Statin Associated Muscle Symptoms and Therapy Adherence

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of the Degree of Master of Pharmacy

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To my parents,

I dedicate this dissertation to you with the utmost gratitude for your unwavering support and encouragement throughout my academic journey. Your constant support has made it possible for me to become who I am today. I am eternally grateful for the sacrifices you have made to provide me with all that I needed. I dedicate this work to you both as a token of my appreciation and a tribute to your endless love and support.

Abstract

Statin associated muscle symptoms (SAMS) may lead to therapy non-adherence and discontinuation. Clinical presentation of SAMS is highly heterogeneous and there are no standardised definitions of SAMS terminologies. The aims were to: 1) Assess adherence and patient experience with statin therapy in a patient cohort undergoing cardiac procedures, and 2) Propose harmonised definitions of SAMS terminologies. The methodology consisted of: 1) Development and validation of a data collection sheet and questionnaire, prospective recruitment of patients on statin therapy who underwent coronary angiography (n=125) or percutaneous coronary intervention (PCI) (n=125) by convenience sampling, and completion of data collection tools using hospital records and patient interview; 2) Compilation of SAMS terminologies definitions from literature, identification of definitions used by cardiologists in practice using a self-administered online questionnaire, followed by proposal of harmonised definitions and validation by an interprofessional focus group. Descriptive statistics were performed. From the 250 patients assessed (75% male, 39% between 65 and 74 years), 65% were prescribed atorvastatin. There was no significant difference in patient responses between coronary angiography and PCI ($p>0.05$). Forty-one percent of patients 'sometimes' or 'frequently' skip a dose, mostly attributed to forgetfulness (47%). Sixteen percent considered stopping the statin without consulting a healthcare professional. SAMS were reported by 28% (n=70) of patients, mostly myalgia (n=54), which made them feel tired requiring rest (n=61). Most patients experiencing SAMS (n=56) informed a physician, and statin was changed in 20 patients. The statin mostly implicated with SAMS was simvastatin (50%). Definitions for myalgia (n=8), myopathy (n=8) and rhabdomyolysis (n=7) were identified from literature. Four definitions for myalgia and myopathy, and 6 definitions for rhabdomyolysis were identified by nine cardiologists as used in

practice. A harmonised definition for each terminology was compiled. Following consensus in the focus group, the harmonised definitions were disseminated to cardiologists. Adherence to statin therapy in the cohort studied is not optimal and patients reported SAMS which impacted their quality of life. Data indicating duration of statin therapy was not available and may have inference on adherence and side-effects reporting. Harmonised definitions of SAMS terminologies may support cardiologists in diagnosis and management of SAMS to facilitate management of statin therapy.

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List of Abbreviations

ACC: American College of Cardiology

ACS: Acute coronary syndrome

AHA: American Heart Association

ASCVD: Atherosclerotic cardiovascular disease

CK: Creatine kinase

CV: Cardiovascular

CVD: Cardiovascular disease

DDI: Drug-drug interaction

EAS: European Atherosclerosis Society

ESC: European Society of Cardiology

LDL-C: Low density lipoprotein cholesterol

PCI: Percutaneous coronary intervention

SAMS: Statin associated muscle symptoms

SAMS-CI: Statin associated muscle symptoms clinical index

ULN: Upper Limit of Normal

Chapter 1:

Introduction

1.1. Significance of Statin Therapy

Statins are widely prescribed to manage dyslipidaemia and hypercholesterolaemia, which are risk factors for various conditions, including hypertension, chronic and acute coronary syndromes, stroke, peripheral artery disease, and diabetes mellitus (Ramakumar *et al.*, 2016; Fernandez *et al.*, 2018; Tsivgoulis *et al.*, 2018). Patients with known cardiovascular disease (CVD), diabetes mellitus with microalbuminuria, chronic kidney disease, and with individual risk factors, such as family history of atherosclerotic cardiovascular disease (ASCVD) and obesity, have a very high total cardiovascular (CV) risk and need active management with lifestyle interventions and lipid lowering drugs, including statins (Chogtu *et al.*, 2015; Grundy *et al.* 2018; Mach *et al.*, 2019; Reiter-Brennan *et al.*, 2020; Visseren *et al.*, 2022).

Evidence from clinical trials and meta-analyses support early, intensive, and continuous statin therapy as the standard of care in patients with clinical ASCVD to reduce low density lipoprotein cholesterol (LDL-C) levels and to decrease the risk of adverse CV events (Ray *et al.*, 2005; Dohi *et al.*, 2010; Schwartz *et al.*, 2017; Xu *et al.*, 2021). The lipid-lowering effect of statins has been associated with reduced CV event risk and mortality in various studies (Chou *et al.*, 2016; Lin *et al.*, 2016; Ramakumar *et al.*, 2016; Fujisue and Tsujita, 2017; Salami *et al.*, 2017; Stewart *et al.*, 2017; Fernandez *et al.*, 2018; Tsivgoulis *et al.*, 2018; Mach *et al.* 2019; Toth and Banach, 2019; Visseren *et al.*, 2022; Badimon *et al.*, 2023; Marcellaud *et al.*, 2023).

The use of statins as preventive treatment is recommended (Mangione *et al.*, 2022; Byrne *et al.*, 2022). In 2022, the 'United States Preventive Services Task Force' recommended prescribing of statin therapy in patients between the ages of 40 to 75 years for the primary prevention of CV events, since statin therapy was reported to have a net-benefit in reducing CV events and all-cause mortality (Mangione *et al.*, 2022). A recent meta-analysis identified a modest absolute risk reduction in terms of all-cause mortality, myocardial infarction, and stroke by statins as preventive treatment (Byrne *et al.*, 2022).

Early and intensive statin therapy is recommended by the European and American guidelines for the management of dyslipidaemias and CVD prevention (Grundy *et al.*, 2019; Mach *et al.*, 2019; Visseren *et al.*, 2022). The European Society of Cardiology/ European Atherosclerosis Society (ESC/EAS) guidelines state that the use of statins should be weighed against the patient's risk factors for developing ASCVD (Mach *et al.*, 2019; Visseren *et al.*, 2022). The target LDL-C level is ≤1.4 mmol/L for very high-risk patients, ≤1.8 mmol/L for high-risk patients and <3.0 mmol/L for patients with low-risk (Mach *et al.*, 2019; Landmasser *et al.*, 2022; Visseren *et al.*, 2022). The American College of Cardiology/American Heart Association (ACC/AHA) guidelines recommend the use of statins for primary and secondary prevention of CV events, chronic kidney disease and diabetes (Grundy *et al.*, 2019; Reiter-Brennan *et al.*, 2020).

Atorvastatin 40mg to 80mg and rosuvastatin 20mg to 40mg are classified by the American guidelines as high-intensity statin therapy (Arnett *et al.*, 2019; Grundy *et al.*, 2019). The ACC/AHA guidelines endorse high-intensity statin therapy recommended in all patients ≤75 years

with clinical ASCVD and who have no safety concerns (Grundy *et al.*, 2019). The ESC/EAS guidelines recommend a 'treat-to-target' strategy, with "a ≥50% LDL-C reduction from baseline and an absolute LDL-C treatment goal of <1.4 mmol/L for very high-risk patients" (Visseren *et al.*, 2022). "A high-intensity statin should be prescribed up to the highest tolerated dose to achieve specified goals", however unlike the American guidelines, the ESC/EAS guidelines do not specify statin intensity (Mach *et al.*, 2019).

The benefits of statin therapy are reported to outweigh the risks (De Vera *et al.*, 2014; Rosenson *et al.*, 2017; Jacobson *et al.*, 2019; Saeed *et al.*, 2021), however monitoring of the safety and tolerance to statins are paramount since adherence may be affected (Hu *et al.*, 2012; De Vera *et al.*, 2014; Hashni *et al.*, 2018; De Backer *et al.*, 2019).

1.2. Adherence to Statin Therapy

A study by Chowdhury *et al.*, (2013) in the United Kingdom found that good adherence to statin therapy was 54% and that a substantial proportion of patients do not adhere adequately to CVD therapy. In a study carried out in South Korea, 33% of patients stopped being adherent to their statin therapy within the first year (Chung *et al.*, 2018). Similarly, a study in the United States identified that 37% of patients who were started on statin therapy stopped adhering to therapy within the first two years (Morotti *et al.*, 2019). The results of another United States study showed that statin adherence and persistence remain low, particularly among individuals starting treatment without a history of CVD (Colantonio *et al*, 2019).

With respect to achieving optimal LDL-C levels, a study in the United Kingdom concluded that statin therapy in patients with CV conditions was suboptimal since LDL-C targets were not reached in up to 80% of high-risk patients (Drexel *et al.*, 2020). Patients who participated in the 'EUROASPIRE V' survey showed less than optimal management of LDL-C levels, with patients on high intensity lipid lowering therapy being more adherent to therapy compared to those on low or moderate intensity statins (De Backer *et al.*, 2019). A recent study carried out in Australia observed low long-term adherence to statin therapy since 49% of patients discontinued treatment within 5 years, and the study identified that statin discontinuation was more likely to occur with low to moderate intensity statin regimens than high intensity regimens (Talic *et al.*, 2022).

Six main barriers to therapy non-adherence by patients were discussed by Marcum *et al.* (2013), namely; 1) lack of understanding on the importance of therapy adherence for a healthy lifestyle; 2) patient perception that the costs of taking medications outweigh the benefits; 3) very complex dosage regimens for patients to comprehend; 4) insufficient vigilance by patients about medications; 5) inaccurate, conflicting or irrational beliefs by patients about medications being taken; and 6) patients not aware of the benefits of medication. Interventions to improving adherence are important as indicated by the paper by Marcum *et al.* (2013), which reported that according to the World Health Organisation, "increasing the effectiveness of adherence interventions may have far greater impact on the health of the population than any improvement in specific medical treatments".

Specifically in relation to patient adherence to statin therapy, barriers identified in a United States study included concerns about use and benefits of statins, logistical barriers such as payment, remembering to taking the statin, complexity of regimen, concerns about side-effects, and lifestyle preferences, such as generally disliking taking medication (Fung *et al.*, 2018). Various studies have reported barriers to statin therapy which include statin-specific documented side-effects, patient awareness of side-effects, lack of immediacy of beneficial effect and patient misperceptions (Hu *et al.*, 2012, Rosenson *et al.*, 2014; Stroes *et al.*, 2015; Manchini *et al.*, 2016; Drexel *et al.*, 2020). Self-reported non-adherence has been attributed to high statin dose, lack of awareness on hyperlipidaemias, and increased number of medication doses compared to the adherent groups (Fujisue and Tsujita, 2017; Salami *et al.*, 2017; Stewart *et al.*, 2017; Fernandez *et al.*, 2018; Toth and Banach, 2019). Muscle symptoms are reported as one of the main reasons for statin non-adherence or discontinuation (Chowdhury *et al.*, 2013; De Vera *et al.*, 2014; Stroes *et al.*, 2015; Rosenson *et al.*, 2017; Brown and Watson 2018; Bytyci *et al.*, 2022).

1.3. Statin Intolerance

Statin intolerance has been defined as “the inability to tolerate at least two statins, one at the lowest starting daily dose and another at any daily dose” (Guyton *et al.*, 2014), “the inability to use statins because of muscle symptoms or elevated creatine kinase” (Ahmad, 2014), and “when a patient is unable to continue statin therapy due to perceived, or objectively documented, adverse effects” (Brown and Watson, 2018).

A meta-analysis carried out in 2022 evaluated over four million patients who were prescribed statin therapy and found that complete statin intolerance is relatively low and overestimated. The study concluded that patients should be thoroughly evaluated before being diagnosed with complete statin intolerance to decrease the risk of unnecessary discontinuation and sub-optimal lipid lowering therapy (Bytyci *et al.*, 2022).

1.3.1. Statin Associated Muscle Symptoms

Statins are usually well-tolerated, however undesirable effects, including statin associated muscle symptoms (SAMS), have been reported (Hu *et al.*, 2012; Navar *et al.*, 2018; Newman *et al.*, 2019). SAMS is a broad term encompassing adverse effects including myopathy, myalgia, and rhabdomyolysis (Wiggins *et al.*, 2016; Rosenson *et al.*, 2017; Rallidis, 2019).

1.3.2. Prevalence and Risk Factors of Statin Associated Muscle Symptoms

More than 50% of patients on statins have experienced muscle symptoms such as aches, cramps and weakness, and complain of fatigue (Chowdry *et al.*, 2013; Rosenson *et al.*, 2017). According to the Summary of Product Characteristics, in the case of simvastatin, atorvastatin and rosuvastatin, occurrence of SAMS including myopathy or rhabdomyolysis is rare, affecting more than 0.01% but less than 0.1% of the population, while with respect to myalgia, occurrence is common for simvastatin and atorvastatin, affecting more than 1% but less than 10% of patients

taking the drugs.[1,2,3] Different risk factors contribute to the incidence of SAMS (Hashni *et al.*, 2018; Navar *et al.*, 2018), and their occurrence may be dose-dependent and/or due to drug-drug interactions (DDIs) (Wiggins *et al.*, 2016).

Mancini *et al.* (2016) classified risk factors into endogenous and exogenous factors. Endogenous factors include anthropometric factors, concurrent conditions, and related history such as previous history of SAMS, while exogenous factors include DDIs, lifestyle, and illicit drug use. Anthropometric factors including advanced age, female sex, a low body mass index and Asian ethnicity are predisposing factors for the development of SAMS (Ronsenson *et al.*, 2014; Stroes *et al.*, 2015; Selva-O'Callaghan *et al.*, 2018). Concurrent conditions including hypothyroidism, diabetes mellitus, human immunodeficiency virus infection, Vitamin D deficiency, organ transplantation, biliary tree obstruction, and impaired renal or hepatic function, may predispose patients to SAMS. These conditions must be managed accordingly to decrease the likelihood of SAMS (Stroes *et al.*, 2015; Ramakumar *et al.*, 2016; Saeed *et al.*, 2021).

A history of previous creatine kinase (CK) elevation more than 10 times the upper limit of normal (ULN), pre-existing/unexplained joint and muscle pain, inflammatory or inherited muscular, neuromuscular, or genetic defects, increase the risk of SAMS. Previous statin-induced myotoxicity while receiving another lipid lowering drug predisposes a patient to SAMS (Stroes *et al.*, 2015;

[1] Electronic medicines compendium (emc). Simvastatin film-coated tablets - Summary of Product Characteristics (SmPC) [Internet]. UK: Datapharm Ltd; 2018 [cited 2022 Dec 14]. Available from: https://www.medicines.org.uk/emc/product/6001/smpc

[2] Electronic medicines compendium (emc). Atorvastatin Film Coated Tablets - Summary of Product Characteristics (SmPC) [Internet]. UK: Datapharm Ltd; 2019 [cited 2022 Dec 14]. Available from: https://www.medicines.org.uk/emc/product/4109/smpc

[3] Electronic medicines compendium (emc). Rosuvastatin film-coated tablets - Summary of Product Characteristics (SmPC) [Internet]. UK: Datapharm Ltd; 2020 [cited 2022 Dec 14]. Available from: https://www.medicines.org.uk/emc/product/8970/smpc

Ward *et al.*, 2019). DDIs may lead to SAMS, and examples of drugs which interact with statins include amiodarone, amlodipine, colchicine, ciclosporin, everolimus, diltiazem, fenofibrate and verapamil, with most interactions reported with simvastatin (Wiggins *et al.*, 2016). A diet high in grapefruit or pomegranate juice and heavy exercise have been reported to increase the incidence of SAMS (Mancini *et al.*, 2016). Genetic polymorphisms have been reported to increase the risk of statin-induced myopathy, however pharmacogenetic testing in patients on statins is not routine practice (Stroes *et al.*, 2015; Mancini *et al.*, 2016; Ramachandran and Wierzbicki, 2017).

