VILNIUS UNIVERSITY

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Institute of Biomedical Sciences (Pharmacy center)

MASTER'S THESIS

PERSISTENCE TO STATIN TREATMENT IN LITHUANIA

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CONTENTS

LIST OF ABBREVIATIONS

AE	adverse events
apoB	apolipoprotein B
ATC	Anatomical Therapeutic Chemical
ATP	adult treatment plan
ASCOT-LLA	Anglo-Scandinavian Cardiac Outcomes Trial–Lipid Lowering
BAS	Bile Acid Sequestrants
CHD	coronary heart disease
CRP	c-reactive protein
CV	cardiovascular
CVD	cardiovascular disease
CYP450	cytochromes P450, a superfamily of enzymes responsible for most drug metabolism
RCT's	randomized controlled trials
EAS	European Atherosclerosis Society
ESC	European Society of Cardiology
EU	European Union
FDA	Food and Drug Administration
HDL	high-density lipoprotein
HMG	hydroxymethylglutaryl
HMGCR	3-Hydroxy-3-Methylglutaryl-CoA Reductase
HMG-CoA	3-hydroxy-3-methylglutaryl coenzyme A
ICD-10	International Classification of Diseases
LDL	low-density lipoprotein
LE	life-expectancy
MI	myocardial infarction
NHIF	National Health Insurance fund
OATP	organic anion transporting polypeptide
OATP1B1	organic anion transporting polypeptide 1B1
OOP	out-of-pocket
PCSK9	proprotein convertase subtilisin kexin type 9
SCORE	Systematic Coronary Risk Estimation
SREBP	sterol regulatory element-binding protein
SRE	sterol regulatory element

SUMMARY

Background. Cardiovascular diseases (CVD) are one of the main causes of death in European Union taking over a million of lives every year. Many different factors increase the chances of build-up of fatty deposits on the walls of the arteries around the heart, which greatly increases the risk of CVD events. Low-density lipoprotein (LDL) lowering medications such as statins play a huge role in the prevention and treatment of cardiovascular diseases. Statins have been shown to have a big impact in reducing the risk of major vascular events and mortality both in primary and secondary prevention. Despite the statin-based benefits, statins are still not sufficiently prescribed for patients and they not properly utilized by patients. In various scientific studies, patients adherence and persistence rate to the treatment is insufficient to achieve the desired result in CVD prevention.

Aim. To evaluate the persistence to statin treatment in Lithuania during 2018-2019 and to investigate factors possibly associated with non-persistence.

Research objectives.

1. To assess whether patients are more likely to be persistent to statins treatment in secondary prevention than the patients treated for primary prevention.
2. To investigate whether there any difference in persistence depending on patient sex, age or previous use of other medicines.
3. To assess whether there is any difference in persistence between different statins and dosages used.
4. To measure what is the persistence to statins during the study period.
5. To investigate whether the title of the specialist qualification influences in patient persistence.

Methods. In this cohort study, data on dispensed and reimbursed prescription medicines were obtained from the information system "Sveidra" of the Lithuanian National Health Insurance Fund (NHIF). All adult patients who had their first statin dispensed in 2018-2019 were included. Persistence was assessed using the anniversary method, i.e. determined the number of patients who had no statin dispensed 365 days after the first dispensing, taking into account a permissible gap of 90 days of supply of the last dispensing. Multivariate logistic regression was used to explore factors associated with persistence.

Results and conclusions. 104’726 patients were initiated on statins treatment, they were dispensed with a statin for the first time in 2018-2019. Overall, patients were most commonly initiated with atorvastatin 60%, rosuvastatin 39%, and around 1% with simvastatin and fluvastatin together. The mean age was 62 years. In total only 41% of all initiated patients with a statin treatment were persistent after one year. Patients who had previous use of medications were 73% more likely to be persistent to statins treatment, than those who have not. Likewise, patients taking higher doses of atorvastatin were 55-62% more likely to stay persistent to the treatment than patients with lighter doses of atorvastatin. Younger patients with no previous use of other medication and patients with lower doses of statins had higher odds to become non-persistent. Patients’ prescriber qualification and gender showed no association with persistence.

