/L) and the highest percentage LDL-C reduction was also with atorvastatin (32%). The highest mean

LDL-C was 1.95 mmol/L with rosuvastatin, however patients achieved a greater percentage reduction from t1 (24%) compared to simvastatin (2%). Mean LDL-C remained constant for patients on simvastatin therapy, achieving negligible reduction throughout the study (Table 3.10).

Table 3.10: Statin efficacy

Statin	**Mean LDL-C in mmol/L** (number of patients)			**% reduction in LDL-C**		**p-value**
	t1 (n=81)	**t2 (n=75)**	**t3 (n=74)**	**After 6 months**	**After 12 months**	
simvastatin	**1.83** (34)	**1.82** (20)	**1.80** (18)	**1**	**2**	<0.001
atorvastatin	**2.30** (39)	**1.56** (48)	**1.56** (44)	**32**	**32**	
rosuvastatin	**2.58** (8)	**1.96** (7)	**1.95** (12)	**24**	**24**	

Results indicate that mean LDL-C reduction throughout the study was significant with atorvastatin and rosuvastatin therapy since the resultant p-value was less than the 0.05 level of significance. Negligible reduction was achieved with simvastatin therapy. Neither statin was able to achieve the mean LDL-C target goal of 1.4 mmol/L or 50% relative reduction after six and twelve months of therapy. Individual LDL-C values were analysed for achievement of target goals in the following sections (3.7.1, 3.7.2).

3.7.1 Patients achieving LDL-C target goal

Patients were analysed for attainment of the LDL-C target goal of 1.4 mmol/L, according to ESC guidelines. Twenty-two patients (27%) achieved target goal at t2 and 24 patients (30%) achieved target goal at t3. Current results are therefore not representative of the sample population since overall LDL-C values achieved differ significantly from the target value ($p<0.05$) (Table 3.11).

Table 3.11: Patients achieving LDL-C target goal

Statin name and dose	Patients achieving target goal (≤1.4 mmol/L)			
	At t2 (n=22)		At t3 (n=24)	
	Number of patients	p-value	Number of patients	p-value
Simvastatin 20mg	3 (14%)	0.003	0 (0%)	0.012
Simvastatin 40mg	6 (27%)		5 (21%)	
Atorvastatin 40mg	2 (9%)		2 (8%)	
Atorvastatin 80mg	**11 (50%)**		**15 (63%)**	
Rosuvastatin 20mg	0 (0%)		1 (4%)	
Rosuvastatin 40mg	0 (0%)		1 (4%)	

Out of the 22 patients who achieved target goal at t2, 11 patients were on atorvastatin 80mg. Similarly, 15 out of the 24 patients who achieved target goal at t3 were on atorvastatin 80mg. Simvastatin 40mg also accounted for 27% of patients who achieved target goal at t2 and 21% who achieved goal at t3.

3.7.2 Patients achieving ≥50% LDL-C reduction from baseline

For those patients who did not achieve the 1.4 mmol/L LDL-C target goal, the study population was checked for achievement of ≥50% LDL-C relative reduction from t1. Nine patients (11%) achieved at least 50% reduction from t1 to t2 and 12 patients (15%) achieved 50% reduction from t1 to t3. All patients were on high-intensity statins, with the majority being treated with atorvastatin 80mg (n=8 at t2; n=7 at t3). Five out of 12 patients achieving 50% reduction at t3 were on rosuvastatin therapy. Patients on atorvastatin 40mg and simvastatin therapy did not achieve sufficient percentage LDL-C reduction from t1 (Table 3.12).

Table 3.12: Patients achieving ≥50% LDL-C reduction from t1

Statin name and dose	Patients achieving ≥50% LDL-C reduction	
	At t2 (n=9)	At t3 (n=12)
	Number of patients	Number of patients
Atorvastatin 80mg	**8 (89%)**	**7 (58%)**
Rosuvastatin 20mg	1 (11%)	3 (25%)
Rosuvastatin 40mg	0 (0%)	2 (17%)

3.7.3 Variance of efficacy between statins

Statins were ranked according to their lipid-lowering potency at each time point after patients were matched for age, gender, diabetes and hypertension. This test was carried out on 55 patients (68%) (Table 3.13). Patients who changed statin throughout the study (n=17) and patients who had missing LDL-C values (n=11) were excluded from the analysis. Two patients had both a statin change and one missing LDL-C value.

Table 3.13: Variance of efficacy between statins (n=55)

Fixed variable	Dependent variable	p-value
Statin	LDL-C at t1	0.355
	LDL-C at t2	0.413
	LDL-C at t3	0.107
Age	LDL-C at t1	0.840
	LDL-C at t2	0.799
	LDL-C at t3	0.080
Gender	LDL-C at t1	0.191
	LDL-C at t2	0.150
	LDL-C at t3	0.103

The results from all three time points indicate that neither variable was significantly contributing to the LDL-C score achieved by patients ($p>0.05$). Since neither statin showed significant lipid-lowering potency over others, statins could not be ranked according to efficacy.