1.3.3. Clinical Presentation and Diagnosis of Statin Associated Muscle Symptoms

There are presently no standardised definitions for myalgia, myopathy, and rhabdomyolysis available in literature (Rosenson *et al.*, 2017; Selva-O'Callaghan *et al.*, 2018; Turner and Pirmohamed, 2020). Several associations and working groups use different definitions for the various SAMS terminologies and these definitions differ in specificity and thresholds required for diagnosis (Thompson *et al.*, 2016). Definitions for SAMS terminologies have been difficult to standardise, mostly due to the various ways in which SAMS may present in a particular patient (Rosenson *et al.*, 2014, Stroes *et al.*, 2015; Thompson *et al.*, 2016, Grundy *et al.*, 2019). The clinical presentation of SAMS is "highly heterogeneous, usually with normal or slightly elevated CK level". As reported in various papers, a "definitive diagnosis of SAMS is challenging since symptoms are subjective and there is no gold standard diagnostic test" (Rosenson *et al.*, 2014; Stroes *et al.*, 2015; Selva-O'Callaghan *et al.*, 2018; Turner and Pirmohamed, 2020).

Attributing muscle symptoms to the use of statins has been identified in literature as difficult to standardise and quantify (Rosenson *et al.*, 2017). The most common type of symptom, affecting more than 80% of patients, is muscle pain (myalgia) which can present with or without elevated CK levels (Rallidis, 2019, Ward *et al.*, 2019). A clinical trial designed to study the effects of statins on skeletal muscle symptoms, 'The Effects of Statins on Muscle Performance (STOMP)' study, showed that in patients not previously exposed to statin therapy randomised to atorvastatin 80 mg daily or placebo for 6 months, "9.4% of the statin-treated and 4.6% of control subjects met the definition of myalgia" utilised in the study (p=0.054) (Parker *et al.*, 2013). The EAS Consensus Panel proposed identifying SAMS by symptoms typical of statin myalgia (muscle pain or aching), elevation of CK levels and the time-based association of the symptoms, with statin initiation and discontinuation and assessment of response to repetitive re-challenging with the statin (Stroes *et al.*, 2015).

The 'Statin-Associated Muscle Symptom Clinical Index (SAMS-CI)' tool assesses the likelihood that a patient's muscle symptoms were caused or worsened by using statins (Rosenson *et al.*, 2014). The tool was psychometrically evaluated and tested clinically, and a revised tool suitable for further testing in clinical practice was developed (Rosenson *et al.*, 2017). The revised tool aims to support better detection of SAMS in clinical practice and to optimise treatment for patients experiencing muscle symptoms, and the authors recommended further research to prospectively validate the tool in different practice settings (Rosenson *et al.*, 2017; Taylor and Thompson 2018).

1.4. Aims of the study

The aims were to:

1) Assess adherence and patient experience with statin therapy in a cohort of patients undergoing cardiac procedures, including clinical presentation, incidence, and impact of SAMS
2) Propose harmonised definitions of SAMS terminologies.

A secondary objective was to explore the practicality of using the SAMS-CI tool by cardiologists in local practice.

Chapter 2:

Methodology

2.1. Study Design and Setting

The methodology consisted of two parts. Part 1 was a cohort study and involved development and validation of a data collection sheet and questionnaire to assess patient experience and adherence to statin therapy, prospective recruitment of 250 patients on statin therapy who underwent cardiac procedures by convenience sampling, and completion of data collection tools using hospital records and patient interview. Part 2 of the study involved compilation of definitions of SAMS terminologies from literature, identification of definitions used by cardiologists in practice through a self-administered online questionnaire, proposal of harmonised definitions, validation of definitions by an interprofessional focus group, and dissemination of harmonised definitions as a point of reference for cardiologists. The practicality of using the SAMS-CI tool by cardiologists in local practice was also explored. The study was conducted at the Cardiac Catheterisation Suite within the Cardiology Department at Mater Dei Hospital (MDH).

2.2. Ethics Approval

Ethics approval was obtained from the University of Malta Faculty of Medicine and Surgery Research Ethics Committee (Appendix 1).

2.3. Part 1: Patient Experience and Adherence to Statin Therapy

Patient experience and adherence to statin therapy, including clinical presentation, incidence and impact of SAMS, were assessed in a cohort of patients undergoing coronary angiography or PCI.

2.3.1. Development and Validation of Data Collection Tools

A data collection sheet and a questionnaire (*'Statin Adherence Questionnaire'*) were developed using various literature sources (Parker *et al.*, 2012; Lee *et al.*, 2013; Tanaka *et al.*, 2014; Khayznikov *et al.*, 2015; Banach *et al.*, 2016; Cerdá Iñesta, 2019; Jacobson *et al.*, 2019; Newman *et al.*, 2019; Rodriguez *et al.*, 2019; Grover *et al.*, 2020). The questionnaire was translated into Maltese and back translated into English.

The developed data collection tools were validated by an expert panel consisting of two cardiologists, a general practitioner, three pharmacists (community, hospital, academia), and two lay persons. The data collection tools were validated in terms of relevance of content, comprehensiveness, and presentation. The suggested amendments to the questionnaire by the panel were; addition of a question assessing patient knowledge about name and dose of statin currently being taken, addition of a question assessing impact of SAMS on overall quality of life, and addition of a question which assesses frequency of patient visits to general practitioner for medication review. After validation, the data collection sheet consisted of three sections and the questionnaire consisted of two sections (Table 2.1) (Appendix 2).

Table 2.1: Data Collection Sheet and Statin Adherence Questionnaire Sections

Section	Description of Content
Data Collection Sheet *(Completed for all patients)*	
1. Patient Characteristics	Sex, age, education level, employment, most recent investigation/ intervention carried out at cardiac catheterisation laboratory, previous CV events, previous revascularisation, cardiac risk factors, comorbidities
2. Investigations	Glycated haemoglobin, thyroid function tests, muscle markers, renal function tests, liver function tests
3. Current medications	Generic name, dose and dosage regimen
Statin Adherence Questionnaire	
1. Adherence	*(This section was completed for all patients)* Awareness of medications prescribed, reason for taking statin, acquisition of statin medication, frequency and timing of taking statin dose, proactiveness at acquiring statin medications, frequency of missing statin dose and reason, consideration of stopping statin therapy without consulting with HCP, frequency of medication review, frequency of taking statin medications when going on holiday, perceived side effects with statin therapy
2. Statin Associated Muscle Symptoms	*(This section was completed only for patients reporting SAMS)* Presentation, frequency and timing of SAMS, seasons which increase frequency of SAMS, pain score of SAMS, impact of SAMS on quality of life, informing physician about occurrence of SAMS and action taken, avoidance of foods which may increase frequency of SAMS

2.3.2. Patient Recruitment and Data Collection

Patients ≥18 years who visited the cardiac catheterisation suite for coronary angiography (n=125) or PCI (n=125), and were on statin therapy at time of recruitment, were prospectively recruited by convenience sampling. An intermediary nurse approached patients fitting the inclusion criteria, and invited them to participate in the study using a patient information sheet available in English and Maltese. For patients who agreed to participate, informed consent was obtained through completion of a consent form available in English and Maltese. The intermediary introduced the participant to the researcher and the questionnaire was administered once through patient interview. The data collection sheet was completed using information provided by the intermediary from hospital records, namely the Cardiovascular Information System (CVIS) and iSOFT clinical manager. Data collection was carried out between June 2021 and September 2022.

2.3.3. Data Analysis

Data collected was analysed using IBM-SPSS version 26. Descriptive statistics and hypothesis testing were carried out. Descriptive statistics included measures of frequency mean and range. Hypothesis testing involved use of the Chi-Square Test and Independent Samples t-Test. The Chi-Square test was used to test for any statistically significant differences that can be observed between patients who underwent coronary angiography and patients who underwent PCI for categorical variables, while the independent samples t-Test was used for continuous variables.

These statistical tests were used to test for any statistically significant differences between adherence to statin therapy and the following variables: gender, age, education level, employment, history of CV events, previous revascularisation, smoking history, alcohol consumption, number of medications taken, number of daily medication doses, whether they obtain their medicines for free, frequency of visiting a GP for a medication review and occurrence of SAMS. A p-value less than 0.05 was considered statistically significant.

2.3.4. Dissemination of Results

A research abstract was presented as a Poster Presentation at the European Society of Clinical Pharmacy (ESCP) Spring Workshop held in Antwerp, Belgium, in April 2023, and was published in the International Journal of Clinical Pharmacy.

2.4. Part 2: Statin Associated Muscle Symptoms Terminologies and Assessment

Various definitions of SAMS terminologies were compiled from literature and harmonised in the second part of the study. The practicality of using the SAMS-CI tool by cardiologists in local practice was also explored. This part of the study was undertaken between October 2022 and June 2023.

2.4.1. Compilation of Statin Associated Muscle Symptoms Definitions

Definitions for myalgia, myopathy and rhabdomyolysis were compiled following literature review carried out using PubMed and Google Scholar. The timeframe applied was 2012 to 2021 and keywords used were: ‘statin associated muscle symptoms’, ‘myalgia’, ‘statin-induced myalgia’, ‘myopathy’, ‘statin-induced myopathy’, ‘rhabdomyolysis’, ‘statin-induced rhabdomyolysis’, ‘statin intolerance’, ‘statin side-effects’, ‘statin adverse effects’, ‘statin adverse events’, ‘SAMS’.

2.4.2. Development of Questionnaire

A self-administered online questionnaire (*Clinical Presentation of Statin Associated Muscle Symptoms*) was developed using Google Forms (Appendix 2). The questionnaire was reviewed by the dissertation supervisor and the Chair of the Department of Cardiology at MDH prior to dissemination. The questionnaire consisted of 3 sections: 1) cardiologist details; 2) SAMS terminologies and definitions and; 3) practicality of SAMS-CI tool. Cardiologists could choose to

identify themselves for further communication with the researcher or to remain anonymous when completing the questionnaire.

Section 1 collected cardiologist name and surname (optional) and grade (consultant, resident specialist, higher specialist trainee, basic specialist trainee); Section 2 contained various referenced definitions of myalgia, myopathy and rhabdomyolysis and; section 3 contained questions relating to practicality of the SAMS-CI tool in local practice (Figure 2.1). The SAMS-CI tool is composed of two sections, each comprising of four questions. The left-hand side of the questionnaire is to be completed for patients who have self-reported SAMS and have only received one statin, whilst the right-hand side is for patients who have received two or more different statins. The questions are the same for both sides of the tool, which assess location and timing of the symptoms, however, the difference between the two sides is that patients who have only ever received one statin are rechallenged with the same statin prior to completing the fourth question of the tool. Once the tool is completed, a total score is obtained which describes the likelihood of SAMS being present in the patient (Rosenson et al., 2017).

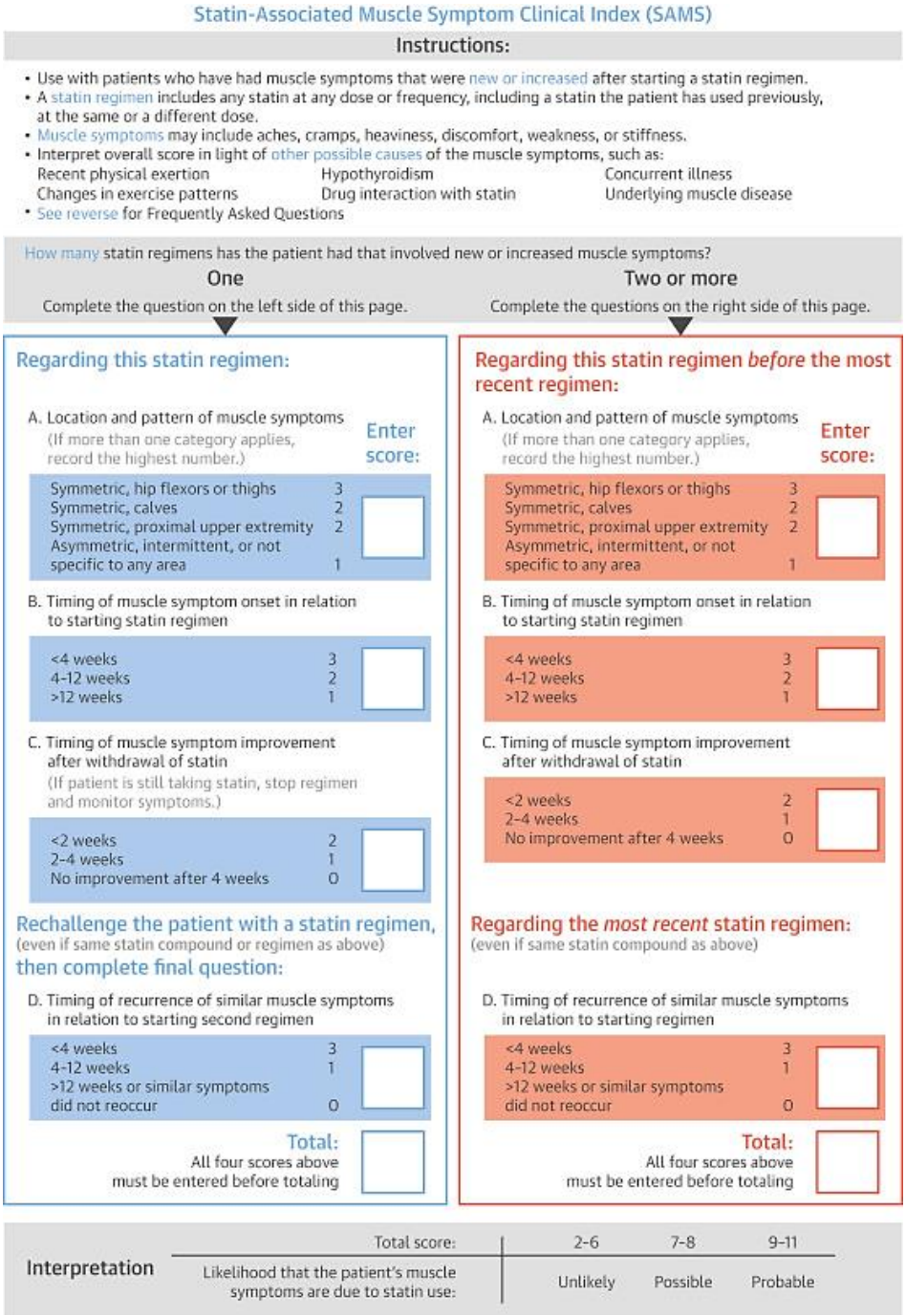

Figure 2.1: SAMS-CI Tool

Reproduced from: Rosenson RS, Miller K, Bayliss M, Sanchez RJ, Baccara-Dinet MT, Chibedi-De-Roche D, *et al*. The Statin-Associated Muscle Symptom Clinical Index (SAMS-CI): Revision for Clinical Use, Content Validation, and Inter-rater Reliability. Cardiovascular drug therapy. 2017; 31: 179-186. doi: 10.1007/s10557-017-6723-4

2.4.3. Dissemination of questionnaire

The link to the questionnaire was sent via email to the Chair of the Department of Cardiology and disseminated via email to all (N=21) consultant cardiologists, resident specialists in cardiology, higher specialist trainees and basic specialist trainees at the Department of Cardiology at MDH. Participants were informed that participation was voluntary and that by completing the questionnaire they were providing consent.

2.4.5. Data Analysis and Harmonisation of Definitions

The definitions chosen by the cardiologists who completed the questionnaire were extracted and analysed. A harmonised definition for each SAMS terminology, myalgia, myopathy and rhabdomyolysis, was compiled using the definitions chosen by the cardiologists.

2.4.6. Focus Group Discussion

The harmonised definitions were proposed to an interprofessional focus group composed of two consultant cardiologists (including the Chair of the Department of Cardiology at MDH), a general practitioner, a clinical pharmacist, a community pharmacist, and a pharmacist working in the regulatory sciences sector in the pharmacovigilance area, and discussed. The focus group discussion was held online using the Zoom® platform in April 2023 with a duration of 1 hour.