SANTRAUKA

Pagrindimas. Širdies ir kraujagyslių ligos (ŠKL) yra viena iš pagrindinių mirties priežasčių Europos Sąjungoje, kasmet nusinešančios daugiau nei milijoną gyvybių. Skirtingų veiksnių įvairovė didina riebalų sankaupų susidarymo tikimybę ant arterijų sienelių aplink širdį, o tai labai sustiprina širdies ir kraujagyslių ligų riziką. Mažo tankio lipoproteinų (MTL) kiekį mažinantys vaistai, tokie kaip statinai, atlieka didžiulį vaidmenį širdies ir kraujagyslių ligų profilaktikoje ir gydyme. Įrodyta, kad statinai turi didelį poveikį mažinant širdies, kraujagyslių ligų ir mirtingumo riziką tiek pirminėje, tiek antrinėje profilaktikoje. Nepaisant pagrįstos statinų naudos, statinai vis dar nepakankamai išrašomi pacientams gydyti, bei pastebimas netinkamas pacientų vaistų vartojimas gydymo metu. Įvairiuose moksliniuose tyrimuose pastebima, kad pacientų vaistų vartojimo tęstinumo rodiklis yra nepakankamas norint pasiekti pageidaujamą ŠKL profilaktikos rezultatą.

Darbo tikslas. Įvertinti gydymo statinais laikymąsi Lietuvoje 2018-2019 m. ir ištirti veiksnius, galimai susijusius su gydymo nesilaikymu.

Darbo uždaviniai.

1. Įvertinti, ar pacientai, kuriems gydymas statinais buvo taikomas antrinėje profilaktikoje laikėsi vaistų vartojimo tęstinumo geriau, nei pacientai gydomi pirminės profilaktikos tikslais.
2. Ištirti, ar skiriasi vaistų vartojimo tęstinumas, priklausomai nuo paciento lyties, amžiaus ar ankstesnio kitų vaistų vartojimo.
3. Įvertinti, ar vaistų vartojimo tęstinumui įtakos turėjo skirtingi statinai ir naudojamos dozės.
4. Išmatuoti vaistų vartojimo tęstinumą statinams tyrimo laikotarpiu.
5. Ištirti ar specialisto kvalifikacija turėjo įtakos paciento vaistų vartojimo tęstinumui.

Metodai. Šiame kohortiniame tyrime duomenys apie išduodamus ir kompensuojamus receptinius vaistus buvo gauti iš Lietuvos valstybinės ligonių kasos (VLK) informacinės sistemos „Sveidra“. Į tyrimą buvo įtraukti visi suaugę pacientai, kuriems pirmasis statinas buvo išduotas 2018–2019 m. Vaistų vartojimo tęstinumas buvo vertinamas sukakties metodu, t.y. nustatytas pacientų skaičius, kuriems statinas nebuvo išduotas praėjus 365 dienoms nuo pirmojo statinų išdavimo, atsižvelgiant į leistiną 90 dienų tarpą nuo paskutinio išdavimo. Su vaistų vartojimo tęstinumu susijusiems veiksniams ištirti buvo naudojama daugiamatė logistinė regresija.

Rezultatai ir išvados. 104’726 pacientams buvo pradėtas gydymas statinais. Pacientams pirmą kartą statinas buvo išduotas 2018-2019m. Pacientai dažniausiai buvo pradėti gydyti atorvastatinu (60 %), rozuvastatinu (39 %) ir iki (1%) simvastatinu bei fluvastatinu. Vidutinis paciento amžius inicijuojant statinus buvo 62 metai. Iš viso tik 41% visų pradėtų pacientų, kuriems buvo skirtas gydymas statinais, po vienerių metų išlaikė vaistų vartojimo tęstinumą. Pacientai, kurie anksčiau vartojo kitus vaistus, buvo 73% labiau linkę išlaikyti vaistų vartojimo tęstinumą statinais nei tie, kurie nevartojo kitų vaistų. Taip pat pacientams, vartojusiems didesnes atorvastatino dozes, buvo 55–62 % didesnė tikimybė, kad vaistų vartojimo tęstinumas bus išlaikytas, nei pacientams, vartojusiems silpnesnes atorvastatino dozes. Jaunesni pacientai, kurie anksčiau nevartojo kitų vaistų, ir pacientai, vartoję mažesnes statinų dozes, turėjo didesnę tikimybę prastam vaistų vartojimo tęstinumui. Gydytojo kvalifikacija ir paciento lytis neparodė jokio ryšio su vaistų vartojimo tęstinumu.

1. INTRODUCTION

Cardiovascular diseases (CVD) are one of the main causes of death in European Union. Every year cardiovascular diseases cause 3.9 million deaths in Europe and over 1.8 million deaths in the European Union (EU). This accounts for 45% of all deaths in Europe and 37% of all deaths in the EU. Cardiovascular disease is the main cause of death in men in all but 12 European countries and the main cause of death in women in all but two countries [2]. 22 000 people on average died from CVD annually between 2018 and 2020 in Lithuania which accounts for 41% of all men and 59% of all women who died during this period [3].