3.8 Safety of statin therapy

In this section, identified drug interactions, documented side-effects of statin therapy and reason for change in statin are presented.

3.8.1 Drug interactions

The most common interaction observed was that of simvastatin with amlodipine, with 11 patients (14%) receiving simvastatin >20mg with amlodipine. Six patients on simvastatin ≥20mg and 5 patients on atorvastatin 80mg were also taking amiodarone 200mg daily for heart failure or arrhythmias. Two patients on atorvastatin 80mg were prescribed fibrates and 2 patients on rosuvastatin were prescribed ezetimibe 10mg, as add on therapy. Four patients were prescribed concomitant ranolazine for chronic angina and one patient was receiving tenofovir 245mg while on atorvastatin 40mg for chronic hepatitis B.

3.8.2 Side-effects of statin therapy

There were 9 cases of documented myalgia in patients treated with simvastatin 40mg, 3 of whom had drug-statin interactions. Myalgia symptoms were also reported by 2 patients on rosuvastatin 40mg, later confirmed by raised CK levels. Renal dysfunction was identified in 7 patients taking atorvastatin 80mg and 3 simvastatin patients, presenting as raised serum creatinine and urea and low eGFR (<45mL/min/1.73m^2). Three cases of deranged LFTs were reported with simvastatin therapy, with one patient having to withdraw statin treatment.

3.8.3 Changes to statin therapy

The most common reason for upgrading statin to a higher intensity one was due to improved lipid-lowering efficacy and tolerance. This holds true for all simvastatin patients who were switched to atorvastatin therapy. Two atorvastatin patients having familial hypercholesterolaemia were switched to rosuvastatin therapy at t2 since LDL-C levels exceeded 4.5mmol/L at t1.

Chapter 4

Discussion

4.1 Study outcomes

This prospective study focused on the achievement of the target LDL-C goal 1.4 mmol/L and at least 50% LDL-C reduction from baseline, as specified by the latest ESC guidelines (Mach *et al,* 2020). Statin efficacy and safety were analysed at three time points; baseline, 6 months and 12 months. Age, gender, hypertension and diabetes, were considered during patient matching to compare statin intensity based on LDL-C reduction.

4.1.1 Statin therapy

Out of 81 patients, 79 were diagnosed with ACS with approximately equal number of patients prescribed simvastatin and atorvastatin at t1. During the first six months, a shift from simvastatin to atorvastatin was most commonly observed. At this time, atorvastatin was being introduced as a first-line statin alongside simvastatin for the management of IHD in Malta.

Throughout the research period, a statistically significant reduction in mean TC, TG and LDL-C was observed. Mean LDL-C values indicate that most participants achieved greatest reduction after twelve months of therapy (2.13 > 1.67 mmol/L). Patients who changed statin achieved a mean LDL-C reduction approximately equal to the majority of patients who did not change statin (0.10 mmol/L and 0.12 mmol/L respectively). Only four patients on

medium-intensity statins had their statin dose intensified, despite AHA, NICE[2] and ESC guidelines recommending a high-intensity statin to all patients with clinical ASCVD (Arnett *et al,* 2019; Mach *et al,* 2020). In fact, the mean LDL-C reduction achieved by these four patients exceeded that of patients who were kept on the same dose of statin (0.25 > 0.16 mmol/L). These results lie in parallel to what was observed by Puri *et al* (2014) who concluded that patients diagnosed with ACS were more susceptible to the lipid-lowering effects of the high-intensity statins atorvastatin and rosuvastatin when initiated early in treatment, regardless of baseline LDL-C value.

4.1.2 Statin efficacy

When comparing mean LDL-C reduction achieved with the different statins at the three time points, patients on atorvastatin and rosuvastatin therapy achieved significant reduction from baseline. Despite this reduction, at t3, mean values were not satisfactory when considering target goals recommended by the ESC. Results from the current study show that after 6 months of therapy, mean LDL-C decreased by 32% with atorvastatin and 24% with rosuvastatin and remained unchanged at t3.

[2]National Institute for Health and Care Excellence (NICE). Clinical guideline 181 [CG181]. Cardiovascular disease: Risk assessment and reduction, including lipid modification [Online]. UK: NICE; 2014 [cited 2020 Apr 20]. Available from: https://www.nice.org.uk/

There is conflicting evidence about the overall mean LDL-C reduction attainable with the different statins in literature. In a study by Prasanth *et al* (2017) who compared simvastatin, atorvastatin and rosuvastatin, the authors concluded that higher-intensity statins lowered LDL-C by 47% to 63% after six months of therapy, whereas the maximum reduction achieved by simvastatin was 41% according to Foody *et al* (2013). In the SATURN trial, difference in efficacies of atorvastatin and rosuvastatin were only evident after two years of therapy and rosuvastatin was found to have superior LDL-C-lowering ability to atorvastatin (Nicholls *et al*, 2011). In other studies, similar efficacies of statins were reported in patients diagnosed with ACS (Aggarwal and Showkathali, 2013; Khurana *et al,* 2015).