A presentation was created using Microsoft® PowerPoint 365 (Appendix 2). The presentation included the results obtained from the questionnaire regarding the various definitions of myalgia, myopathy and rhabdomyolysis used by the cardiologists in practice, as well as a harmonised definition for each of the SAMS terminologies proposed by the researcher. Participants were requested to discuss the proposed definitions and to provide feedback. The definitions were modified to reflect the feedback given by the participants and consensus on all definitions was obtained.

2.4.7. Dissemination of Harmonised Definitions

A document containing the harmonised definitions, and criteria for physicians to consider when using the definitions as a disclaimer, as suggested during the focus group discussion, was developed (Appendix 3). This document was sent to the Chair of the Department of Cardiology by email for final approval, and was forwarded by the Chair to cardiologists as a point of reference.

Chapter 3:

Results

3.1. Part 1: Results of cohort study

A total of 250 patients were recruited; 125 patients underwent coronary angiography only and 125 patients underwent PCI. There was no statistically significant difference between populations ($p>0.05$), hence the sample was analysed as one cohort (N=250).

3.1.1. Patient Characteristics

Most patients (75%, n=187) were male and 25% (n=63) were female. With respect to age, most patients were between 65-74 years (39%, n=98) (Figure 3.1). Most patients had primary education level (40%, n=99), followed by secondary (38%, n=95), post-graduate (11%, n=27), graduate (8%, n =21) and post-secondary education (3%, n=8). Most patients were retired (56%, n=140), followed by employed (39%, n=97) and unemployed (5%, n=13).

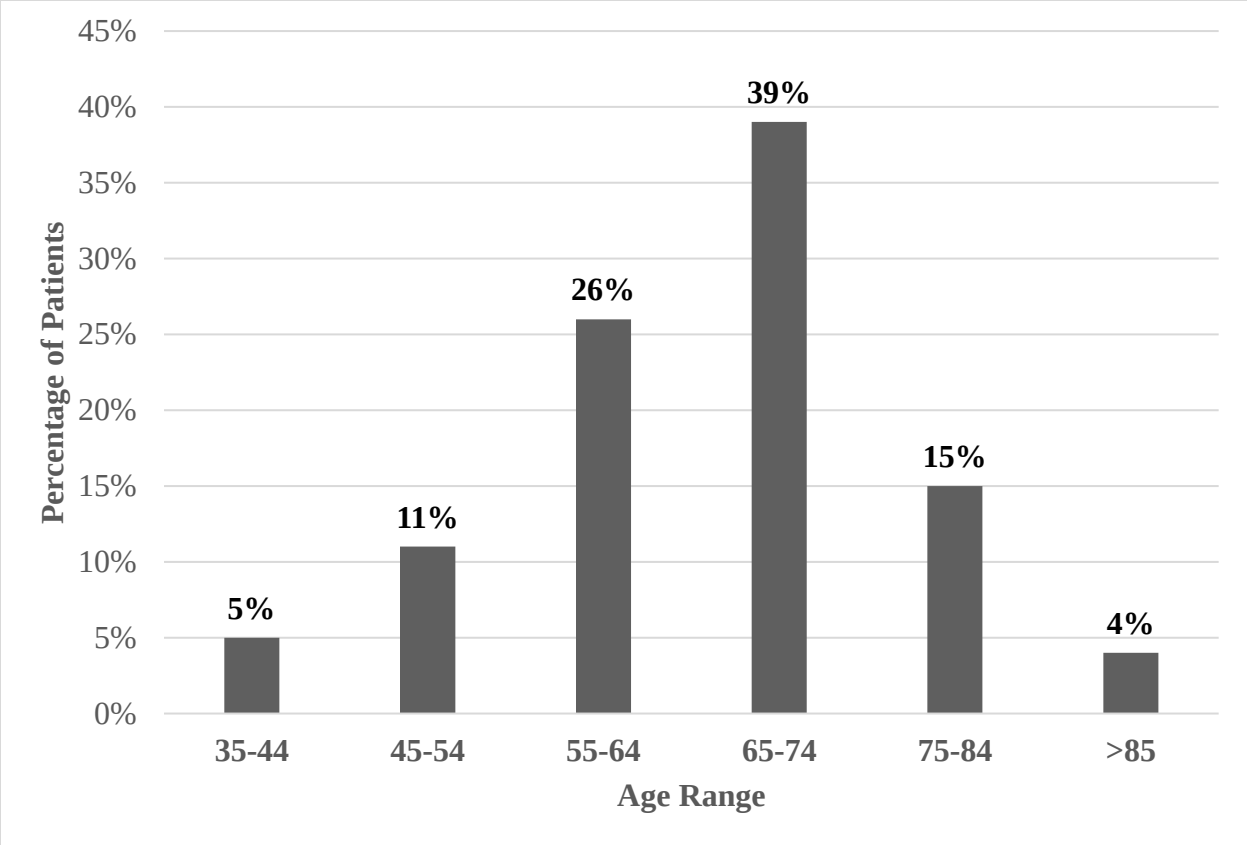

Figure 3.1: Patient Age Range (N=250)

With regards to previous cardiovascular events, 11% (n=28) of the total population had a history of acute coronary syndrome, and 3 patients had a previous cerebrovascular accident. Previous revascularisation occurred in 15% (n=38) of the total population, with 31 patients having had a previous PCI and 6 patients had coronary artery bypass graft surgery. From the 125 patients treated with PCI at time of recruitment, the most common reason for revascularisation was myocardial infarction (74%, n=93), followed by stable angina (16%, n=20) and unstable angina (10% n=12). The mean number of stents deployed was 2 (range 1 to 4), and the mean number of culprit lesions was 1 (range 1 to 3).

With regards to cardiac risk factors, most patients were obese (39%, n=97), followed by pre-obese (32%, n=80), normal weight (26%, n=66) and underweight (3%, n=7). The mean BMI was 28.8 kg/m^2 (range 16.3-49.6 kg/m^2). At time of recruitment, most patients (66%, n=165) were current smokers, with 38% (n=62) smoking between 11-20 cigarettes per day, 34% (n=57) smoking more than 20 cigarettes per day and 28% (n=46) smoking less than 10 per day. In terms of alcohol consumption, 45% of patients (n=112) reported that they do not consume any alcohol, 38% (n=94) socially or during weekends, and 18% (n=44) drank alcohol daily.

With respect to investigations, only 3 of the 250 patients had documented CK levels with a mean of 252 U/L (range 78 – 571 U/L). Of these, 1 patient had an elevated CK level (571 U/L). The mean values of the lipid profile parameters of the study population can be seen in Table 3.1.

Table 3.1: Lipid Profile (N=250)

Parameter (Reference range in mmol/L)	**Mean** in mmol/L	**Range** in mmol/L
Total Cholesterol (2.00 - 5.00)	4.57	1.86 - 9.52
LDL-C (<2.0)	2.76	0.57 – 6.87
HDL-C (0.90 – 1.45)	1.33	0.41 – 13.60
Triglycerides (0.10 - 2.26)	1.84	0.13 – 16.0

Hypertension was the most common comorbidity (80%, n=199) (Figure 3.2).

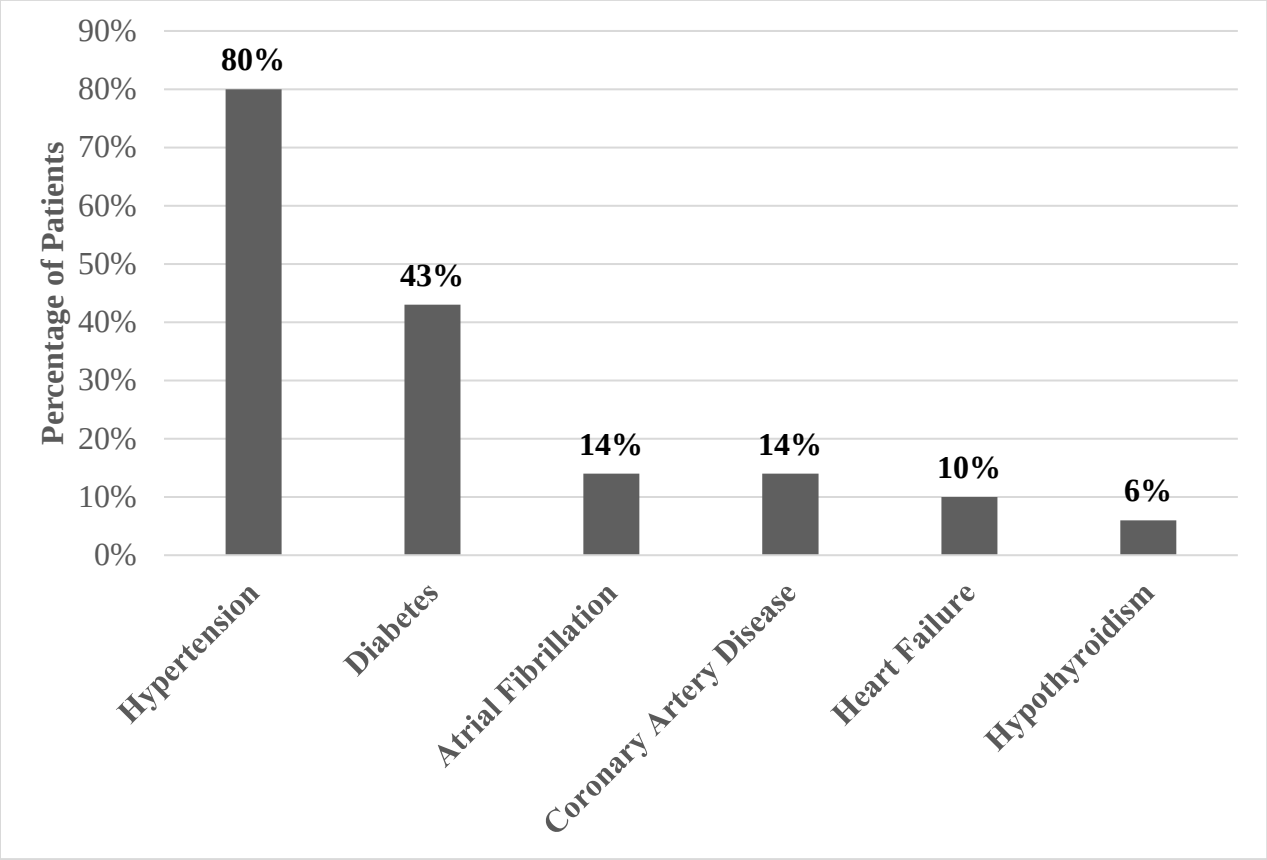

Figure 3.2: Patient Comorbidities (N=250)

The mean number of different medications taken by patients was 7 (range 1-15), and the mean number of different medication doses per day was 9 (range 1-27). The most common classes of medications can be seen in Table 3.2.

Table 3.2: Classes of Medications (N=250)

Class of Medication	Percentage of Patients
Drugs acting on the renin-angiotensin-aldosterone system	77%
Antiplatelets	56%
Proton Pump Inhibitors	47%
Beta-Blockers	41%
Diuretics	38%
Oral hypoglycaemic agents	36%
Calcium Channel Blockers	19%
Anticoagulants	16%
Nitrates	12%
Insulin	9%

3.1.2. Statin Therapy Prescribed

Most patients were prescribed atorvastatin (65%, n=163) (Figure 3.3). As regards statin intensity, most patients (66%, n=166) were prescribed a high intensity statin regimen (atorvastatin 40-80mg or rosuvastatin 20-40mg), 32% (n=80) moderate intensity (atorvastatin 10-20mg, rosuvastatin 5-10mg, or simvastatin 20-40mg), and 2% (n=4) low intensity (simvastatin 10mg).

The majority of patients (99%, n=248) stated that their physician advised them to take the statin at bedtime, while 2 patients reported that they were prescribed a twice daily dose.

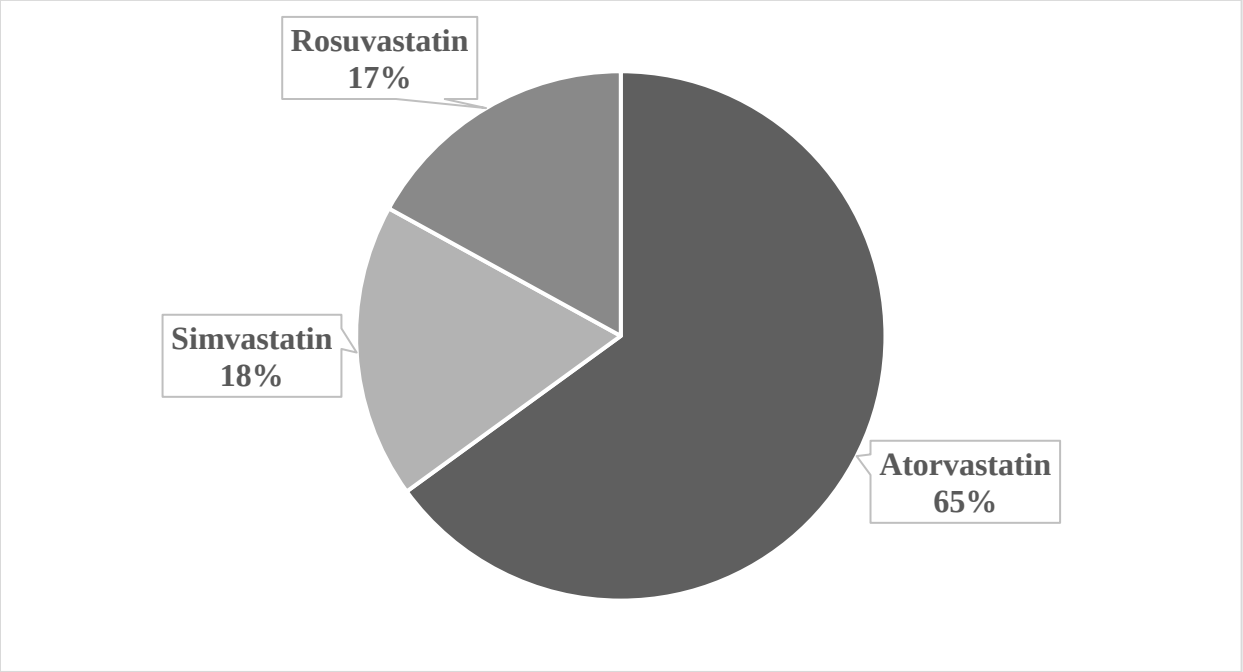

Figure 3.3: Statin Prescribed (N=250)

3.1.3. Patient Perspectives Towards Treatment

Most patients (91%, n=228) were aware of why they were prescribed a statin. These patients reported the following reasons; for high cholesterol (85%, n=197), for prevention of cardiac episodes (11%, n=24), diabetes (3%, n=7), and due to cigarette smoking (1%, n=3).

From the total population, 84% (n=211) obtain their medications for free through the Schedule V scheme provided by the Ministry for Health. Of these patients, 17% (n=35) reported that they would not purchase the statin if it was no longer available for free. Reasons given by these patients

were: finances (89%, n=31), perception that statin therapy is not useful (6%, n=2), are taking too many medicines (3%, n=1), and patients experience pain when taking statin therapy (3%, n=1).

Most patients reported taking the statin everyday (91%, n=227), followed by whenever they remember (6%, n=16), every other day (2%, n=5), and when they eat high fat foods (1%, n=2). Patients reported that they take the statin before bedtime (89%, n=222), when they remember (5%, n=13), in the afternoon (3%, n=7), in the morning (2%, n=5), and twice daily (1%, n=3). Ninety-eight percent (n=244) of patients reported that they collect or buy the statin on time.

3.14. Adherence to Statin Therapy

Forty-one percent of patients (n=103) ‘sometimes’ or ‘frequently’ miss a dose (Figure 3.4). The reason mostly attributed to missing a statin dose was forgetfulness (73%, n=183), followed by occurrence of SAMS after taking the statin (9%, n=22), felt good and did not think s/he needed to take them (6%, n=15), medications finished (5%, n=13), and too many medicines (4%, n=9).