Cardiovascular diseases are the consequence of various behaviour and genetic factors such us unhealthy diet, lack of physical activity and other. Hypercholesterolemia is recognized as a causative factor in the development of atherosclerosis where atherosclerosis becomes the main pathophysiologic mechanism for fatty streaks to build up on the walls of arteries and restrict the blood flow in the vessels. Therefore, it is important to lower LDL cholesterol for the prevention of cardiovascular diseases. The evidence that lowering the plasma LDL cholesterol reduces cardiovascular (CV) disease risk is unequivocal [6]. In meta-analyses of numerous randomized controlled trials (RCTs) on over 170,000 patients by the Cholesterol Treatment Trialists' Collaboration was clearly stated that a reduction of 1 mmol/L (approximately 38 mg/dl) of LDL-C is associated with a 20–25% reduction in the relative risk of new major cardiovascular events (cardiovascular mortality and non-fatal myocardial infarction) [8, 9]. For the treatment of dyslipidemia, statins remain the first-choice therapy, as they have shown to reduce the risk of major vascular events by lowering low-density lipoprotein cholesterol (LDL-C). However, due to adherence to statin therapy or statin resistance, many patients do not reach LDL-C target levels [35]. One of the key reasons affecting statins is the poor adherence to therapy. It is known from the literature that approximately 50% of patients treated with statins are not adherent to therapy. Adherence to therapy has a very important impact in terms of decreasing the risk of cardiovascular events (RR 0.85, IC 95%: 0.81–0.89) and mortality from any cause (RR 0.55, IC 95%: 0.46–0.67). Therefore, adherence should be assured by the patients and monitored by the physicians to control LDL-C levels and reach treatment goals.

Aim. To evaluate the persistence to statin treatment in Lithuania during 2018-2019 and to investigate factors possibly associated with non-persistence.

2. LITERATURE REVIEW

2.1. Cardiovascular diseases and hyperlipidemia

Cardiovascular diseases are a large group of heart and circulatory system disorders. They include coronary heart and cerebrovascular disease, peripheral arterial disease, rheumatic heart and congenital heart disease as well as deep vein thrombosis and pulmonary embolism [1]. Every year cardiovascular diseases cause over 1.8 million deaths in the European Union (EU). The exact cause of coronary heart disease (CHD) is not clear, but there are lots of "risk factors" that can increase the odds of getting it. Factors such as high blood pressure, cholesterol, and diabetes lead to a build-up of fatty deposits (atheroma) on the walls of the arteries around the heart (coronary arteries). There is a strong relationship between low-density lipoprotein cholesterol (LDL-C) levels and cardiovascular disease. Atherosclerosis is part of one of the main pathophysiologic mechanisms for ischemic heart disease, stroke and it is also a major cause of vascular death. It is a chronic lipid-driven arterial disease when fatty streaks build up on the walls of arteries to become an atheromatous plaque that narrows the diameter of the blood vessel and so restricts blood flow. The acute rupture of these atheromatous plaques can cause thrombosis with partial or total occlusion of the artery, which could then lead to other clinical manifestations – myocardial infarction, ischemic stroke and peripheral arterial disease [4]. Hypercholesterolemia also known as dyslipidemia is the main factor determining the initiation of atherosclerosis and the risk of CVD events. Hypercholesterolemia can be defined as a condition with the presence of high plasma cholesterol levels and normal plasma triglycerides, as a consequence of increased levels of cholesterol and apolipoprotein B (apoB)-rich lipoproteins, called low-density lipoprotein (LDL) [5]. To put it simply dyslipidemia can be characterized as the presence of an excess of the complex particles that transport lipid in the blood, known as plasma lipoproteins. The evidence that lowering plasma LDL cholesterol reduces cardiovascular (CV) disease risk is unequivocal [6]. The Framingham Heart Study has helped to elucidate major risk factors for CVD [7]. One of the most common risk factors mentioned in the study was cholesterol. High cholesterol was strongly associated with CVD. The benefits of cholesterol-lowering treatment have subsequently been confirmed by meta-analyses of numerous randomized controlled trials (RCTs) on over 170,000 patients by the Cholesterol Treatment Trialists' Collaboration [8, 9]. They have concluded that a reduction of 1 mmol/L (approximately 38 mg/dl) of LDL-C is associated with a 20–25% reduction in the relative risk of new major cardiovascular events (cardiovascular mortality and non-fatal myocardial infarction) [8, 9].

Recommended target levels for lipids can be achieved by changing lifestyle and/or by using lipid-lowering medication. World Health Organization notes that “regular physical activity is proven to help prevent and manage non communicable diseases such as heart disease, stroke, diabetes.” [10] Unfortunately, most patients face insufficient physical activity in their daily life. In order to balance vital parameters and reduce the risk of likely occurring CV disease lipid-lowering medications can be prescribed to patients. In newer guidelines from ESC, including the 2019 European Society of Cardiology (ESC) Guidelines for the diagnosis and management of chronic coronary syndromes and the 2019 ESC/EAS Guidelines for the management of dyslipidemia respectively, the treatment goal for LDL-cholesterol is reduced even further to <1.4 mmol/L and at least 50% reduction from baseline [11, 36].