4.1.3 Patients achieving LDL-C target goals

When analysing individual LDL-C values, only 24 patients achieved the 1.4 mmol/L mark and 12 patients achieved at least 50% LDL-C reduction at t3. The majority of these patients were prescribed atorvastatin 80mg. Five patients on rosuvastatin at t3 achieved a 50% reduction within a year of therapy. These results compare to what was observed by Tramcere *et al* (2019) in patients with IHD and on simvastatin, atorvastatin or rosuvastatin therapy. High-intensity statins had the best LDL-C outcome with strong evidence indicating the most benefit with atorvastatin 80mg compared to other statins.

4.1.4 Variance between statins

Before September 2019, the target LDL-C goal was 1.8 mmol/L and by then all patients had completed at least six months of therapy. This restriction in LDL-C levels meant that statin therapy had to be intensified for patients to achieve the new target goal in the shortest time possible. For this reason, no conclusion could be drawn regarding the ranking of statins in the analysis of variances. Naturally, the addition of the fixed variables age and gender, contributed to greater p-values. However, it can be noted that variance of efficacy for the different statins became apparent the more time elapsed from start of statin therapy, with p-values decreasing from 0.36 to 0.11. Further analysis beyond twelve months of statin therapy could have possibly determined true significance between statin efficacies. Shutta *et al* (2020) obtained a similar outcome during propensity score matching in patients with established ASCVD and diabetes. No significant interactions were observed between cardiac risk factors and statin treatment and neither statin was significantly better at preventing the occurrence of MACE.

4.1.5 Statin safety

The majority of participants had comorbidities other than diabetes and hypertension, the most common being heart failure, hyperlipidaemia and CKD. Therefore, side-effects reported by patients could not be attributed to statins alone. Concomitant use of liver enzyme inhibitors such as alcohol, allopurinol, amiodarone, amlodipine, ezetimibe, fibrates, ranolazine and tenofovir, not only increase bioavailability of statins and the risk of rhabdomyolysis, but also the strain on liver function.

Myalgia was the most common side-effect with statins, particularly simvastatin. During patient contact, two patients became non-adherent to simvastatin therapy after noticing improvement of symptoms when stopping treatment. One patient who experienced myalgia while on rosuvastatin 40mg, had his dose reduced to 20mg on alternate days. All eleven patients who had documented myalgia had raised CK levels and the patients on simvastatin had concomitant high serum creatinine levels exceeding the reference range, possibly increasing the risk of myotoxicity. Similar findings were reported in a recent study on statin-related myalgia and patient adherence, where patients on simvastatin therapy had the most documented muscle-related side-effects and non-compliance to therapy (Kennedy *et al,* 2020).

Hepatic effects were also observed with simvastatin therapy. Three cases of deranged LFTs were documented, with patients having serum transaminases exceeding two times the upper limit of normal. In one case, liver enzymes were four times the upper limit of normal which led to the withdrawal of treatment. This patient was reported deceased a few months later. Although studies have similarly reported higher transaminase levels with statin therapy when compared to placebo, hepatic effects are a characteristic of all the lipid-modifying agents and may be secondary to LDL-C reduction itself and not statin-specific (Jose, 2016; Mach *et al,* 2018).

The inclusion criteria for all participants was the diagnosis of hypertension and diabetes, both known to negatively affect kidney function if uncontrolled. Renal dysfunction can further contribute to other comorbidities such as heart failure and arrhythmias. The hydrophilic nature of rosuvastatin is expected to have more renal effects than the lipophilic statins, simvastatin and atorvastatin. This was not the case in the current study, where most renal effects were documented with atorvastatin therapy. Studies show that the effect of statin therapy on the kidney is dose-dependent and there is still conflicting evidence about whether statins contribute to the progression of CKD (Dormuth *et al*, 2013; Verdoodt *et al,* 2018).

4.2 Study limitations

Since the study was based on a prospective approach, compiling patient information was the main limitation. Information found on hospital files and CVIS were not always comprehensive for analysis of all the patient data. CVIS notes taken during outpatient visits were not sufficient to determine cardiovascular risk status, especially for patients who did not attend all follow-up procedures at hospital. As a result, telephone interviews were required to obtain information about statin therapy. Upon interview, patients found it difficult to recall the exact start date of statin therapy and whether side-effects could be attributed to the chronic use of statins.

Clinical parameters were accessed through iSoft, and while ESC guidelines recommend a six-month follow-up of lipid profiles, not all patients had results recorded. It was noted however, that patients who did not present with new symptoms and ischaemia adequately controlled, were followed-up on a yearly basis. Towards the end of the study, the Coronavirus outbreak affected the majority of outpatient visits. Follow-up visits were either postponed or patients relocated to their local polyclinic. Some patients chose not to attend follow-up visits and were contacted by their respective cardiologist. As a result, some LDL-C values at 12 months could not be retrieved.