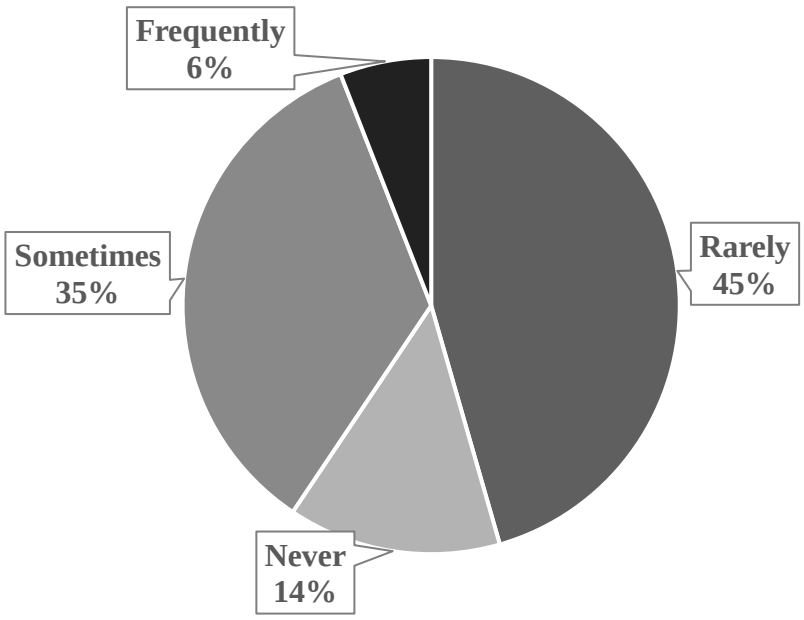

Figure 3.4: Frequency of missing a statin dose (N=250)

Sixteen percent of patients (n=41) considered stopping the statin without consulting a healthcare professional. The attributed reasons were painful adverse effects (28%, n=11), too many medicines (23%, n=9), and financial difficulties (18%, n=7).

Most (70%, n=176) patients remind their physicians that they are taking a statin and check with their community pharmacist if any medication that they are about to purchase interacts with the statin they are taking (74%, n=184). Forty-six percent (n=114) of patients never visit a physician for a medication review, while 2% (n=6) ask the physician to review their medications every time they visit for a consultation (Figure 3.5).

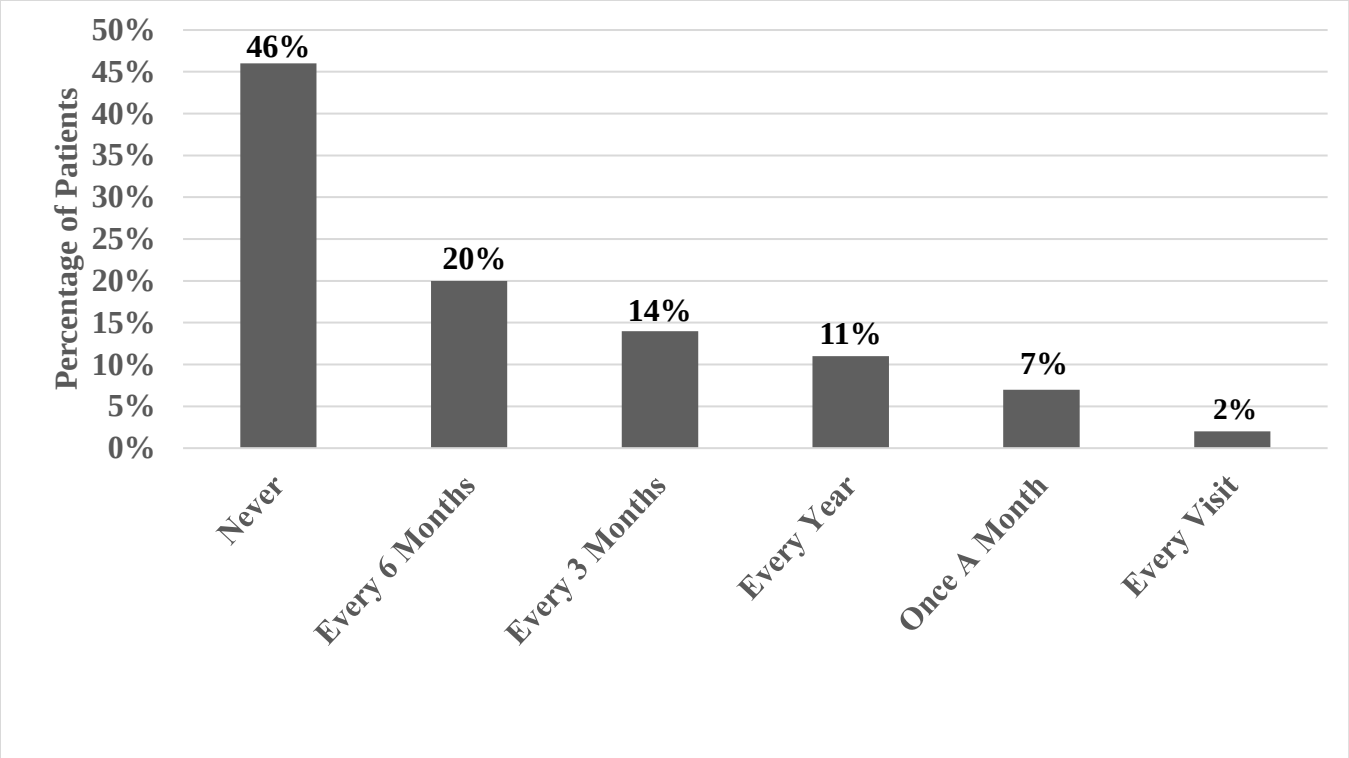

Figure 3.5: Frequency of visiting a physician for a medication review (N=250)

When going on holiday, 93% (n=232) of patients always take the statin with them, 3% (n=8) frequently, 2.4% (n=6) never, and 1.6% (n=4) sometimes. The reasons attributed to not taking the statin with them on holiday were forgetfulness (67%, n=12), and extra weight (33%, n=6).

3.1.5. Occurrence of Statin Associated Muscle Symptoms

Seventy of the 250 patients (28%, n=70) reported experiencing SAMS. Sixty-six percent (n=46) of the patients with self-reported SAMS experienced one symptom, 31% (n=22) reported experiencing two symptoms, while 3% (n=2) reported experiencing three symptoms. Muscle pain

(myalgia) was the most common complaint (56%, n=54) (Figure 3.6). The patient with documented elevated CK level did not report experiencing SAMS.

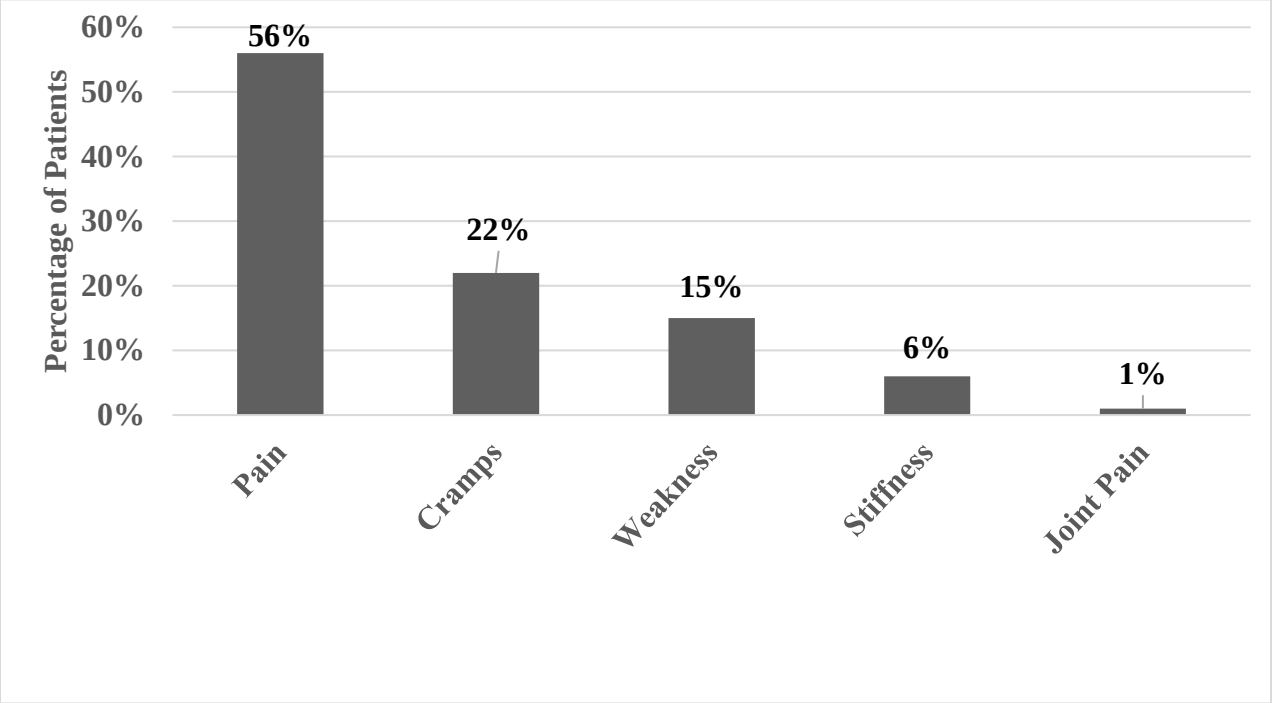

Figure 3.6: Frequency of Symptom Complaint (n=70)

Of the 70 patients with self-reported SAMS, 56% (n=39) of patients were taking atorvastatin, 33% (n=23) simvastatin, and 11% (n=8) rosuvastatin. In the context of the whole population, 23 of the 46 (50%) patients receiving simvastatin reported experiencing SAMS, 39 of the 163 (24%) patients receiving atorvastatin reported experiencing SAMS, and 8 of the 42 (19%) patients receiving rosuvastatin reported experiencing SAMS, indicating the simvastatin was the statin mostly implicated with SAMS.

Of the 70 patients with self-reported SAMS, most patients experience these symptoms every day (64%, n=45) (Figure 3.7).

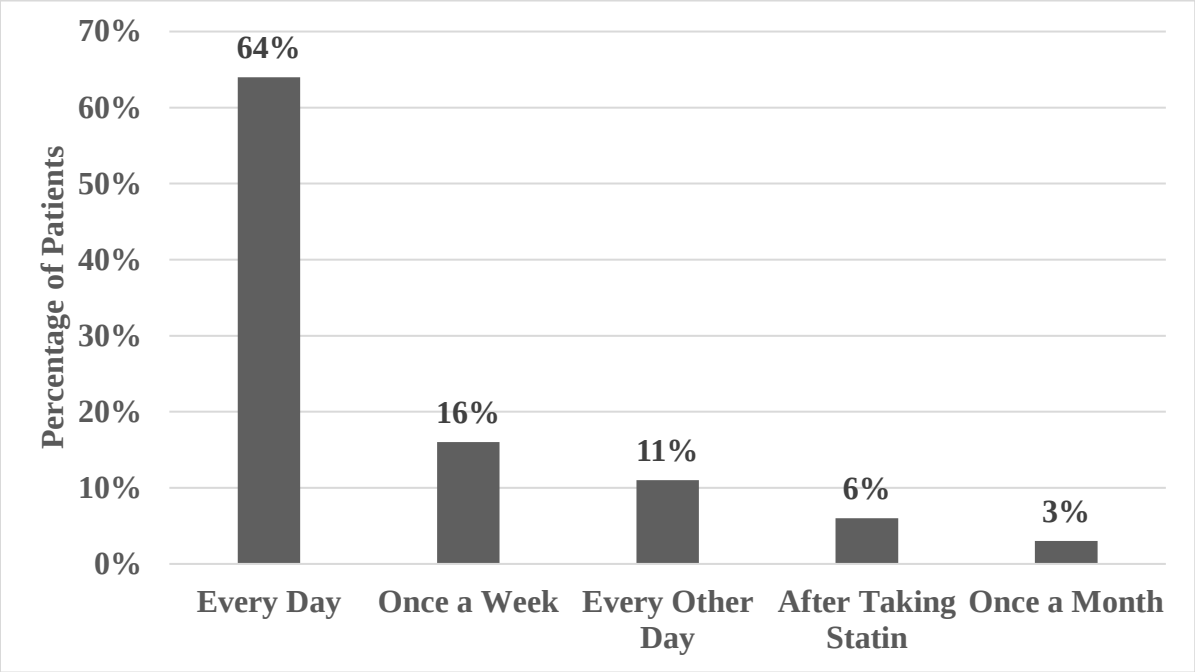

Figure 3.7: Frequency of Symptom Occurrence (n=70)

The time in which almost all patients experience SAMS was at night (96% n=67), followed by afternoon (3%, n=2) and morning (1%, n=1). The season in which most patients report an increase in experiencing these symptoms was winter (66%, n=46), followed by summer (16%, n=11), autumn (11%, n=8) and spring (7%, n=5). The mean perceived pain score reported by patients was 6 out of 10 (range 1-10) (Figure 3.8).

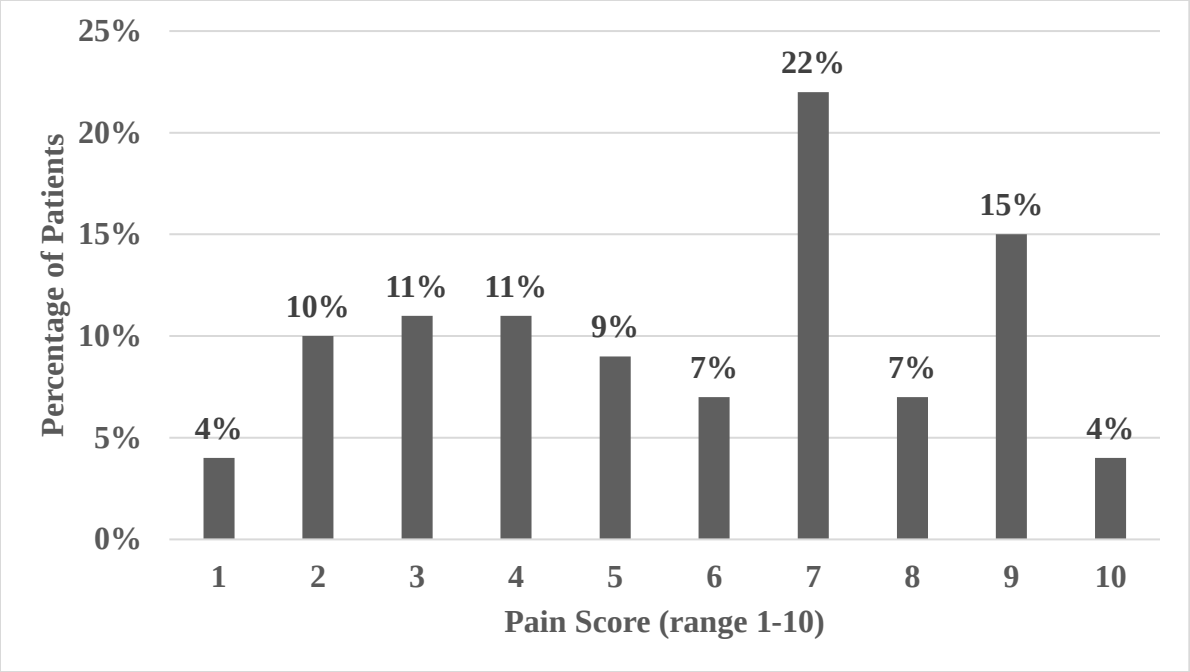

Figure 3.8: Frequency of Perceived Pain Score (n= 70)

3.1.6. Impact of Statin Associated Muscle Symptoms

Most patients stated that the occurrence of SAMS made them feel tired requiring rest (87%, n=61) (Table 3.3). Twelve percent (n=8) of the 70 patients reported a reduced overall quality of life with the occurrence of these symptoms. Most patients (96%, n=67) stated that these symptoms are relieved by rest.