2.2. Lipid lowering therapy

Lipid-lowering medications are useful for primary or secondary prevention in combination with lifestyle modification to reduce the risk of cardiovascular events. Primary prevention includes patients without prior events but with risk factors such as diabetes mellitus and hypertension. Secondary prevention includes patients with a history of cardiovascular events. Lipoprotein modifying agents encompass several classes of drugs including hydroxymethylglutaryl (HMG) CoA reductase inhibitors (statins), cholesterol absorbing inhibitors, fibric acid derivatives, bile acid sequestrants, PCSK9 inhibitors, and nicotinic acid: [12]

Statins - lowers low-density lipoprotein and triglyceride concentrations (at higher doses) while increasing high-density lipoprotein (HDL) concentrations.by interfering with the cholesterol biosynthetic pathway.

Ezetimibe - impairs cholesterol absorption and lowers LDL-C, apolipoprotein B by selectively inhibiting intestinal cholesterol absorption by the intestines leading to the decreased delivery of cholesterol to the liver. Meanwhile, ezetimibe is very useful as supplement on therapy when statin therapy is not sufficient or in statin intolerant patients;

Fibrates - decrease the levels of fatty acids and triglycerides by stimulating the peroxisomal β-oxidation pathway;

Bile Acid Sequestrants (BAS) - sequester bile acids and increase HDL-C levels. These are usually used in combination with statins or nicotinic acid. Likewise, bile acid has the additional benefit to improve glycemic control in patients with diabetes;

PCSK9 Inhibitors - lowers LDL-C, by decreasing PCSK9, which decreases the degradation of LDL receptors. PCSK9 Inhibitors are useful when maximally tolerated statin therapy does not reduce LDL sufficiently in statin intolerant patients.

Nicotinic Acid (Niacin) - increases high-density lipoprotein cholesterol by modifying lipoproteins.

By far statins are the principal class and the first line of lipid-lowering drugs for treating lipid disorders and can lower LDL-C levels by as much as 60% [47]. Their efficacy in reducing cardiovascular events and mortality has been documented during the last two decades [13, 8].

2.3. Pharmocological therapy

2.3.1. Statins

2.3.1.1. Mechanism of action

The main therapeutic mechanism of statins is the inhibition of the rate-limiting enzyme 3-hydroxy-3-methylglutaryl-coA reductase (HMGCR) in the liver. HMGCR reduces the cellular amount and biosynthesis of cholesterol in the hepatocytes. The Acetyl-Coa enzyme converts the HMG-CoA into mevalonic acid, which is a precursor in the cholesterol biosynthetic pathway

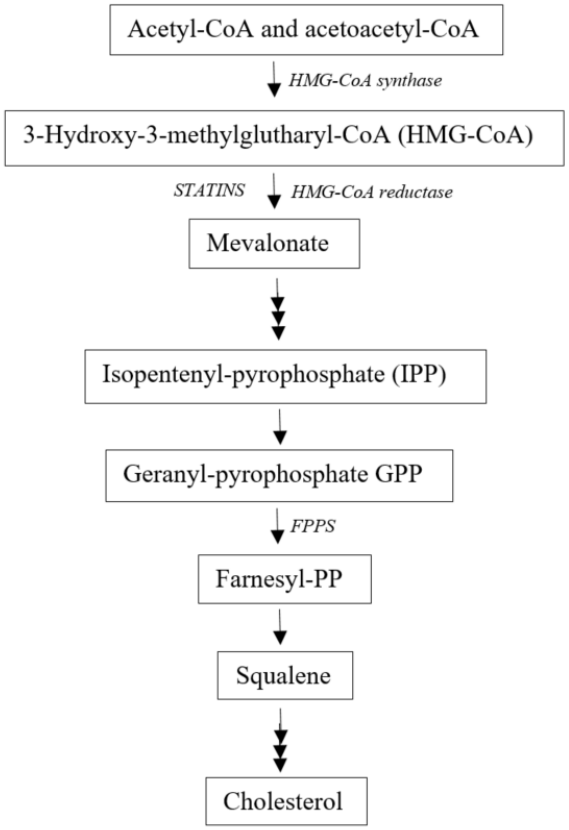

Figure 1. The cholesterol synthesis pathway, showing the inhibition of HMG-CoA reductase by statins.

Statins accomplish this by binding reversibly to the enzyme's active site, bringing about a structural change in the enzyme and disabling it. This structural change makes statins very effective and specific. These structural changes lead to an enhanced expression of the LDL-receptors in the liver cell membranes which then enhances the reuptake of LDL-cholesterol particles that are already circulating in the blood [64].