4.3 Recommendations

The strength of this study was its specificity to include only patients diagnosed with hypertension, diabetes and IHD while on statin therapy, at the expense of sample size. The majority of patients recruited were prescribed simvastatin and atorvastatin therapy. Only eight patients on rosuvastatin were recruited by convenience sampling. An ideal study would have equal subjects receiving different statin intensities in order to evaluate true statin efficacy. Moreover, the study focused on LDL-C reduction achieved with statin therapy alone and did not include other lipid-modifying agents such as ezetimibe and its added advantage in the management of dyslipidaemias, despite known interaction. Patients not achieving target goals despite optimal statin therapy are recommended to be tried on ezetimibe (Mach *et al,* 2020).

Patients were analysed over a twelve-month period, throughout which major changes in statin protocols and guidelines occurred. Results showed no variance of efficacies between statins, hence a study on a larger sample population over an extended period is warranted for a definitive result. Analysis of patient profiles did not include pharmacogenomics testing. This is an important factor to consider when evaluating response to treatment and further investigations into this topic should be performed.

4.4 Conclusion

Results indicate that after twelve months, patients on the high-intensity statins atorvastatin and rosuvastatin, maintained better control on LDL-C levels and were least associated with side-effects. The change from simvastatin to atorvastatin resulted in a consequently larger mean LDL-C reduction compared to those who maintained simvastatin therapy. Despite atorvastatin and rosuvastatin reducing LDL-C at a faster rate, only 30% of participants achieved the LDL-C target goal of 1.4 mmol/L within 1 year. This highlights the importance of a more intensive immediate LDL-C lowering regime, including rosuvastatin as first-line therapy for patients to achieve target goals sooner and to reduce cardiovascular risk.

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List of Publications and Abstracts

SIG on Pharmacy Practice Research
FIPSUB-1577 /

Comparative Analysis of Lipid Profile Management in Ischaemic Heart Disease

Maia Zarb[1], **Robert G.** Xuereb[2], **Francesca** Wirth[1], **Lilian M** Azzopardi*[1]
[1]**Department of Pharmacy, Faculty of Medicine and Surgery, University of Malta,** [2]**Department of Cardiology, Mater Dei Hospital, Msida, Malta**

My preferred method of presentation is: **Poster Presentation**
Please fill in the presenting author's organization: **Department of Pharmacy, Faculty of Medicine and Surgery, University of Malta**

Background: **The European Society of Cardiology guidelines for management of dyslipidaemias recommend a target low density lipoprotein cholesterol (LDL-C) goal of <1.4 mmol/L or ≥50% relative reduction. Patients with documented cardiovascular disease and elevated individual risk factors are candidates for early intervention with higher intensity statins.**

Purpose: **To compare effectiveness and safety of statins in patients with ischaemic heart disease (IHD)**

Methods: **Patients with IHD on statin therapy, matched for age, gender, hypertension and diabetes, were recruited from the Cardiology Department at Mater Dei Hospital. LDL-C levels and side effects at time of recruitment (t1) and 6-month follow-up (t2) were documented. Mean LDL-C level and percentage LDL-C reduction from t1 achieved with different statins was analysed.**

Results: **Eighty-four patients (64 male, mean age 70 years, 45 with previous revascularisation) were recruited. Statin therapy prescribed was simvastatin (n=36), atorvastatin (n=40) and rosuvastatin (n=8). Twelve patients switched from simvastatin to atorvastatin at t2. Mean LDL-C t1 on simvastatin was 1.96 mmol/L and decreased by 3% to 1.90 mmol/L at t2. Mean LDL-C t1 on atorvastatin was 2.28 mmol/L and decreased by 28% to 1.64 mmol/L at t2. Mean LDL-C t1 on rosuvastatin was 3.16 mmol/L and decreased by 23% to 2.43 mmol/L at t2. Four cases of myalgia and 1 case of deranged liver function tests with simvastatin and no side-effects with atorvastatin and rosuvastatin were documented.**

Conclusion: **Mean LDL-C levels achieved with all statins after 6 months were higher than 1.4 mmol/L. A more intensive LDL-C lowering regime is required to attain targets recommended in the guidelines.**

FIP VIRTUAL 2020 SEPTEMBER

Comparative Analysis of Lipid Profile Management in Ischaemic Heart Disease

Maia Zarb[1], Robert G. Xuereb[2], Francesca Wirth[1], Lilian M Azzopardi[1]

[1] Department of Pharmacy, Faculty of Medicine and Surgery, University of Malta, Msida, Malta
[2] Department of Cardiology, Mater Dei Hospital, Msida, Malta
email: maia.zarb.14@um.edu.mt