Table 3.3: Impact of SAMS on patient quality of life (n=70)

Complaint	Percentage of Patients (%)
Feel tired requiring rest	87
Disturbed sleep	60
Drains my energy	46
Hinders my ability to exercise	10
Reduced ability to concentrate on work	3

3.1.7. Management of Statin Associated Muscle Symptoms

From the patients with self-reported SAMS, 80% (n=56) reported the occurrence of these symptoms to their physician. Most patients (36%, n=20) had a change in statin (Table 3.4). Most patients had a change from simvastatin to atorvastatin (55%, n=11), atorvastatin to rosuvastatin (35%, n=7), atorvastatin to simvastatin (5%, n=1), and simvastatin to rosuvastatin (5%, n=1)

Table 3.4: Management of SAMS (n=56)

Management Strategy	Number of Patients
Change in statin	20
Reported no change	13
Reduction in dose	9
Change in timing	1
Told to avoid grapefruit and increase fluid intake	1

Forty percent (n=28) of patients with self-reported SAMS stated that they avoid certain foods to reduce the chances of these symptoms from occurring; 19 avoid grapefruit and 9 patients stated that they avoid all citrus fruits.

No statistically significant difference ($p>0.05$) between frequency of missing a statin dose and the following variables was observed; gender, age, education level, employment, history of CV events, previous revascularisation, smoking history, alcohol consumption, number of medications taken, number of daily medication doses, whether patients obtain their medicines for free, frequency of visiting a physician for a medication review and occurrence of SAMS.

3.2. Results of Harmonisation of Definitions and Statin Associated Muscle Symptoms Assessment

Nine cardiologists completed the online questionnaire; consultant cardiologists (n=7), resident specialist in cardiology (n=1), and higher specialist trainee in cardiology (n=1).

3.2.1. Compiled Definitions of Statin Associated Muscle Symptoms Terminologies

Tables 3.5 to 3.7 show the definitions compiled for myalgia, myopathy, and rhabdomyolysis respectively, and the number of cardiologists using each definition in clinical practice. Definitions for myalgia (n=8), myopathy (n=8) and rhabdomyolysis (n=7) were identified from literature. The definitions were published between 2012 and 2020.

Table 3.5: Definitions of myalgia from literature and use in clinical practice

Definition (Reference)	**Number of cardiologists using definition in clinical practice (N=9)**
Diagnosed if all the following occurred: (1) New or increased muscle pain, cramps or aching not associated with exercise; (2) symptoms persisted for at least 2 weeks; (3) symptoms resolved within 2 weeks of stopping the drug; and (4) symptoms reoccurred within 4 weeks of restarting the drug (Parker *et al,* 2012)	5
Mild muscle complaints; Can occur with or without CK elevation (Parker and Thompson, 2013)	2
Muscle ache or weakness without CK elevation (Hu *et al.*, 2012)	1
Muscle pain or aching (Stroes *et al.*, 2015)	1
Unexplained muscle discomfort often described as ‘‘flu-like’’ symptoms with normal CK level; spectrum of myalgia complaints includes muscle aches, soreness, stiffness, tenderness, and cramps with or shortly after exercise (not nocturnal cramping) (Rosenson *et al.*, 2014)	0
Weakness and/or cramps without significant elevation in blood creatine kinase (CK) levels (Hashni *et al.*, 2018)	0
Muscle pain (Selva O’ Callaghan *et al.*, 2018)	0
Muscle pain or aches (Newman *et al.*, 2019)	0

Table 3.6: Compiled Definitions of Myopathy and Use in Clinical Practice

Definition (Reference)	**Number of cardiologists using definition in clinical practice (N=9)**
General term referring to any disease of muscles (Hu *et al.*, 2012)	3
Pain that is typically generalised and proximal and there may be muscle tenderness and weakness and with CK elevations 10x ULN (Stroes *et al.*, 2015)	3
Manifested as muscle pain, tenderness, or weakness with CK >10X ULN[4])	2
Unexplained muscle pain or weakness accompanied by CK concentrations >10 times ULN (Newman *et al.*, 2019)	1
Myositis or rhabdomyolysis and require CK levels to be >10X ULN (Parker *et al.*, 2012)	0
Presence of symptoms of myalgia and >10X ULN (Mohassel and Mammen, 2013)	0
Muscle weakness not attributed to pain and not necessarily associated with elevated CK (Ronsenson *et al.*, 2014)	0

[4] Electronic medicines compendium (emc). Zocor 20mg film-coated tablets - Summary of Product Characteristics (SmPC) [Internet]. UK: Datapharm Ltd; 2018 [cited 2022 Dec 14]. Available from: https://www.medicines.org.uk/emc/product/7791/smpc

Table 3.7: Compiled Definitions of Rhabdomyolysis and Use in Clinical Practice

Definition (Reference)	**Number of cardiologists using definition in clinical practice (N=9)**
Acute and massive lysis of skeletal muscle cells with significant shifts in electrolytes in the extracellular fluid and release of large amounts of CK and myoglobin into the blood plasma (Ronsenson *et al.*, 2014)	2
Severe form of myopathy with CK typically >40x ULN which can cause myoglobinuria and acute renal failure (Newman *et al.*, 2019)	2
Potentially life-threatening condition characterised by markedly elevated CK levels (>10 times ULN), myoglobinaemia and myoglobinuria which may lead to renal failure[5]	2
Muscle symptoms with significant CK elevation (typically >10 X ULN), and creatinine elevation usually with brown urine and urinary myoglobin (Hu *et al.*, 2012)	1
Severe form of muscle damage associated with very high CK levels, myoglobinaemia and/or myoglobinuria with an increased risk of renal failure and CK >40 X ULN (Stroes *et al.*, 2015)	1
High CK concentrations (>100-fold the ULN), myoglobinuria and renal impairment due to acute tubular necrosis caused by myoglobin precipitation in the renal tubules (Selva O'Callaghan *et al.*, 2018)	1
Clinical syndrome of acute muscle weakness, myalgia, and muscle swelling combined with a CK cut-off value of > 1000 IU/L or CK > 5x ULN (Stahl *et al.*, 2020)	0

[5] Electronic medicines compendium (emc). Lipitor 40mg film-coated tablets - Summary of Product Characteristics (SmPC) [Internet]. UK: Datapharm Ltd; 2018 [cited 2022 Dec 14]. Available from: https://www.medicines.org.uk/emc/product/5238/smpc#gref

A harmonised definition for the each of the SAMS terminologies was compiled and proposed for discussion in the focus group. Amendments were suggested only for the definition of myalgia. The amendments made were the addition of reducing the dose or switching to an alternative agent in point 3, and the removal of point 4 from the definition (Table 3.8). The harmonised definitions were disseminated to cardiologists (Appendix 3).

Table 3.8: Harmonised Definitions for SAMS Terminologies

SAMS Terminology	Definition presented to focus group	Definition after focus group discussion
Myalgia	Diagnosed if all of the following occurred: (1) New or increased muscle pain, cramps or aching not associated with exercise; (2) symptoms persisted for at least 2 weeks; (3) symptoms resolved within 2 weeks of stopping the drug; and (4) symptoms reoccurred within 4 weeks of restarting the drug' (Parker *et al.* 2012).	Diagnosed if all the following occurred: (1) New or increased muscle pain, cramps or aching not associated with exercise; (2) symptoms persisted for at least 2 weeks; (3) symptoms resolved within 2 weeks of stopping the drug, reducing the dose or switching to an alternative agent within the same therapeutic class.
Myopathy	A term relating to any disease of the muscle which presents with a CK level 10X ULN, pain that is typically generalised and proximal, and may also present with muscle tenderness and weakness.	A term relating to any disease of the muscle which presents with a CK level 10X ULN, pain that is typically generalised and proximal, and may also present with muscle tenderness and weakness.
Rhabdomyolysis	A potentially life-threatening condition that presents with acute and massive lysis of skeletal muscle cells, significant shifts in electrolytes in the extracellular fluid, CK level >40X ULN, myoglobinuria and potential acute renal failure.	A potentially life-threatening condition that presents with acute and massive lysis of skeletal muscle cells, significant shifts in electrolytes in the extracellular fluid, CK level >40X ULN, myoglobinuria and potential acute renal failure.

3.2.2. Practicality of Statin Associated Muscle Symptoms Clinical Index Tool

When asked about the likelihood of using the SAMS-CI tool in their daily practice, 4 of the 9 cardiologists stated they were ‘likely’ to use this tool, 3 ‘neither likely or unlikely’, and 2 marked ‘unlikely’. When asked about the likelihood of using a modified version of this tool, 1 cardiologist stated, ‘very likely’, 4 stated ‘likely’, 2 ‘neither likely or unlikely’, and 2 ‘unlikely’. The main reasons given by the cardiologists who chose ‘unlikely’ were that they still consider experience and judgement to be better tools, and that the tool was too cumbersome to be used in a clinical setting.

Chapter 4:

Discussion

To the researcher's best knowledge, this is the first local study which assessed experience with statin therapy in patients presenting to the cardiac catheterisation laboratory for angiography or PCI, and proposed harmonised the definitions for the SAMS terminologies myalgia, myopathy, and rhabdomyolysis.

4.1 Patient Experience with Statin Therapy and Barriers to Adherence

Findings from the present study showed that 41% of patients undergoing cardiac procedures and receiving statin therapy sometimes or frequently miss a dose. This result is similar to findings of other international studies carried out in cardiac patients and patients with a history of cerebrovascular accident, which found that non-adherence to statin therapy ranged between 33% and 49% (Chung *et al.*, 2018; Morotti *et al.*, 2019; Talic *et al.* 2022). The most common reason for missing a statin dose in the present study (73%) was attributed to forgetfulness. A study carried out in the United States also identified forgetfulness as a reason for non-adherence, such that 9% of the patients completely stopped refilling their statin prescriptions due to forgetfulness (Fung *et al.*, 2018). A 2020 position paper by the ESC identified cognitive issues as a main barrier to adherence, such that caregivers were recommended to help in improving medication adherence in patients taking statins (Drexel *et al*., 2020).

The majority of patients in the present study who reported sometimes or frequently missing a statin dose were prescribed a low to moderate intensity statin (56%, n=57). This finding correlates with results of other studies carried out in the United States and Australia which found that

discontinuation to statin therapy is more likely to occur in patients with low to moderate intensity statins, rather than those prescribed high intensity statins (Brown and Watson, 2018; Talic *et al.*, 2022).

The mean LDL-C value of the cohort in the present study was 2.76mmol/L. This is significantly higher than the target value set by the ESC guidelines for very high risk and high-risk patients which are <1.4mmol/L and <1.8mmol/L respectively (Mach *et al.*, 2019; Visseren *et al.*, 2022). Recent studies carried out in the United Kingdom also found that the majority of high-risk patients fail to meet their LDL-C targets, which the authors attributed to non-adherence to statin therapy (Drexel *et al.*, 2020; Reynolds *et al.*, 2021). The lack of adherence to statin therapy and less than optimal decrease in LDL-C increases patient risk for CV events (Rosenson *et al.*, 2014; Stroes *et al.*, 2015; Drexel *et al.*, 2020).

In the present study, 15% of patients who obtain their medications for free would not purchase their statins if they were no longer available for free, indicating that finances may be a barrier to adherence. Furthermore, 18% of patients who considered stopping their statin medications without consulting a healthcare professional, attributed this to finance issues. International studies carried out in the United Kingdom and in the United States also identified finances as a barrier to statin adherence for patients who had to purchase their medications (Marcum *et al.*, 2013; Fung *et al.*, 2018; Ju *et al.*, 2018; Grover *et al.*, 2020)

Another potential barrier to adherence that was identified in the present study is that 46% of patients never visit a physician or pharmacist for a medication review, and 30% of patients do not remind their physician that they are taking statins when visiting the physician for other complaints. Furthermore, 26% of patients do not check with a pharmacist if any of the medications or supplements they are purchasing have the potential to interact with the statin. Locally, medication use reviews (MURs) in community pharmacy have been recently implemented in 2023, where pharmacists are encouraged to carry out a medication review for each patient registered with the pharmacy collecting medication through the Schedule V. Pharmacists are encouraged to carry out MURs every 6 months for each patient to ensure that any complaints or problems that the patient may encounter with treatment are identified early. A study in Singapore identified that medication reviews by pharmacists improved patient adherence to chronic medications, and patient knowledge on their treatment, ensuring that patients understand the repercussions of discontinuing treatment (Goh *et al.*, 2014). A retrospective study carried out in the United States by Castelli *et al.*, (2018) found that pharmacists were able to identify and work with clinicians to address medication therapy problems. Furthermore, the study identified that pharmacist interventions had a 98% acceptance rate by physicians (Castelli *et al*, 2018). A study carried out in Canada in 2019 found that patients are receptive to having a medication review carried out by pharmacists, and that patients with chronic conditions such as dyslipidaemias, cardiovascular conditions and diabetes tend to have improved outcomes from these services (Dolovich *et al.*, 2019). A study carried out in Denmark in 2022 identified that interprofessional medication reviews between physicians and pharmacists reduced the chances for adverse drug reactions and drug-drug interactions (Fransden *et al.*, 2022).

SAMS were identified in the present study as a barrier to adherence to statin therapy since 28% of the total population reported experiencing SAMS, 9% reported missing doses due to painful adverse effects when taking a statin dose, and 4% considered stopping the statin due to the occurrence of these symptoms. Furthermore, 12% of patients with self-reported SAMS reported an overall negative impact on their quality of life, and 60% of patients reported disturbed sleep, reduced ability to exercise (10%) and decreased ability to concentrate on work (3%). These results are comparable to findings from other international studies carried out in the United Kingdom, the United States, and Europe, which identified SAMS as one of the main barriers for statin discontinuation and reduced adherence (Chowdry *et al.*, 2013; Stroes *et al.*, 2015; Rosenson *et al.*, 2017). Patients who experienced SAMS in the present study, reported an overall reduction in productivity, with the occurrence of these symptoms draining their energy and requiring rest, and resulting in patients having to stop and rest until the symptoms subside. Fung *et al.* (2018) found that the reduction in productivity due to SAMS is are a barrier to adherence since patients are reluctant to risk not being able to carry out their daily activities.

In the present study, myalgia was the most reported symptom by patients with self-reported SAMS. From the results obtained, simvastatin was the statin mostly implicated with the occurrence of SAMS, since half of the patients taking simvastatin in the study cohort self-reported experiencing SAMS. Taylor and Thompson (2018) also found that simvastatin was the statin mostly responsible for the occurrence of myalgia. Similarly, a recent meta-analysis carried out in 2022 identified simvastatin as the statin with the highest occurrence of SAMS (Reith *et al.*, 2022).

The GAUSS-2 trial identified that myalgia was the most reported symptom with 80% of patients in the trial reporting muscle pain (Taylor and Thompson, 2018). This is supported by other international studies carried out in the United States, that identified myalgia as the symptom that is most reported by patients on statin therapy (Hu *et al.*, 2012; Rosenson *et al.*, 2017; Hashni *et al.*, 2018; Newman *et al.*, 2019). Other symptoms reported in the present study were muscle cramps, muscle weakness, muscle stiffness, and joint pain. This demonstrates the highly heterogenous presentation of SAMS. Studies carried out in the United States (Hashni *et al.*, 2018) and Greece (Rallidis *et al.*, 2019) also identified that the presentation of SAMS is highly heterogenous and is very difficult to standardise between each patient.

4.2. Harmonisation of Statin Associated Muscle Symptoms Definitions to improve diagnosis and management

Findings from the present study showed that cardiologists in Malta use different definitions for myalgia, myopathy, and rhabdomyolysis in clinical practice. This finding is concordant with findings from other studies carried out in the United States and Poland which suggest that standardisation of the definitions of SAMS terminologies is lacking internationally (Stroes *et al.*, 2015; Banach *et al.*, 2016; Rosenson *et al.*, 2017). This lack of standardisation in definitions may result in patients being diagnosed with SAMS inappropriately, and have their statin medication stopped prematurely. A meta-analysis carried out in 2022 identified that complete statin intolerance is overestimated, and that diagnosis of statin intolerance should be based on very careful assessment to reduce the risk of unnecessarily stopping lipid lowering therapy (Bytyci *et*

al., 2022). The present study proposed harmonised definitions of SAMS terminologies to potentially improve the identification, diagnosis, and management of SAMS by cardiologists.