Statins also inhibit the hepatic synthesis of apolipoprotein that reduces the synthesis and secretion of triglyceride-rich lipoproteins and increases the production of receptors for apolipoproteins. This would mean fewer lipoproteins available to transport LDL around the body, thus lower levels of LDL in the system. This could be the reason why statins are capable of reducing LDL in patients suffering from homozygous family hypercholesterolemia [25].

2.3.1.2. Types of statins

In 1987, the Food and Drug Administration (FDA) approved the first statin for human use – Mevacor (lovastatin). At the time of approval, there was no evidence that statins could reduce heart attacks, only that they were well tolerated and that LDL levels could be reduced. In 1994, through Merck's 4S study, the second-generation statin called simvastatin reduced heart attacks and prolonged life in middle-aged people who were at a high risk of a coronary adverse event [26]. The chemical structure of all statins consists of the pharmacophore and its moiety containing a ring system with different substituents. Statins can be classified into two groups: naturally occurred (type 1) and synthetically obtained (type 2). (Figure 2)

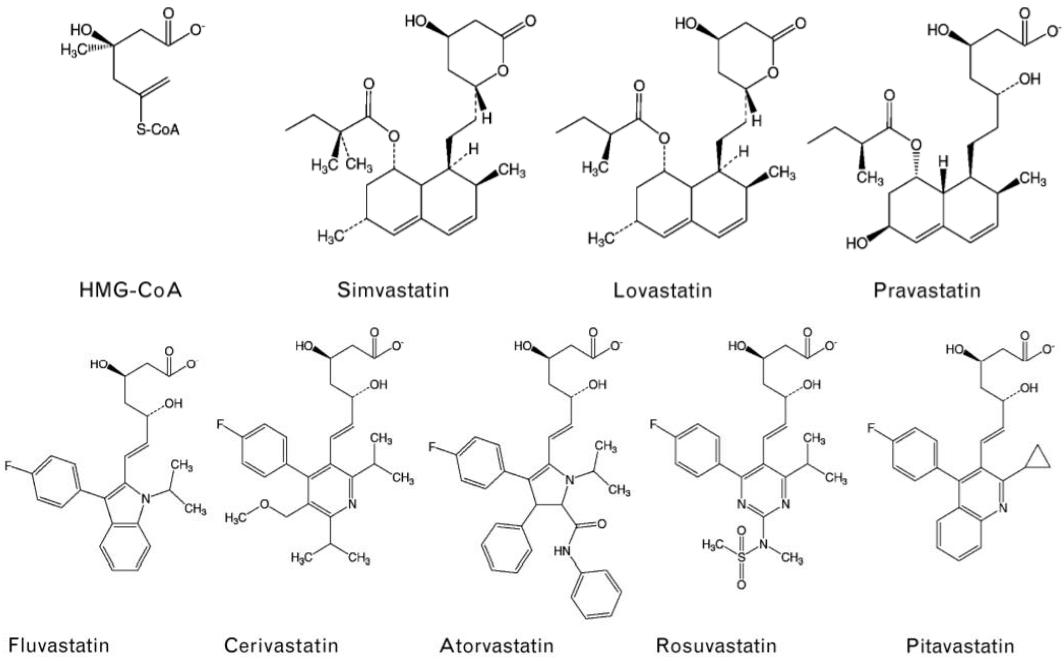

Figure 2. Chemical structures of the main statins.

Naturally occurring statins are lovastatin, simvastatin, pravastatin. They are derived from the fungus *Aspergillus terreus* and share a similar hydro-naphthalene ring structure [27]. Synthetically obtained statins comprise fluvastatin, atorvastatin, cerivastatin, pitavastatin, rosuvastatin and contain a large fluorinate phenol group or other HMG-like attached moiety. The main difference between the two types of statins is the replacement of the fluorophenyl group of type 2 statins with the butyryl group in type 1 statins. All statin molecules contain a HMG-like moiety that binds to the catalytic domain of target enzymes. In addition, the base structures of these compounds determine how well the molecule fits into the binding pocket of the enzyme and binds with it [28]. Based on chemical nature, statins are classified into hydrophilic (dissolving in water) - pravastatin, fluvastatin, rosuvastatin or lipophilic (dissolving in fats) - lovastatin, cerivastatin, simvastatin or combined (atorvastatin) and most recently approved, pitavastatin [29, 30]. Highly lipophilic statins are readily reabsorbed through the renal tubule walls and hence are not excreted in the urine. As a result, they must be metabolized, usually hepatically and enterically, to hydrophilic derivatives before they can be excreted from the kidney. Pravastatin and rosuvastatin showed to have more hydrophilic properties because they have polar groups like sulfonamide, hydroxyl, carboxylate and other polar substituents attached to the hydrophobic ring structures [28]. A unique polar interaction is formed between the sulfonamide group and the HMG-CoA reductase enzyme, as a result, rosuvastatin has a stronger binding affinity to the HMGR enzyme compared to other statins, which relates to its higher efficiency in lowering LDL-C [29]. Whereas atorvastatin, lovastatin, pitavastatin, fluvastatin and simvastatin, due to their hydrophilic properties, are soluble in fats.