L-Università ta' Malta Faculty of Medicine & Surgery | Department of Pharmacy

INTRODUCTION

According to the 2019 European statistics, 4.1 million deaths in Europe are caused by cardiovascular disease, with ischaemic heart disease (IHD) being a leading cause of mortality.[1]

The European Society of Cardiology (ESC) guidelines for the management of dyslipidaemias recommend a target low density lipoprotein cholesterol (LDL-C) goal of ≤1.4 mmol/L or ≥50% relative reduction.[2]

Patients with documented cardiovascular disease and elevated individual risk factors are candidates for early intervention with higher intensity statins alongside lifestyle modifications.[2]

METHOD

Ethics Approval and Patient recruitment (t1)

Study information and consent form | Patients ≥18 years with IHD and receiving statin therapy

Data collection

LDL-C level at recruitment (t1) | Patient matching: age, gender, hypertension, diabetes mellitus

Patient follow-up

6 months (t2) and 12 months (t3) | Assessment of statin effectiveness and side-effects

Data analysis

Achievement of target LDL-C goals | Comparison of efficacy and safety of different statins

Table 1: Statin efficacy

Statin	Mean LDL-C in mmol/L (number of patients)			% reduction in LDL-C		p-value
	t1 (n=81)	t2 (n=75)	t3 (n=74)	t2	t3	
simvastatin	**1.83** (34)	**1.82** (20)	**1.80** (18)	1	2	<0.001
atorvastatin	**2.30** (39)	**1.56** (48)	**1.56** (44)	32	32	
rosuvastatin	**2.58** (8)	**1.96** (7)	**1.95** (12)	24	24	

Table 2: Achievement of target LDL-C goals at t3

Statin name and dose	Patients achieving ≤1.4 mmol/L LDL-C (n=24)	Patients achieving ≥50% LDL-C reduction (n=12)
Simvastatin 40mg	5 (21%)	0 (0%)
Atorvastatin 40mg	2 (8%)	0 (0%)
Atorvastatin 80mg	**15 (63%)**	**7 (58%)**
Rosuvastatin 20mg	1 (4%)	3 (25%)
Rosuvastatin 40mg	1 (4%)	2 (17%)

AIMS

- To compare the effectiveness of statin therapy in patients with IHD by assessing attainment of target LDL-C goals
- To analyse side-effects reported for simvastatin, atorvastatin and rosuvastatin

SETTING

Cardiac Catheterisation Suite, Cardiac Medical Ward and Critical Cardiac Care Unit within the Department of Cardiology at Mater Dei Public General Hospital.

Follow-up sessions were carried out at Cardiology Outpatients.

RESULTS

- 81 patients assessed: 62 male, mean age 68 years, 42 with previous revascularisation
- Statin therapy at t1: atorvastatin (n=39), simvastatin (n=34), rosuvastatin (n=8)
- 17 patients underwent statin intensification and achieved similar LDL-C reduction to patients with unchanged statin status (p>0.05)
- The lowest calculated mean LDL-C was with atorvastatin 80mg (1.56 mmol/L) and the highest percentage LDL-C reduction was also with atorvastatin 80mg (32%). Patients on rosuvastatin achieved a greater percentage reduction from t1 (24%) compared to simvastatin (2%) (p<0.05) (Table 1)
- Patients on simvastatin achieved negligible LDL-C reduction throughout the study
- 24 patients achieved the 1.4 mmol/L target goal and 12 patients achieved ≥50% relative reduction with high-intensity statins (Table 2)
- 11 cases of myalgia were reported with simvastatin (n=9) and rosuvastatin (n=2); renal dysfunction was recorded in patients on atorvastatin (n=7) and simvastatin (n=3); 3 cases of deranged liver function tests were documented with simvastatin

CONCLUSION

- After 12 months, the high-intensity statins atorvastatin 80mg and rosuvastatin 20-40mg were associated with the greatest LDL-C reduction from baseline
- Statin intensification resulted in a consequently larger mean LDL-C reduction
- Atorvastatin and rosuvastatin have safer side-effect profiles compared to simvastatin
- Only 30% of the study population achieved the LDL-C target goal of 1.4 mmol/L
- A more intensive LDL-C lowering regime is required to attain targets recommended in ESC guidelines[2] and to reduce cardiovascular risk

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Appendices

Appendix 1: Ethics approval

L-Università ta' Malta

Faculty of
Medicine & Surgery
University of Malta
Msida MSD 2080, Malta

Tel: +356 2340 1879/1891/1167
umms@um.edu.mt

www.um.edu.mt/ms

Ref No: **FRECMDS_1718_039**

Tuesday 17th July 2018

Ms. Maia Zarb
39, 'Sardinella'
Triq il-Kappella ta' Xaghra
San Pawl tat-Targa
Naxxar NXR2017

Dear Ms. Zarb

Please refer to your application submitted to the Research Ethics Committee in connection with your research entitled:

Use of Newer Generation Statins in Cardiovascular Disease

The University Research Ethics Committee granted ethical approval for the above mentioned protocol.