In Malta, presently, for a patient to be entitled to rosuvastatin for free from the Schedule V scheme, the patient must show an inadequate response in LDL-C reduction with atorvastatin 80mg daily. Due to this situation, two participants in the focus group discussion, suggested to modify the definition of myalgia to include a reduction in dose and switching to an alternative agent within the same therapeutic class. The participants suggested that this definition for defining the occurrence of statin induced myalgia could potentially be used to help change the current entitlement protocol and advocate for rosuvastatin to be available for free in patients whom atorvastatin results in SAMS. A suggestion from the focus group discussion was that patients could purchase rosuvastatin and use it for trail period of 3 months, and if successful the patient would be entitled to acquiring this medication for free from Schedule V.

A disclaimer as suggested by the focus group was provided with the harmonised definitions of SAMS advising cardiologists that prior to using the definitions as a reference point in the diagnosis of SAMS, all other possible sources for the muscle symptoms should be ruled out. Physicians were provided with a list of other common causes for muscle symptoms which include, but are not limited to, recent physical exertion, physical trauma, changes in exercise pattern, hypothyroidism, rheumatoid arthritis, some active infections, fibromyalgia, underlying muscle disease or drug interactions with statins (Rosenson *et al*, 2017; Drexel *et a*l, 2020; Ruscica *et al*, 2022).

In 23% of patients who reported the occurrence of SAMS to their physician, patients reported that nothing was done to address their symptoms. Cardiologists in the present study reported that they have no standardised guidelines to follow to guide patients in the best way possible when managing SAMS, and management is usually based on their experience. A study by Rosenson *et al.*, (2017) identified the need for standardisation and aimed to standardise the way SAMS are diagnosed by developing a tool that could be used by clinicians in practice. Most cardiologist in the present study perceived the tool by Rosenson *et al.*, (2017) as too cumbersome and time consuming to be applied to local practice, however are open to using a modified version of the tool. The harmonised definitions of SAMS terminologies developed are the first step in facilitating standardised identification and management of SAMS, and further work is warranted.

4.3. Limitations

A limitation of the present study is patient self-reporting, particularly with respect to SAMS. Patients may incorrectly attribute muscle symptoms from other causes to the statin, which may impact on the reported prevalence of SAMS. Hospital records were checked for patients with self-reported SAMS for verification of a document4ed SAMS diagnosis, however documentation for SAMS was very limited and was only found for 4 of the 70 patients. Furthermore, CK levels were only recorded for 3 of the 250 patients, and none of the patients with self-reported SAMS had CK levels evaluated, hence occurrence of SAMS could not be verified. Another limitation was that data on the duration of statin therapy was not available; this may have an inference on adherence and side-effects reporting. Reliability testing of the adherence questionnaire was not performed due to feasibility issues.

4.4. Recommendations for further study

Future work could include the updating, validation, feasibility testing and implementation of a modified version of the SAMS-CI tool that can be used by cardiologists and other physicians to support correct identification and management of SAMS.

Use and impact of the developed harmonised definitions of SAMS terminologies in practice is recommended to be assessed, and disseminated to other specialties that may encounter patients presenting with SAMS such as general medicine, rheumatology, family medicine, diabetes, orthopaedics, and neurology.

A tool that could be used to the determine the risk for patients to develop SAMS could be developed to possibly improve patient adherence by providing high risk patients with more frequent medication reviews to ensure that the occurrence of such symptoms does not lead to premature therapy discontinuation.

Other future work could include the implementation of pharmacist intervention at community level to identify patients at risk of statin non-adherence and discontinuation, and to identify patients in whom SAMS occur and may impact their daily lives. A framework could be developed to support and educate patients in whom adherence to statin therapy is not optimal, to reduce the risk of future CV events.

4.5. Conclusion

Most patients in this study reported ‘rarely’ missing a statin dose, however 41% reported skipping doses indicating sub-optimal adherence to statin therapy. Most patients failed to achieve the target LDL-C goals which may be attributed to adherence issues. SAMS were reported in the cohort studied (28%) and impacted patient quality of life. Regular medication review of patients on statins by pharmacists in collaboration with physicians may improve patient experience and therapy adherence. Data indicating duration of statin therapy was not available and may have inference on adherence and side-effects reporting. Harmonised definitions of SAMS terminologies may support cardiologists in the appropriate identification, diagnosis and management of SAMS to decrease the risk of unnecessary statin therapy discontinuation.

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List of Publications and Abstracts

Calleja JC, Wirth F, Xuereb RG, Azzopardi LM. PP20: Experience with statin therapy in patients undergoing cardiac procedures. *ESCP Spring Workshop, Antwerp, 20–21 April 2023.* International Journal of Clinical Pharmacy (IJCP). 2023; 45:795. doi: 10.1007/s11096-023-01599-5

Setting and Method: The study included 114 patients with a history of at least six months of type 2 diabetes mellitus, using at least one antidiabetic drug, and having an HbA1c level higher than 7%, who were admitted to a training and research hospital in Istanbul between 8 September 2021 and 2 September 2022. Their medication adherence was measured using the Morisky–Green–Levine scale. Disease knowledge level was evaluated by 18 items self-structured questionnaire, and the patients' quality of life was measured by using Whoqol-bref which is currently scored in four domains and has no total score. Each domain has a score of a maximum of 20 points. Higher scores indicate better quality of life.
Main outcome measures: Medication adherence, quality of life and diabetes knowledge.
Results: The mean age of the patients participating in the study was 60.10 ± 9.89 years and 50% were female. Their mean diabetes age was 14.6 ± 7.35 years. Of them, 65.8% were low-educated patients. Mean HbA1c levels of patients 9.21 ± 0.16. Smoking history was 23.7% while alcohol consumption history was 7.9%. It was determined that 48.3% of the patients were non-adherent to their medication regimens. It was seen that the HbA1c value of non-adherent patients was higher than adherent patients (9.7% vs 8.1%, $p = 0.018$). Also, a weak correlation was found between medication adherence and the HbA1c value (r = ,298 $p < 0.01$). Median score of patients' knowledge level was 9.00 over 18 items. The quality of life of the patients was slightly above the average (physical health was 14.72, psychological was 15.22, social relations was 13.88, and the environment was 15.21). Although quality of life of the patients subdomain scores were slightly higher in adherent patients than in non-adherent patients, statistical significance was only seen in physical health ($p = 0.010$). It was seen that 38.8% of the patients did not come to their routine controls for their diabetes on time. Patients aged 65 and over were more adherent to their medications ($p = 0.018$).
Conclusion: It was concluded that the adherence and knowledge levels of type 2 diabetes patients were not very high, and their quality of life was slightly above average. We believe that clinical pharmacy services will contribute positively to the medication adherence, knowledge, and quality of life of type 2 diabetic patients.
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Disclosure of Interest
None Declared.

PP20 Experience with statin therapy in patients undergoing cardiac procedures

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Background and Objective: Statin associated muscle symptoms (SAMS) may lead to therapy non-adherence and discontinuation. The aim was to assess experience with statin therapy in patients undergoing cardiac procedures.
Setting and Method: The study was undertaken at the Cardiac Catheterisation Suite of an acute general hospital. A data collection sheet and questionnaire were developed and validated. Following ethics approval, patients who underwent coronary angiography (n = 125) or percutaneous coronary intervention (PCI) (n = 125) at time of recruitment and were on statin therapy were prospectively recruited by convenience sampling (July 2021-September 2022). The data collection sheet and questionnaire were completed using hospital records and patient interview respectively. Descriptive statistics were performed.
Main outcome measures: Statin therapy adherence; SAMS incidence, clinical presentation and impact.
Results: From the 250 patients (75% male, 39% between 65 and 74 years, 40% primary education level, 71% obese), 65% were prescribed atorvastatin, 18% simvastatin, 17% rosuvastatin. There was no significant difference in patient responses between coronary angiography and PCI ($p > 0.05$). Forty-one percent of patients 'sometimes' or 'frequently' skip a dose, mostly attributed to forgetfulness (47%). Sixteen percent of patients considered stopping treatment without consulting a healthcare professional, and 46% never visit a physician for medication review. Twenty-eight percent (n = 70) of patients self-reported SAMS. Patients reported a mean perceived pain score of 6 out of 10 (range 1–10). The most common symptom was myalgia (n = 54), and 29 of these patients were taking atorvastatin. Other symptoms were muscle weakness (n = 7), cramps (n = 6) and stiffness (n = 3). Patients stated that SAMS made them feel tired requiring rest (n = 61), reduced their ability to be active (n = 42) and disturbed their sleep (n = 42). From the 70 patients experiencing SAMS, 56 informed a physician and the statin was changed in 20 patients.
Conclusion: Adherence to statin therapy in the patient cohort studied is not optimal and patients reported SAMS which impacted their quality of life. Data indicating how long patients had been prescribed statin therapy was not available, and may have inference on adherence and side-effects reporting. Regular medication review of patients on statins by pharmacists in collaboration with physicians may improve patient experience and therapy adherence.
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Disclosure of Interest
None Declared.

PP23 Prescribing appropriateness and cost-analysis of mifepristone: an Italian women's hospital experience

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Background and Objective: In recent years, the birth control has become an important social theme connected to the personal freedom of women. According to Italian law, the main therapeutic indication of Mifepristone (MIF) is ongoing medical interruption of intrauterine pregnancy (IIP) in combination with prostaglandin analogues. To obtain access to MIF, the MD needs to fill-out a special drug request-form containing two sections: anamnestic patient's data and therapeutic indication.
Thus, Hospital Pharmacists on one hand evaluate prescription appropriateness, and on the other one they collect data to monitor patients receiving MIF. The aim of this work is to assess the MIF's prescribing trend of an Italian Women's Hospital and to perform a cost-analysis.
Design: It was conducted a retrospective observational study from January 2021 to December 2022, by considering all patients who received MIF therapy. For each patient, therapeutic indications and treatment costs were collected in an Excel datasheet thanks to the Pharmacy management software and then they were analyzed.
Results: The nominal drug request-form was introduced at the beginning of 2021. Throughout 2021, 128 MIF tablets have been prescribed: only 16 prescriptions (equal to 12.5%) were appropriate for IIP(6.25% of therapeutic abortion 6.25% of voluntary interruption of pregnancy (VIP)). Inappropriateness was of 87.5%. Throughout 2022, the total number of MIF prescriptions decreased to 115 (− 5.37%) with an increase in prescription appropriateness of 11.4%: 27 prescriptions (equal to 23.47%) were appropriate for IIP (9.80% for therapeutic abortion as fetal chromosomal abnormality, 13.72% for VIP). Inappropriateness was of 76.53%.Regarding the MIF costs,

Appendices

Appendix 1: Approvals from University of Malta Faculty of Medicine and Surgery Research Ethics Committee

L-Università ta' Malta

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

Tel: +356 2340 1879/1891/1167
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Ref No: FRECMDS_2021_135

6 July 2021

Jean Claude Calleja
3 St Joseph
Triq il- Gizi
SGN1061
San Gwann
Malta

Dear Mr Calleja,

With reference to your application submitted to the Faculty Research Ethics Committee in connection with your research entitled:

Adherence to Statin Therapy

The Faculty Research Ethics Committee is granting ethical approval for the above-mentioned application reviewed on 30 June 2021.

Yours sincerely,

Professor Pierre Mallia
Chairman
Faculty Research Ethics Committee

Name:

Jean Claude

Surname:

Calleja

Email:

jean.c.calleja.18@um.edu.mt

Submit New REDP Form

Draft/Submitted REDP Forms

Show 10 entries Search:

Application ID	Application Date	Project Title	Faculty	Status
MED-2022-00405	22/11/2022	Statin Associated Muscle Symptoms and Therapy Adherence	Faculty of Medicine & Surgery	Acknowledged

Appendix 2: Data Collection Tools

Data Collection Sheet

To be completed using CVIS and ISoft.

Those marked with * shall be completed through patient interview and are translated to Maltese.

Patient Study Number: _____

Section 1: Patient characteristics

Sex	○Male ○Female ○Other
Age (years)	○<35 ○35-44 ○45-54 ○55-64 ○65-74 ○75-84 ○≥85
Education Level* Livell ta' Edukazzjoni*	○Primary ○Secondary ○Post-Secondary ○Graduate ○Post-Graduate ○Primarja ○Sekondarja ○Post-Sekondarja ○Gradwat ○Post-Gradwat
Employment* Impjieg*	○Employed ○Unemployed ○Retired ○Impjegat ○Bla xogħol ○Irtirat
Most recent investigation/ intervention carried out at cardiac	○ Coronary Angiogram (Date: _____)

<table>
<tr><td>catheterisation laboratory</td><td>〇 PCI

(Date: _____)</td><td>Reason for PCI:
〇STEMI
〇NSTEMI
〇Unstable Angina
〇Stable Angina

Number of stents deployed:

Number of culprit lesions:

Which culprit lesion/s:</td></tr>
<tr><td rowspan="2">Previous

CV Events</td><td colspan="2">〇 Acute Coronary Syndrome (NSTEMI, STEMI, Unstable Angina)

(Date: _____)</td></tr>
<tr><td colspan="2">〇 Cerebrovascular Accident/Transient Ischaemic Attack

Date: _____)</td></tr>
<tr><td rowspan="2">Previous Revascularisation</td><td colspan="2">〇 Percutaneous Coronary Intervention

Date: _____)</td></tr>
<tr><td colspan="2">〇 Coronary Artery Bypass Graft (CABG) Surgery
Date: _____)</td></tr>
<tr><td>Cardiac Risk

Factors</td><td>Last Lipid Profile

Date: _____</td><td>TC: _____ (2.0-5.0 mmol/L)
TG: _____ (0.1-2.26mmol/L)
HDL: _____ (1.15-1.68F/0.9-1.45M mmol/L)
LDL: _____ (<2.0 mmol/L)</td></tr>
</table>

	BMI _____ Kg/m^2	BMI Category ○ 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)
	Smoking* Tipjip*	○≤10 cigarettes daily ○11-20 cigarettes daily ○ >20 cigarettes daily ○ Past smoker ○ Never smoked ○≤10 sigaretti kuljum ○11-20 sigaretti kuljum ○ >20 sigaretti kuljum ○ Kont inpejjep imma waqaft ○ Qatt ma pejjipt
	Alcohol Consumption* Konsum tal- Alkoħol*	○None ○Daily ○Weekends ○Socially (At an event/ on occasions only) ○Ma nixrobx ○Kuljum ○Fil- *weekend* ○F'xi attività/ waqt xi okkażżjoni

Comorbidities	Cardiovascular	○Heart Failure ○Hypertension ○Arrhythmia ○Coronary artery disease ○Other:
	Endocrinology	○Hypothyroidism ○Diabetes ○Other:

Section 2: Investigations

Glycated Haemoglobin	Date of Last HBA_{1c} Test:	_____% (4.7-6.4%)
Thyroid Function Tests	Date of Last Thyroid Panel:	TSH: _____ (0.3-3.0 mIU/L) Free T4: _____ (11-18 pmol/L) Free T3: _____ (2.3-4.1 pg/mL)
Muscle Markers	Date of Last CK Test:	_____ (26-192F/39-308M U/L)
Renal Function Tests	Date of last Renal Function Tests:	Cr: _____ (44-80F/62-106M µmol/L) eGFR: _____(>60ml/min/1.73m^2)
Liver Function Tests	Date of Last Liver Function Tests:	ALP: _____ (40-104F/40-129M U/L) ALT: _____ (5-33F/5-41M U/L) GGT: _____ (5-36F/8-61M U/L) Bilirubin: _____ (1.72-17.1µmol/L) Albumin: _____ (34-48g/L)

Section 3: Current Medications:

Generic Name	Dose	Dosage Regimen
○Simvastatin ○Atorvastatin ○Rosuvastatin		
○Ezetimibe		

Statin Adherence Questionnaire (English)

Patient Study Number: _____

Section 1: Adherence *(to be asked to ALL patients)*

1	Which medication to lower cholesterol (statin) are you currently taking and at what dose?	○Atorvastatin ○Rosuvastatin ○Simvastatin Dose:
2	Are you aware why you have been prescribed this medication?	○Yes ○No If Yes, why?
3	Do you obtain your cholesterol medication through the POYC scheme?	○Yes ○No
4	If the cholesterol medication was not available for free, would you buy it?	○Yes ○No If No, why?
5	How often do you take your cholesterol medication?	○Every day ○Every other day ○Once a week ○When I remember ○Never ○Other (specify):
6	At what time do you take your cholesterol medication?	○Morning ○Afternoon ○Before Bedtime ○When I remember ○Other (specify):

7	Do you always collect/buy your cholesterol medication on time?	○Yes ○No

8	How often do you miss a dose?	○Always ○Often ○Sometimes ○Rarely ○Never
9	If you have ever missed a dose, what was the reason?	○Forgot ○Ran out of statin ○Have too many medications ○Felt good and did not feel like taking the medication ○Misplaced your statin ○Experienced adverse effect ○Other (specify):
10	Have you ever considered stopping your cholesterol medication out of your own free will?	○Yes ○No If yes, Why?
11	When buying any medicine from the pharmacy, do you check if the medication can interact with your cholesterol medication?	○Yes ○No
12	When you visit your GP, do you remind him/her that you are taking medication to lower cholesterol ?	○Yes ○No
13	How often do you go to the GP for a medication review?	○Once a month ○Once every 3 months ○Once every 6 months ○Once a year ○Never ○Other(Specify):

14	When you go on holiday, do you take your cholesterol medication with you?	○Always ○Often ○Sometimes ○Rarely ○Never
		If not always, why?
15	Have you ever had any muscle symptoms that you suspect are from your cholesterol medication?	○Yes ○No

If yes continue with section 2.