Statins exist in two forms, lactone (inactive) and open-ring hydroxy acid (active) forms. Lovastatin and simvastatin are administered to the body as lactone pro-drugs that need to be hydrolyzed to corresponding β-hydroxy acid to become active metabolites [30]. All others are administered in their active β-hydroxy acid form. The solubility profile is a fundamental characteristic that governs the hepatoselectivity of the statins and their inhibitory effect on HMG-CoA reductase. Statin solubility determines its transportation. The drugs enter the cells via either passive or active transport. Lipophilic statins passively diffuse through the hepatic cell membranes, whereas hydrophilic statins undergo a carrier-mediated uptake using a carrier such as transmembrane receptor OATP1B1, which belongs to the organic anion transporting polypeptide (OATP) carrier family. Because of the passive and non-selective diffusion, lipophilic statins are less hepatoselective compared to hydrophilic ones, it means that they can penetrate other tissues as well [31]. Statins undergo first-pass metabolism in the liver which can reduce their bioavailability. Statins differ mainly in the degree of metabolism and the number of active and inactive metabolites. All statins have active metabolites so their activity depends also on the profile of both the parent compound and the active metabolites. Pravastatin has the lowest

protein-binding (around 50%) when compared to other statins (>90%); furthermore, statins have a low half-life (1–4 h), while atorvastatin and rosuvastatin possess the longest terminal half-life (11–20 h). However, the statin lipid-lowering effect is more dependent on the exposure to the liver and not systemic concentrations. Therefore, extensive first-pass metabolism brings more advantages than disadvantages [31]. The cytochrome P450 (CYP450) enzyme family is responsible for the metabolism of most statins. Simvastatin, lovastatin, atorvastatin and cerivastatin are predominantly metabolized by CYP3A4 isoenzyme. Rosuvastatin is metabolized to a small degree by CYP2C9 and to a lesser extent by CYP2C19 isoenzymes. Fluvastatin is mainly metabolized by CYP2C9 isoenzyme. Pravastatin, pitavastatin and rosuvastatin do not undergo hepatic metabolism and are excreted by the kidney and liver mostly unchanged [32].

2.3.1.3. Statin efficacy and safety

Clinical manifestations of atherosclerosis such as myocardial infarction (MI), sudden cardiac death or ischemic stroke are the leading causes of morbidity and mortality in industrialized countries [33]. Statins are currently considered as the first-line pharmacological treatment of dyslipidemia and hypercholesterolemia [34, 35]. For each 1.0 mmol/L reduction of LDL-C, there is a 21% reduction in the risk of major vascular events like myocardial infarctions, coronary deaths, strokes and a reduction of 10% for all-cause mortality. It is known that efficacy of statins slightly differs within the class and individual statins. The intensity of statin therapy is divided into 3 categories: high-intensity, moderate-intensity, and low-intensity. High-intensity statin therapy typically lowers LDL-C levels by ≥50%, moderate-intensity statin therapy by 30% to 49%, and low-intensity statin therapy by <30%. However, the magnitude of LDL-C lowering will vary in clinical practice (Figure 3).

Statin	High Intensity ≥50%	Moderate Intensity 30% to 49%	Low Intensity <30%
	Atorvastatin 40–80 mg	Atorvastatin 10–20 mg	Fluvastatin 20–40 mg
	Rosuvastatin 20–40 mg	Fluvastatin 80 mg	Lovastatin 20 mg
		Lovastatin 40–80 mg	Pravastatin 10–20 mg
		Pitavastatin 1–4 mg	Simvastatin 10 mg
		Pravastatin 40–80 mg	
		Rosuvastatin 5–10 mg	
		Simvastatin 20–40 mg	

Figure 3. The intensity of statins therapy is divided into 3 categories based on ”ACC/AHA lipid guidelines: Personalized care to prevent cardiovascular disease” guidelines.