Yours sincerely,

Dr. Mario Vassallo
Chairman
Research Ethics Committee

Appendix 2: Data collection form

PATIENT DATA COLLECTION FORM

Date of recruitment:	Patient study number:

SECTION 1: PATIENT DEMOGRAPHIC INFORMATION	
Age	
Gender	○ Male ○ Female ○ Other
Hospital Status	○ Inpatient ○ Outpatient

<table>
<tr><th colspan="4">SECTION 2: CARDIAC RISK FACTORS</th></tr>
<tr><td colspan="2">Smoking</td><td colspan="2">○ Active (_____ cigarettes/ day)
○ Past (date/year stopped _____)
○ Never</td></tr>
<tr><td>Alcohol consumption</td><td colspan="2">○ Regularly (daily)
○ Socially (weekly)
○ Socially (occasionally)
○ Never</td><td>Number of units:
○ 1-5
○ 6-10
○ >10</td></tr>
<tr><td>Weight (kg)</td><td colspan="2">Height (m)</td><td>BMI (kg/m^2)</td></tr>
<tr><td colspan="2">Waist circumference (cm)</td><td colspan="2" rowspan="3">○ Underweight (<18.5)
○ Normal weight (18.5-24.99)
○ Pre-obesity (25-29.99)
○ Obesity Class I (30-34.99)
○ Obesity Class II (35-39.99)
○ Obesity Class III (≥ 40)
○ Not recorded</td></tr>
<tr><td>Female</td><td>Male</td></tr>
<tr><td>○ $\leq$ 80 cm
○ $>$ 80 cm
○ Not recorded</td><td>○ $\leq$ 94 cm
○ $>$ 94 cm
○ Not recorded</td></tr>
<tr><td colspan="3">Family history of hypercholesterolaemia</td><td>○ Parent
○ Sibling
○ Don’t know
○ No</td></tr>
</table>

SECTION 3: COMORBIDITIES		
○ Hypertension	○ Diabetes mellitus	○ Cerebrovascular Disease (stroke/TIA)
○ Gastro-Oesophageal Reflux Disease	○ Congestive Heart Failure	○ Chronic Kidney Disease
○ Peripheral Artery Disease	○ Thyroid disorders	○ Arrhythmia
○ Others:		

SECTION 4: PROCEDURE AT TIME OF RECRUITMENT		
Reason for admission	Procedure carried out	Diagnosis
○ Symptoms of angina ○ Positive stress test ○ ECG abnormalities ○ Troponin rise ○ Other:	○ Angiogram ○ PCI (1st time: YES / NO) ○ CABG (1st time: YES / NO) ○ Other:	○ Stable angina ○ ACS: ○ Unstable angina ○ STEMI ○ NSTEMI ○ Not specified

SECTION 5: INVESTIGATIONS					
Test parameter	Baseline (at time of recruitment, t_1)	Follow-up			Reference range
		6 months t2	12months t3		
	Date	Date	Date		
TC					2.0-5.0 mmol/L
HDL					1.15-1.68 mmol/L
LDL					<1.4 mmol/L
TGs					0.1-2.26 mmol/L
AP					40-104 U/L
ALT					5-33 U/L
GGT					5-36 U/L
Bilirubin					0-21 umol/L
Albumin					32-52 g/L
CK					26-192 U/L
HbA1c %					4.7-6.4%
eGFR					>60ml/min/1.73m^2
Cr					59-104 umol/L
Urea					1.7-8.3 mmol/L
Free T_4					11-18 pmol/L
TSH					0.3-3 mIU/L

SECTION 6: MEDICATIONS AT TIME OF RECRUITMENT (BASELINE)					
	Class	Generic Name	Dose	Dosage regimen	Start date (if known)
1	Statin				
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
13					
14					
15					

SECTION 7: PROBLEMS RELATED TO STATIN THERAPY		
	Side effects *Have you experienced any side effects/undesirable symptoms related to your medication?* *Ġieli ħassejt xi effetti sekondarji/ sintomi mhux mixtieqa relatati mal-mediċini li qed tieħu?*	Drug interactions
At baseline		
At 6 months		
At 12 months		

SECTION 8: CHANGES TO STATIN THERAPY DURING FOLLOW-UP	
Date	
	○ Statin & dose at 6 months: _____
	○ Statin & dose at 12 months: _____

Appendix 3: Patient information sheets and Consent forms in English and Maltese

PATIENT INFORMATION SHEET

I, Maia Zarb, B.Sc. Pharmaceutical Science student at the University of Malta, am currently undertaking a research project entitled **'Use of Newer Generation Statins in Cardiovascular Disease'**, under the supervision of Professor Lilian M Azzopardi and Dr Francesca Wirth from the Department of Pharmacy at UoM, in collaboration with the Department of Cardiology at Mater Dei Hospital.

You have been identified to participate in this research which involves the following:

Aim of research and how will you benefit?