If no, tell the patient that the questionnaire is finished and thank them for their time.

Section 2: Statin Associated Muscle Symptoms

This section is **to be filled out only if the patient has experienced any statin associated muscle symptoms**.

1	How would you describe your muscle symptoms?	○Muscle pain/aches ○Muscle Stiffness ○Muscle weakness ○Muscle Cramps ○Other:
2	How frequent do you experience these muscle symptoms?	○Every day ○Every other day ○Once a week ○Once a month ○Less than once a month ○Other (specify):
3	What time do you usually experience these symptoms?	○Morning ○Afternoon/evening ○Night
4	In which season do you feel you experience these symptoms more?	○Autumn ○Spring ○Summer ○Winter
5	Severity: On a scale of 1 to 10, 1 being the lowest and 10 being the highest, how painful are the muscle symptoms?	
6	Would you say these symptoms reduce your ability to be physically active or to exercise, or reduce productivity (missed days of work)	○Yes ○No If yes, how?
7	Would you say these symptoms disturb your sleep?	○Yes ○No If yes, how?
8	Would you say these symptoms make you feel tired and need to rest?	○Yes ○No

9	Would you say these symptoms are relieved when you rest?	○Yes ○No
10	Have you ever informed your doctor about the occurrence of these symptoms?	○Yes ○No If yes, did your doctor take any action? If yes, what action?
11	Do you try to avoid certain foods which may increase the occurrence of these symptoms?	○Yes ○No If yes, which foods do you avoid?
12	Would you say that these symptoms reduce your overall quality of life?	○Yes ○No If yes, how?

Tell the patient that the questionnaire is finished and thank them or their time.

Kwestjonarju dwar l-Aderenza mal-Mediċini tal-Kolesterol

Numru Tal- Pazjent fir-Riċerka: _____

Sezzjoni 1: Aderenza *(Din il-parti trid tiġi mimlija għal kull pazjent)*

Statin = Mediċini tal-Kolesterol (Enfasizza dan lill-pazjent)

1	Liema *Mediċina tal-Kolesterol* u doża qed tieħu bħalissa?	❍Atorvastatin ❍Rosuvastatin ❍Simvastatin Doża:
2	Taf għaliex qed tieħu din ilmediċina?	❍Iva ❍Le Jekk Iva, għaliex?
3	Inti tiġbor il-mediċini tiegħek mis-sistema tal-Ispiżjar talGħażla Tiegħek?	❍Iva ❍Le
4	Li kieku il-mediċini tal-kolesterol ma kienux b'xejn, kont tixtrihom?	❍Iva ❍Le Jekk le, għaliex?
5	Kull meta teħodhom il-mediċini tal-kolesterol?	❍Kulljum ❍Ġurnata Iva u Ġurnata Le ❍Darba f'Ġimgħa ❍Kull meta niftakar ❍Qatt ❍Mod ieħor (speċifika):
6	Fi x'ħin teħodhom il-mediċini tal-kolesterol?	❍Filgħodu ❍Wara nofsinhar ❍Qabel norqod ❍Meta niftakar ❍F'xi ħin ieħor (speċifika):

7	Dejjem tiġbor/tixtri il-mediċini tal-kolesterol fil-ħin?	○Iva

		○Le
8	Kemm il-darba ma tieħux id-doża tal-mediċini tal-kolesterol ?	○Dejjem ○Spiss ○Ġieli ○Rari ○Qatt
9	Jekk xi darba ma ħadtx il-mediċina tal-kolesterol, x'kienet irraġuni ?	○Nsejt ○Spiċċawli il-pilloli ○Għandi wisq mediċini ○Ħassejtni tajjeb u ma ħassejtx li kelli neħodhom ○Tlift il-mediċini ○Ħassejt xi sintomi wara li ħadthom ○Raġuni oħra (speċifika):
10	Ġieli kkunsidrajt li tieqaf tieħu il-mediċini tal-kolesterol minn jeddek ?	○Iva ○Le Jekk Iva, għaliex?
11	Meta tixtri xi mediċini mingħand l-ispiżjar, tiċċekkja jekk ilmediċini li ser tixtri jaqblux mal-mediċini tal-kolesterol li diġà tieħu?	○Iva ○Le
12	Meta tmur għand it-tabib tiegħek, tfakkru/tfakkarha li tieħu il-mediċini tal-kolesterol?	○Iva ○Le

13	Kull meta tmur għand it-tabib tiegħek biex jiccekjalek ilmediċini li tieħu?	○Darba f'xahar ○Darba kull 3 xhur ○Darba kull 6 xhur ○Darba f'sena ○Qatt ○Mod ieħor (Speċifika):
14	Meta tmur fuq xi vaganza, kemm il-darba tieħu il-mediċini tal-kolesterol miegħek?	○Dejjem ○Spiss ○Ġieli ○Rari ○Qatt Jekk mhux dejjem, għala?
15	Ġieli esperjenzajt xi sintomi fil-muskoli li tissuspetta kienu minħabba il-mediċini tal-kolesterol?	○Iva ○Le

Jekk Iva kompli b'sezzjoni 2.

Jekk Le, għid lill-pazjent li l-kwestjonarju huwa lest u rringrazzjahom tal-ħin tagħhom.

Sezzjoni 2: Sintomi fil-muskoli assoċjati mal-mediċini tal-kolesterol (Statins)

Din is-sezzjoni **għandha tiġi kompluta biss jekk il-pazjent/a xi darba esperjenza/t xi sintomi filmuskoli assoċjati mal-mediċini tal-kolesterol** (statins)

1	Kif tiddeskrivi is-sintomi tal-muskoli?	○Uġiegħ fil-muskoli ○Ebusija fil-muskoli ○Djufija fil-muskoli ○Bugħawwieġ fil-muskoli ○Sintomi Oħra (speċifika):
2	Kull meta t'esperjenza dawn is-sintomi?	○Kuljum ○Ġurnata iva, ġurnata le ○Darba f'ġimgħa ○Darba f'xahar ○Inqas minn darba f'xahar ○Frekwenza oħra (speċifika):
3	Fi x'ħin tesperjenza dawn is-sintomi?	○Filgħodu ○Wara nofsinhar ○Filgħaxija
4	F'liema staġun taħseb li tesperjenza dawn is-sintomi l-iżjed?	○Ħarifa ○Rebbiegħa ○Sajf ○Xitwa
5	Severità: Fuq skala ta' 1 sa 10, fejn 1 huwa l-iktar baxx u 10 huwa l-ogħla, kemm huma ta uġiegħ is-sintomi tal-muskoli?	
6	Taħseb li dawn is-sintomi inaqssulek l-abbilta' li tkun attiv, li tagħmel l-eżerċizzju jew li tkun produttiv/a? (Din tista' tirreferi ukoll għall-ġranet mitlufa mix-xogħol)	○Iva ○Le Jekk Iva, kif?
7	Taħseb li dawn is-sintomi itellfulek l-irqad?	○Iva ○Le Jekk Iva, kif?

8	Taħseb li dawn is-sintomi jgħejjuk u tkun trid tistrieħ ?	○Iva ○Le
9	Taħseb li dawn is-sintomi jonqsu meta tistrieħ?	○Iva ○Le
10	Ġieli infurmajt lit-tabib tiegħek fuq dawn is-sintomi?	○Iva ○Le Jekk Iva, it-tabib tiegħek ħa xi azzjoni? U jekk iva, x'azzjoni ħa?
11	Ġieli tipprova tevita xi ikel li taħseb iżid il frekwenza ta dawn is-sintomi?	○Iva ○Le Jekk iva, liem ikel tipprova tevita?
12	Taħseb li dawn is-sintomi jaffetwaw il-kwalità ta' ħajtek?	○Iva ○Le Jekk Iva, kif?

Għid lill-pazjent/a li l-kwestjonarju huwa lest u rringrazzjah/a għall-ħin tiegħu/tagħha.

Clinical Presentation of Statin Associated Muscle Symptoms

Dear Cardiologist,

I am currently reading for a Master of Pharmacy degree at the University of Malta. As part of my pharmacy practice project titled

Statin Associated Muscle Symptoms and Therapy Adherence , I would like to assess cardiologist feedback regarding terminologies, definitions and diagnostic strategies related to Statin Associated Muscle Symptoms. This project is being supervised by Dr. Francesca Wirth.

Statin-associated muscle symptoms (SAMS) is a broad term encompassing various adverse events, including myopathy, myalgia, and rhabdomyolysis. These symptoms are one reason for statin non-adherence or discontinuation, which may result in adverse cardiovascular outcomes (Stroes et al., 2015).

Various definitions of myalgia, myopathy, and rhabdomyolysis are documented by different sources and these definitions are not consistent. The aim is to standardise the definitions of SAMS among cardiologists and to develop a practical tool for diagnosis of SAMS by cardiologists.

Participation is entirely voluntary and by answering this questionnaire, you are providing consent to participate.

Your time and participation are greatly appreciated.

If you have any questions kindly contact me on jean.c.calleja.18@um.edu.mt.

Best Regards,

Jean Claude Calleja

* Indicates required question

Section 1: Participant Details

You may wish to identify yourself for further discussion. This section is not obligatory to answer the other sections.

1. Name and Surname

2. Are you a:

Mark only one oval.

- ◯ Consultant
- ◯ Resident Specialist (RS)
- ◯ Higher Specialist Trainee (HST)
- ◯ Basic Specialist Trainee (BST)

Section 2: Terminologies and Definitions of SAMS

In this section, you can find the 4 terminologies (Myalgia, Myopathy, and Rhabdomyolysis) related to SAMS and various definitions found in literature.

Kindly rate your agreement or otherwise with each definition.

Section 1(i): Myalgia

Definition	Source
A) Muscle aches or weakness without CK elevation	Hu et al. Safety of statins: An update. Therapeutic Advances in Drug Safety. 2012; 3(3):133-144.
B) Diagnosed if ALL of the following occurred: (1) New or increased muscle pain, cramps or aching not associated with exercise; (2) symptoms persisted for at least 2 weeks; (3) symptoms resolved within 2 weeks of stopping the drug; and (4) symptoms reoccurred within 4 weeks of restarting the drug	Parker BA, Thompson PD. Effect of statins on skeletal muscle: Exercise, myopathy, and muscle outcomes. Exercise and Sport Sciences Reviews. 2012; 40(4):188.
C) Mild muscle complaints; Can occur with or without CK elevation	Parker BA, et al. Effect of statins on skeletal muscle function. Circulation. 2013;127(1):96-103
D) Unexplained muscle discomfort often described as "'flu-like"' symptoms with normal CK level; spectrum of myalgia complaints includes muscle aches, soreness, stiffness, tenderness and cramps with or shortly after exercise (not nocturnal cramping)	Rosenson RS, et al. An assessment by the statin muscle safety task force: 2014 Update. Journal of Clinical Lipidology. 2014; 8:S58-S71.
E) Muscle pain or aching	Stroes ES, et al. Statin-Associated Muscle Symptoms: Impact on Statin Therapy—European Atherosclerosis Society Consensus Panel Statement on Assessment, Aetiology and Management. European Heart Journal. 2015; 36(17): 1012–1022. Selva-O'Callaghan A, et al. Statin-induced myalgia and myositis: An update on pathogenesis and clinical recommendations. Expert Review of Clinical Immunology. 2018; 4;14(3):215-224. Newman CB, et al. Statin Safety and associated adverse events: A Scientific Statement from the American Heart Association. Arteriosclerosis, Thrombosis and Vascular Biology. 2019;39: e38-e81.
F) Weakness and/or cramps without significant elevation in blood creatine kinase (CK) levels	Hashni S, et al. Statin Safety: What Every Health Care Provider Needs to Know. Current Cardiovascular Risk Reports. 2018; 12:1-7

3. Which definition do you believe is the most suitable/correct for use in your practice? *

Mark only one oval.

- ◯ A
- ◯ B
- ◯ C
- ◯ D
- ◯ E
- ◯ F
- ◯ None of the above
- ◯ Other: _____

4. If you do not use any of the above definitions in your practice, which definition / criteria do you use for myalgia?

_____

_____

_____

_____

_____

5. Additional comments

_____

_____

_____

_____

_____

Section 1(ii): Myopathy

Definition	Source
A) General term referring to any disease of the muscle	Hu M, et al. Safety of statins: An update. Therapeutic Advances in Drug Safety. 2012; 3(3):133-144.
B) Myositis or rhabdomyolysis and require CK levels to be >10X ULN	Parker BA, Thompson PD. Effect of statins on skeletal muscle: Exercise, myopathy, and muscle outcomes. Exercise and Sport Sciences Reviews. 2012; 40(4):188.
C) Presence of symptoms of myalgia and CK >10X ULN	Mohassel P, Mammen AL. Statin-associated Autoimmune Myopathy and anti-HMGCR Autoantibodies. Muscle Nerve. 2013;48(4):477-483.
D) Muscle weakness not attributed to pain and not necessarily associated with elevated CK	Rosenson RS, et al. An assessment by the statin muscle safety task force: 2014 Update. Journal of Clinical Lipidology. 2014; 8:S58-S71.
E) Pain that is typically generalised and proximal and there may be muscle tenderness and weakness and with CK elevations 10X ULN	Stroes ES, et al. Statin-Associated Muscle Symptoms: Impact on Statin Therapy—European Atherosclerosis Society Consensus Panel Statement on Assessment, Aetiology and Management. European Heart Journal. 2015; 36(17): 1012–1022.
F) Unexplained muscle pain or weakness accompanied by CK concentrations >10 times ULN	Newman CB, et al. Statin Safety and associated adverse events: A Scientific Statement from the American Heart Association. Arteriosclerosis, Thrombosis and Vascular Biology. 2019;39: e38-e81.
G) Manifested as muscle pain, tenderness or weakness with CK >10X ULN	Zocor 20mg film-coated tablets - Summary of Product Characteristics (SmPC) - (emc) [Internet]. Medicines.org.uk. 2020 [cited 15 December 2020]. Available from: https://www.medicines.org.uk/emc/product/7791/smpc

6. Which definition do you believe is the most suitable/correct for use in your practice? *

Mark only one oval.