A systematic review and meta-analysis of statin effect on LDL-C levels demonstrated that 10 mg/day of simvastatin achieved a 27% estimated absolute reduction of LDL-C and a higher

doses could improve the lowering effect even more [53]. Other studies showed that fluvastatin, lovastatin, and pravastatin have a limited effect on LDL levels in homozygous familial hypercholesterolemic patients who are unable to produce LDL receptors, meanwhile, atorvastatin, rosuvastatin, and simvastatin are effective in this disease [36, 37]. In the case of hypercholesterolemia, the recommended dose of simvastatin and atorvastatin is 10–20 mg/day administered in a single dose in the evening; patients requiring a large reduction in LDL-C (greater than 45%) may start with 20–40 mg/day administered in a single dose in the evening. Only rosuvastatin should be initiated with a dosage of 5–10 mg/day, reaching maximum doses of up to 40 mg/day only in patients who have not reached the therapeutic goals established with the lowest doses [38]. Atorvastatin has been extensively studied in the primary and secondary prevention of cardiovascular events, and may have stronger clinical advantages over various other statins in LDL lowering [39]. The principal primary prevention study of atorvastatin, Anglo-Scandinavian Cardiac Outcomes Trial–Lipid Lowering (ASCOT-LLA), revealed that atorvastatin reduced the relative risk of primary coronary heart disease (CHD) events by 36% ($p = 0.0005$) compared with placebo in patients with hypertension. Intensive atorvastatin therapy (80 mg/day) reduced the risk of nonfatal myocardial infarction by 17–22% ($p \leq 0.02$). In terms of primary prevention, the ASCOT-LLA trial highlighted the significant efficacy of atorvastatin in reducing the risk of CV events [40]. Another study conducted in the treatment of dyslipidemia among diabetic patients showed that rosuvastatin (10 mg) was the most effective in reducing low-density lipoprotein cholesterol (LDL-C; 28.59%), followed by simvastatin 20 mg (16.7%), atorvastatin 20 mg (15.9%), and pravastatin 20 mg (11.3%). Atorvastatin was the safest statin as it resulted in the least number of patients with microalbuminuria (10.92%) as compared to other statins. Treatment with 10 mg of rosuvastatin was more effective in allowing patients to reach European and Adult Treatment Plan (ATP) III LDL-C goals as compared to other statins ($P < 0.0001$) and produced greater reductions in LDL-C, total cholesterol, and non-HDL-C, produced similar or greater reductions in triglycerides (TGs) and increased in HDL-C. Rosuvastatin 10 mg was more effective than atorvastatin in reducing serum lipids and total cholesterol in dyslipidemic diabetic patients [41]. Additional benefit was provided by atorvastatin and rosuvastatin compared with simvastatin. Assessing a cohort of 55-year-old Finnish men study it was discovered that rosuvastatin 10 mg was both more effective and less expensive than atorvastatin 20 mg, rosuvastatin dominates over atorvastatin. The average life expectancy (LE) for the Finnish male population without statin therapy was 21.0 years. The use of simvastatin extended the LE by 1.4 years compared to no treatment [42].

In addition to the effects on lipid metabolism, statins also have pleiotropic effects that may not be directly related to alterations in lipid metabolism. For example, statins are anti-

inflammatory and consistently decrease CRP levels. Other pleiotropic effects of statins include anti-proliferative effects, antioxidant properties, anti-thrombosis, improving endothelial dysfunction and attenuating vascular remodeling. Whether these pleiotropic effects contribute to the beneficial effects of statins in preventing cardiovascular disease is uncertain and much of the beneficial effect of statins on cardiovascular disease can be attributed to reductions in lipid levels [50].

2.3.1.4. Guideline recommendations for statins and lipid-lowering treatment goals

2019 ESC/EAS represents the views of the European Society of Cardiology and European Atherosclerosis Society (EAS) guidelines for the management of dyslipidemia. Guidelines consist of various criteria which should be individually tailored to each patient to reach lipid-lowering treatment targets. Each patient should follow basic principles of a healthy lifestyle such as a healthy diet, no exposure to tobacco and 30-60 min of moderately vigorous physical activity per day to achieve a lipid-lowering effect. However, healthy lifestyle intervention is often not sufficient, therefore concomitant drug intervention becomes necessary. For the management of dyslipidemia, statins are the first-choice drugs for patients, both for primary and secondary prevention. Medication therapy is indicated for all risk groups, both primary and secondary, when LDL-C concentrations are ≥4.9 mmol/l. Based on the Systematic Coronary Risk Estimation (SCORE) chart, patients that have a value of ≥5 to 10 mmol/l or are at high risk because of other risk factors, should receive the lipid-lowering treatment when their untreated LDL-C levels are higher than 2.6 mmol/l. And those patients with SCORE value of ≥10 mmol/l or at very-high risk due to other risk conditions, should be prescribed with a statin treatment if their untreated LDL-C levels are ≥1.8 mmol/l. Due to the 2019 ESC/EAS guidlines there are 4 risk levels for CVD [55] (Table 1).