Statins are the drugs of choice to lower blood cholesterol levels and have a cardioprotective effect. There are different types of statins available at Mater Dei and pharmacies around Malta and Gozo. This research, together with your consultant cardiologist, will determine the statin which is best suitable for you to help improve cholesterol levels and cardiac health.

Your involvement

- Approach you when your angiogram is due
- Be followed-up by your consultant cardiologist and myself

Other important information

- There are no foreseeable risks or discomfort to the patient as the study entails data collection
- Participation in this research is entirely voluntary. The information gathered will be kept strictly confidential and used solely for the purpose of the research, according to the Data Protection Act
- Refusal to participate will in no way affect the treatment you receive as a patient at the Cardiology Department at Mater Dei Hospital
- You may discontinue participation in the research at any time without prejudice
- Results of this research will not influence the routine treatment/service you receive
- Confidentiality of data will be maintained throughout the duration of the research project. Access to your patient records is limited to the researcher, supervisors, caring cardiologists and team of doctors.

Kindly sign the attached consent form if you agree to participate in this research.

Should you require any further information about this research project, please do not hesitate to contact me via email at maia.zarb.14@um.edu.mt or mobile phone on 79961808.

Thank you in advance for your cooperation.

Maia Zarb

343496M

INFORMAZZJONI GHALL-PAZJENT/A

Jiena, Maia Zarb, studenta tal-farmaċija fl-Università ta' Malta, qiegħda nagħmel proġett ta' riċerka għall-Baċċellerat fil-Farmaċija, intitolat ***'Use of Newer Generation Statins in Cardiovascular Disease'***, taħt is-superviżjoni tal-Professur Lilian M Azzopardi u Dr Francesca Wirth mid-Dipartiment tal-Farmaċija fl-Università ta' Malta, b'kollaborazzjoni mad-Dipartiment tal-Kardjoloġija fl-Isptar Mater Dei.

Inti ġejt identifikat/a biex tipparteċipa f'din ir-riċerka li tinvolvi dan li ġej:

L-għan tar-riċerka u l-benefiċċju għalik

Il-mediċini *statins* huma l-mediċini ewlenin li jgħinu biex inaqsu l-kolesterol fid-demm. Din ir-riċerka ser tevalwa kif l-i*statin* li qed tieħu qiegħed jikkontrolla l-livell tal-kolesterol tiegħek.

L-involviment tiegħek

- Navviċinawk fil-ġurnata li żżur id-Dipartiment tal-Kardjoloġija fl-Isptar Mater Dei. Ikun jeħtieġ li naċċessa l-fajl tiegħek tal-isptar u nintervistak biex niġbor informazzjoni li tikkonsisti minn: informazzjoni demografika, fatturi li jaffettwaw il-livell tal-kolesterol, mediċini li qed tieħu u riżultati tat-testijiet tal-kolesterol.
- Ikun jeħtieg ukoll lill-konsulent/tabib tiegħek u jien insegwu l-każ tiegħek fuq perjodu ta' 12-il xhar.

Informazzjoni importanti oħra

- Ma hemm ebda riskju previst għall-pazjent f'dan l-eżerċizzju ta' ġbir u analiżi ta' *data*
- Il-parteċipazzjoni tiegħek f'din ir-riċerka hija kompletament volontarja. L-informazzjoni miġbura tibqa' strettament kunfidenzjali u użata biss għar-ricerka skont l-Att dwar il-Protezzjoni u l-Privatezza tad-*Data*
- It-trattament tiegħek, bħala pazjent/a fl-Isptar Mater Dei, bl-ebda mod ma jiġi affettwat jekk int tirrifjuta milli tipparteċipa
- Inti tista' tieqaf milli tipparteċipa fi kwalunkwe ħin, mingħajr ebda preġudizzju
- Riżultati ta' din ir-riċerka mhux ħa jaffettwaw it-trattament/servizz regolari li tirċievi
- Kunfidenzjalità ta' *data* ser tinżamm tul ir-riċerka kollha. Aċċess għall-fajl tiegħek tal-isptar huwa permess biss għar-riċerkatur, superviżuri, kardjoloġisti u tobba li jieħdu ħsiebek

Inti gentilment mitlub/a tiffirma l-formola ta' kunsens mehmuza jekk taccetta li tippartecipa f'din ir-ricerka.

F'kaz li jirrikjedi li tkun taf aktar informazzjoni dwar din ir-ricerka, jekk joghgbok ikkuntattjani permezz tal-*email* fuq maia.zarb.14@um.edu.mt jew mowbajl fuq in-numru 79961808.

Grazzi bil-quddiem ghall-kooperazzjoni tieghek.

Maia Zarb

343496M

CONSENT FORM

I am a Maltese citizen and am over eighteen (18) years of age. I have been asked to participate in a research study entitled:

'Use of Newer Generation Statins in Cardiovascular Disease'

The purpose and details of the study have been explained to me by

Maia Zarb

and any difficulties which I raised have been adequately clarified.