- ◯ A
- ◯ B
- ◯ C
- ◯ D
- ◯ E
- ◯ F
- ◯ G
- ◯ None of the above
- ◯ Other: _____

7. If you do not use any of the above definitions in your practice, which definition / criteria do you use for myopathy?

8. Additional comments

Section 1(iii): Rhabdomyolysis

Definition	Source
A) **Muscle symptoms with significant CK elevation (typically >10 X ULN), usually with brown urine and urinary myoglobin**	Hu M, et al. Safety of statins: An update. Therapeutic Advances in Drug Safety. 2012; 3(3):133-144.
B) **Acute and massive lysis of skeletal muscle cells with significant shifts in electrolytes in the extracellular fluid and release of large amounts of CK and myoglobin into the blood plasma**	Rosenson RS, et al. An assessment by the statin muscle safety task force: 2014 Update. Journal of Clinical Lipidology. 2014; 8:S58-S71.
C) **Severe form of muscle damage associated with very high CK levels, myoglobinaemia and/or myoglobinuria with an increased risk of renal failure and CK >40 X ULN**	Stroes ES, et al. Statin-Associated Muscle Symptoms: Impact on Statin Therapy—European Atherosclerosis Society Consensus Panel Statement on Assessment, Aetiology and Management. European Heart Journal. 2015; 36(17): 1012–1022.
D) **Severe myocyte death with subsequent myoglobinuria, possibly leading to acute kidney failure.**	Selva-O'Callaghan A, et al. Statin-induced myalgia and myositis: An update on pathogenesis and clinical recommendations. Expert Review of Clinical Immunology. 2018; 4;14(3):215-224.
E) **Severe form of myopathy with CK typically >40x ULN which can cause myoglobinuria and acute renal failure**	Newman CB, et al. Statin Safety and associated adverse events: A Scientific Statement from the American Heart Association. Arteriosclerosis, Thrombosis and Vascular Biology. 2019;39: e38-e81.
F) **Clinical syndrome of acute muscle weakness, myalgia, and muscle swelling combined with a CK cut-off value of > 1000 IU/L or CK > 5x ULN**	Stahl K, et al. A systematic review on the definition of rhabdomyolysis. Journal of Neurology. 2020;267(4):877-882.
G) **Potentially life-threatening condition characterised by markedly elevated CK levels (> 10 times ULN), myoglobinaemia and myoglobinuria which may lead to renal failure**	Lipitor 40mg film-coated tablets - Summary of Product Characteristics (SmPC) - (emc) [Internet]. Medicines.org.uk. 2020 [cited 15 December 2020]. Available from: https://www.medicines.org.uk/emc/product/5238/smpc

9. Which definition do you believe is the most suitable/correct for use in your practice? *

Mark only one oval.

- ◯ A
- ◯ B
- ◯ C
- ◯ D
- ◯ E
- ◯ F
- ◯ G
- ◯ None of the above
- ◯ Other: _____

10. If you do not use any of the above definitions in your practice, which definition / criteria do you use for rhabdomyolysis? *

_____

_____

_____

_____

_____

11. Additonal comments

_____

_____

_____

_____

_____

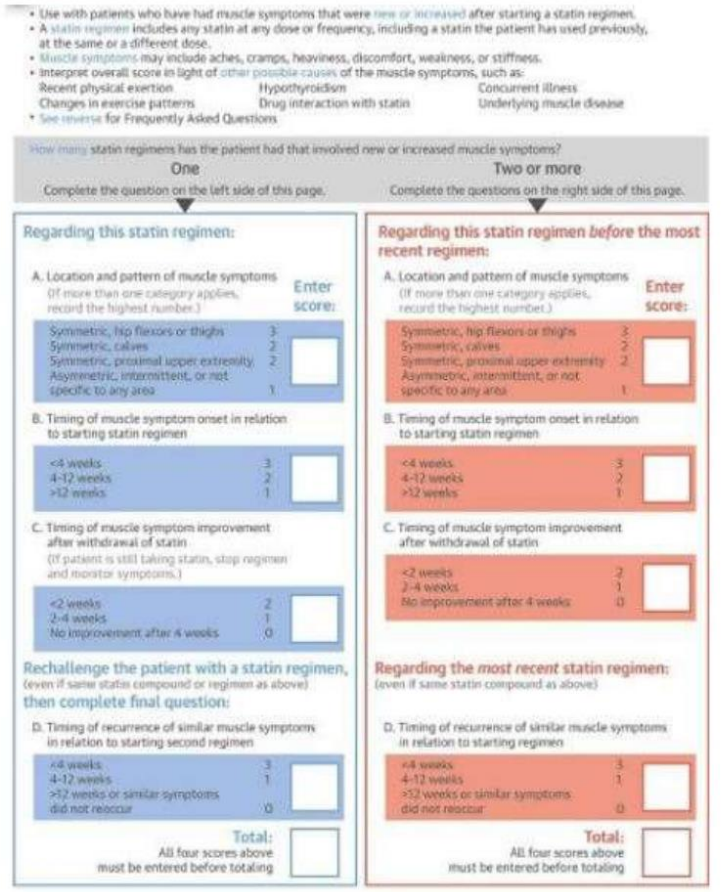
Section 3: SAMS- Clinical Index

The Statin-Associated Muscle Symptom Clinical Index (SAMS-CI) is a tool to assess the likelihood that a patient's muscle symptoms were caused or worsened by the use of STATINS.

The tool was psychometrically evaluated and tested clinically and a revised instrument suitable for further testing in clinical practice was developed. The tool aims to support better detection of SAMS in clinical practice and to optimise treatment for patients experiencing muscle symptoms, and the authors recommend further prospective validation of the index (Rosenson et al., 2017)

In this section, I would appreciate your feedback about the relevance and practicality of this tool in your daily practice.

SAMS-CI



Total Score	2-4	5-8	9-11
Likelihood that the patient's muscle symptoms are due to statin use	Unlikely	Possible	Probable

12. How likely are you to use this tool in your practice? *

Mark only one oval.

Highly Unlikely

1 ◯

2 ◯

3 ◯

4 ◯

5 ◯

Highly likely

13. If you marked 1, 2 or 3 for the above, kindly give your reason/s.

14. How likely are you to use a modified version of this tool in your practice?

Mark only one oval.

Highly Unlikely

1 ◯

2 ◯

3 ◯

4 ◯

5 ◯

Highly Likely

15. If you marked 1, 2 or 3 for the above, kindly give your reason/s

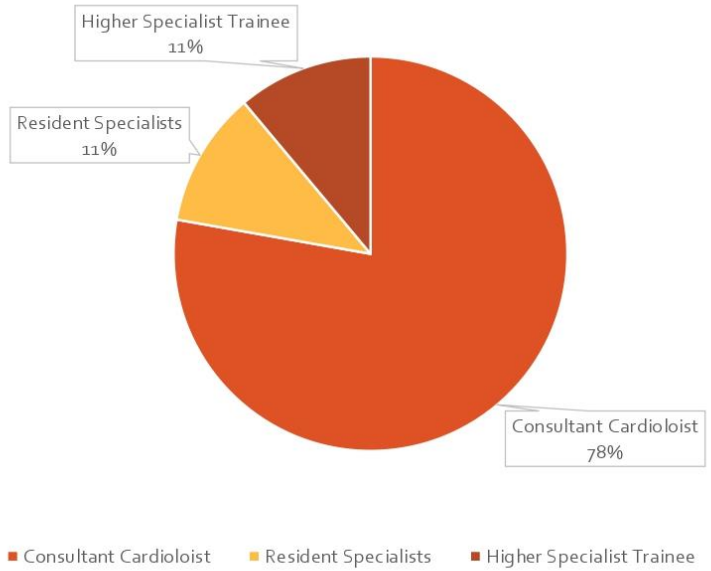
16. Additional comments

STATIN ASSOCIATED MUSCLE SYMPTOMS AND THERAPY ADHERENCE

Focus Group Discussion

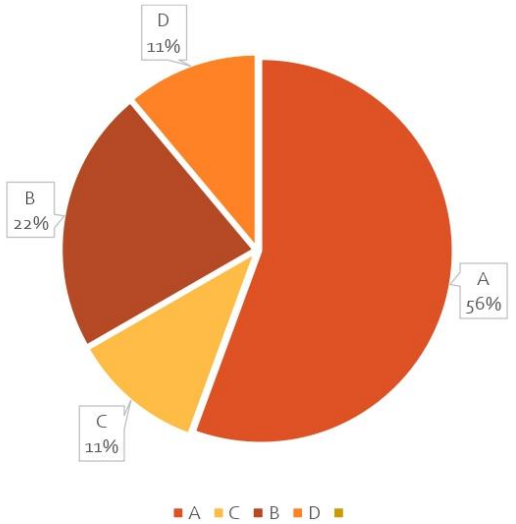
Participants

N=9



Myalgia

Definition	Source	Number of Votes (N=9)
A: Diagnosed if all of the following occurred: (1) New or increased muscle pain, cramps or aching not associated with exercise; (2) symptoms persisted for at least 2 weeks; (3) symptoms resolved within 2 weeks of stopping the drug; and (4) symptoms reoccurred within 4 weeks of restarting the drug	Parker et al., 2012	5
B: Mild muscle complaints; Can occur with or without CK elevation	Parker and Thompson, 2012	2
C: Muscle pain or aching	Stroes et al., 2015	1
D: Muscle ache or weakness without CK elevation	Hu et al., 2012	1

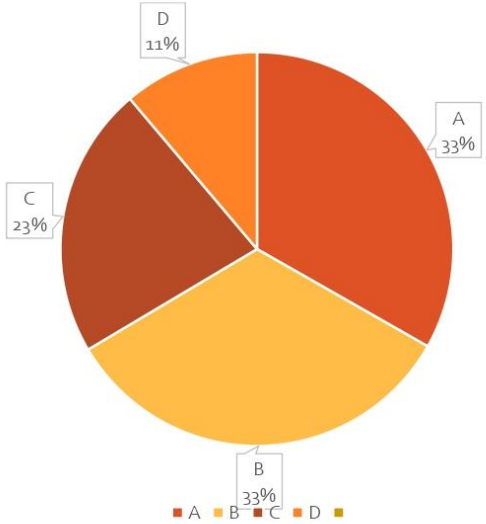


Myalgia – Proposed Definition

Diagnosed if all of the following occurred: (1) New or increased muscle pain, cramps or aching not associated with exercise; (2) symptoms persisted for at least 2 weeks; (3) symptoms resolved within 2 weeks of stopping the drug; and (4) symptoms reoccurred within 4 weeks of restarting the drug

Myopathy

Definition	Source	Number of Votes (N=9)
A: Pain that is typically generalised and proximal and there may be muscle tenderness and weakness and with CK elevations 10x ULN	Stroes et al., 2015	3
B: General term referring to any disease of muscles	Hu et al., 2012	3
C: Manifested as muscle pain, tenderness, or weakness with CK>10x ULN	Zocor 20mg SmPC	2
D: Unexplained muscle pain or weakness accompanied by CK concentrations >10 times ULN	Newman et al., 2019	1

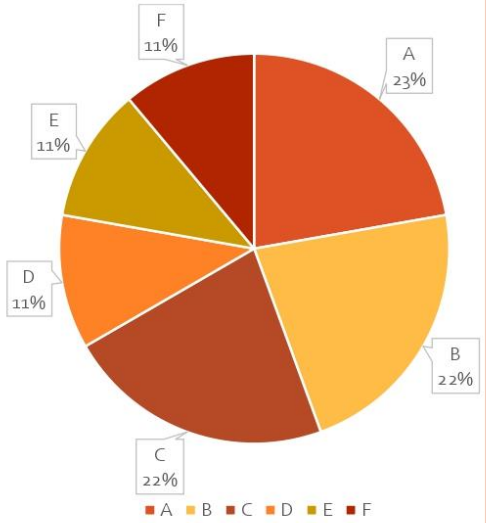


Myopathy – Proposed Definition

A term relating to any disease of the muscle which presents with a CK level 10X ULN, pain that is typically generalised and proximal, and may also present with muscle tenderness and weakness.

Rhabdomyolysis

Definition	Source	Number of Votes (N=9)
A: Acute and massive lysis of skeletal muscle cells with significant shifts in electrolytes in the extracellular fluid and release of large amounts of CK and myoglobin into the blood plasma	Ronsenson et al., 2014	2
B: Severe form of myopathy with CK typically >40x ULN which can cause myoglobinuria and acute renal failure	Newman et al., 2019	2
C: Potentially life-threatening condition characterised by markedly elevated CK levels (>10 times ULN), myoglobinaemia and myoglobinuria which may lead to renal failure.	Lipitor 40mg SmPC	2
D: Muscle symptoms with significant CK elevation (typically >10 X ULN), and creatinine elevation usually with brown urine and urinary myoglobin	Hu et al., 2012	1
E: High CK concentrations (>100-fold the ULN), myoglobinuria and renal impairment due to acute tubular necrosis caused by myoglobin precipitation in the renal tubules	Selva O'Callaghan et al., 2018	1
F: Severe form of muscle damage associated with very high CK levels, myoglobinaemia and/or myoglobinuria with an increased risk of renal failure and CK >40 X ULN	Stroes et al., 2015	1



Rhabdomyolysis – Proposed Definition

A potentially life-threatening condition that presents with acute and massive lysis of skeletal muscle cells, significant shifts in electrolytes in the extracellular fluid, CK level >40x ULN, myoglobinuria and potential acute renal failure.

Thank you very much for your participation

Appendix 3: Harmonised Definitions of SAMS

Statin Associated Muscle Symptoms: Definitions

Intended for Cardiologists

Lack of harmonisation in the definitions for terminologies relating to statin associated muscle symptoms (SAMS) has been reported, which may impact on appropriate identification, diagnosis and management of SAMS (Rosenson et al, 2014; Stroes et al, 2015; Selva-O'Callaghan et al, 2018). As part of a research study carried out in partial fulfilment of the degree of Master of Pharmacy (MPharm) at the University of Malta, various definitions of SAMS terminologies available in literature were compiled and presented to a nine-member panel comprising consultant cardiologists, resident specialists, higher specialist and basic specialist trainees in cardiology for their level of agreement and feedback.

From the feedback obtained, definitions for myalgia, myopathy and rhabdomyolysis, were compiled and presented to a focus group consisting of two consultant cardiologists, a general practitioner, a clinical pharmacist, a community pharmacist and a pharmacist practicing in regulatory sciences in the area of pharmacovigilance. Recommendations from the focus group were implemented and consensus for each definition was obtained.

The agreed definitions by the focus group which may be used in your clinical practice include:

Myalgia	Diagnosed if all of the following occurred: (1) New or increased muscle pain, cramps or aching not associated with exercise; (2) symptoms persisted for at least 2 weeks; (3) symptoms resolved within 2 weeks of stopping the drug, reducing the dose or switching to an alternative agent within the same therapeutic class
Myopathy	A term relating to any disease of the muscle which presents with a creatine kinase (CK) level 10X the upper limit of normal (ULN), pain that is typically generalised and proximal, and may also present with muscle tenderness and weakness
Rhabdomyolysis	A potentially life-threatening condition that presents with acute and massive lysis of skeletal muscle cells, significant shifts in electrolytes in the extracellular fluid, CK level >40X ULN, myoglobinuria and potential acute renal failure

Disclaimer: Prior to using these definitions for SAMS diagnosis, it is important to rule out any other possible causes for the muscle symptoms. Most common conditions presenting with muscle symptoms include, but are not limited to, recent physical exertion, physical trauma, changes in exercise pattern, hypothyroidism, rheumatoid arthritis, some active infections, fibromyalgia, underlying muscle disease or drug interactions with statins (Rosenson et al, 2017; Drexel et al, 2020; Ruscica et al, 2022).

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