I give my consent to the Principal Investigator to make the appropriate observations. I am aware of the inconveniences which this may cause.

I understand that the results of this study may be used for medical or scientific purposes and that the results achieved from the study in which I am participating may be reported or published: however, I shall not be personally identified in any way, either individually or collectively, without my expressing written permission. I have the right to access, rectify and where applicable erase data concerning me.

I am under no obligation to participate in this study and am doing so voluntarily.

I may withdraw from the study at any time, without giving any reason. This will not influence in any way the care and attention and treatment normally given to me *(applicable only in case of patients receiving treatment).*

I understand that any complications and/or adverse effects which may arise during or as a consequence of the study will be recorded and any treatment which this may entail will be given within the Government Health Services. Access to your patient records is limited to the researcher, supervisors, caring cardiologists and team of doctors for the duration of the study and all the individual data collected will be securely disposed thereafter.

~~I am~~**/ I am not** receiving any remuneration for participating in this study.

In case of queries during the study I may contact

Signature of participant	
Name of participant	
Signature of Chief Investigator	
Name of Chief Investigator	Maia Zarb
Email of Chief Investigator	maia.zarb.14@um.edu.mt
Contact number of Chief Investigator	7996108
Name of Chief Supervisor	Prof Lilian M Azzopardi
Email of Chief Supervisor	lilian.m.azzopardi@um.edu.mt
Contact number of Chief Supervisor	23402896
Name of Supervisor	Dr Francesca Wirth
Email of Supervisor	francesca.wirth@um.edu.mt
Contact number of Supervisor	23402902
Date	

PROPOSTA GĦALL-FORMULA TAL-KUNSENS

Jien/a ċittadin/a Malti/ja u għalaqt tmintax (18)-il sena talbuni biex nieħu sehem fi studju riċerka bl-isem ta':

'Use of Newer Generation Statins in Cardiovascular Disease'

Il-għan u d-dettalji tal-istudju spejgathomli Maia Zarb

li wkoll iċċaratli xi mistoqsijiet li għamilt.

Nagħti l-kunsens tiegħi lill-persuna responsabbli għal din ir-riċerka u l-assistenti tagħha biex jagħmlu l-osservazjonijiet li hemm bżonn u nifhem li dan jista' jkun ta' skomdu għalija.

Jiena nifhem lir-riżultati ta' dan l-istudju jistgħu jintużaw għal skopijiet xjentifiċi u jista' jiġi ppubblikat rapport bil-miktub: jekk isir hekk b'ebda mod ma nista' nkun identifikat/a, individwalment jew bħala parti minn grupp, mingħajr il-kunsens tiehħi bil-miktub. Jiena għandi d-dritt naċċessa, nirrettifika u saħansitra nitlob li titħassar xi informazzjoni li tikkonċernani.

Jiena ma għandi l-ebda dmir li niehu sehem f'dan l-istudju u dan qed nagħmlu minn rajja. Jiena nista', meta rrid, ma nkomplix niehu sehem fl-istudju, u mingħajr ma' nagħti raġuni. Jekk nagħmel hekk xorta nibqa' nieħu l-kura li ssoltu tingħatali *(tapplika biss għal pazjenti li qed jieħdu kura).*

Jiena nifhem li jekk ikun hemm xi kumplikazzjoniji jew effetti mhux mistennija waqt l-istudju, dawn jiġu mniżżla bil-miktub u jekk ikun hemm bżonn xi kura, tiġi mgħotija fis-Servizz Nazjonali tas-Saħħa. Aċċess għall-fajl tiegħek tal-isptar huwa permess biss għar-riċerkatur, superviżuri, kardjoloġisti u tobba li jieħdu ħsiebek. Kunfidenzjalità ta' data ser tinżamm tul ir-riċerka kollha u l-informazzjoni miġbura ser tiġi abolita b'mod sigur wara li tintemm ir-riċerka.

Jiena ~~qed nitħallas~~/mhux qed nitħallas biex nieħu sehem f'dan l-istudju.

Jekk ikolli xi diffikulta' waqt l-istudju, nista' nistaqsi għal:

Firma tal-parteċipant _____

Isem tal-parteċipant _____

Firma tal-persuna responsabbli għal din ir-riċerka _____

Isem tal-persuna responsabbli għal din ir-riċerka Maia Zarb_____

Email tal-persuna responsabbli għal din ir-riċerka maia.zarb.14@um.edu.mt_____

Numru tal-mowbajl tal-persuna responsabbli għal din ir-riċerka 79961808_____

Isem tas-superviżur prinċipali Prof Lilian M Azzopardi_____

Email tas-superviżur prinċipali lilian.m.azzopardi@um.edu.mt_____

Numru tas-superviżur prinċipali 23402896_____

Isem tas-superviżur Dr Francesca Wirth_____

Email tas-superviżur francesca.wirth@um.edu.mt_____

Numru tas-superviżur 23402902_____

Data _____