Table 1. 2019 ESC/EAS guidelines adjusted table of 4 risk levels for CVD. (55)

Very-high-risk
People with any of the following: – Documented ASCVD, either clinical or unequivocal on imaging. Documented ASCVD includes previous ACS (MI or unstable angina), stable angina, coronary revascularization (PCI, CABG, and other arterial revascularization procedures), stroke and TIA, and peripheral arterial disease. Unequivocally documented ASCVD on imaging includes those findings that are known to be predictive of clinical events, such as significant plaque on coronary angiography or CT scan (multi vessel coronary disease with two major epicardial arteries having >50% stenosis), or on carotid ultrasound; – Severe CKD (eGFR <30 mL/min/1.73 m^2); – A calculated SCORE ≥10% for a 10-year risk of fatal CVD; – DM with target organ damage*, or at least three major risk factors, or early onset of T1DM of long duration(>20 years);

– FH with ASCVD or with another major risk factor.
High-risk
People with: – Markedly elevated single risk factors, in particular TC>8 mmol/L (>310 mg/dL), LDL-C >4.9 mmol/L(>190 mg/dL), or BP ≥ 180/110 mmHg; – Patients with FH without other major risk factors; – Patients with DM without target organ damage*, with DM duration ≥ 10 years or another additional risk factor; – Moderate CKD (eGFR 30-59 mL/min/1.73 m^2); – A calculated SCORE ≥ 5% and <10% for a 10-year risk of fatal CVD.
Moderate-risk
– Young patients (T1DM <35 years; T2DM <50 years) with DM duration <10 years, without other risk factors. Calculated SCORE ≥1% and <5% for 10-year risk of fatal CVD.
Low-risk
– Calculated SCORE <1% for 10-year risk of fatal CVD.

ASCVD = atherosclerotic cardiovascular disease; ACS = acute coronary syndrome; BP = blood pressure; CABG = coronary artery bypass graft surgery; CKD = chronic kidney disease; CT = computed tomography; CVD = cardiovascular disease; DM = diabetes mellitus; eGFR = estimated glomerular filtrationrate; FH = familial hypercholesterolaemia; LDL-C = low-density lipoprotein cholesterol; MI = myocardial infarction; PCI = percutaneous coronary intervention; SCORE = Systematic Coronary Risk Estimation; T1DM = type 1 DM; T2DM =type 2 DM; TC = total cholesterol; TIA = transient ischaemic attack.

* Target organ damage is defined as microalbuminuria, retinopathy, or neuropathy

People in the low-risk level should be adviced to maintain healthy lifestyle. Thus, the intensity of preventive actions should be tailored to the patient's total CV risk. The strongest driver of total CV risk is age, which can be considered as 'exposure time' to risk factors. For people with a very high risk level it is recommended to prescribe high-intensity statin treatment up to the highest tolerated dose to reach the target set according to the risk levels (Table 2). If treatment goals are not achieved with statin monotherapy, the guidelines suggest to add a second lipid-lowering medication.

Table 2. Treatment targets for CVD prevention differ based on the baseline risk (55).

Very-high risk in primary or secondary prevention:	A therapeutic regimen that achieves ≥50% LDL-C reduction from baseline band an LDL-C goal of <1.4 mmol/L (<55 mg/dL). No current statin use: this is likely to require high-intensity LDL-lowering therapy. Current LDL-lowering treatment: an increased treatment intensity is required.
High-risk:	A therapeutic regimen that achieves ≥50% LDL-C reduction from baseline band an LDL-C goal of <1.8 mmol/L (<70 mg/dL).
Moderate-risk:	A goal of <2.6 mmol/L (<100 mg/dL).
Low-risk	A goal of <3.0 mmol/L (<116 mg/dL).

A systematic review of 102 research studies compared bile acid, ezetimibe, fibrate, niacin and Omega-3 fatty acid medication combinations with statin monotherapy showed that ezetimibe plus simvastatin therapy is more likely to result in attainment of LDL-C target than a higher dose of simvastatin. The results for statin-fibrate combination were indeterminate and no evidence was found for any other statin combination to be more efficient than statin monotherapy [54].

2.4. Reimbursement system in Lithuania and statin reimbursement

Lithuania has a compulsory health insurance system where all residents in the country are required to have health insurance coverage. This includes all legally employed persons paying the compulsory health insurance contributions. The majority of funds to the National Health Insurance fund (NHIF) comes from the contributions paid by the insured residents and from those contributions that are paid on their behalf. The State pays for retired people, disabled, children and students, unemployed people that are registered with the Labour Exchange office, mothers taking care of their children in maternity leave etc. The compulsory health insurance makes sure that all insured people would receive a compensation for their healthcare expenses from the NHIF including compensation for reimbursed medications [43].

For CVD prevention all four, simvastatin, fluvastatin, atorvastatin, rosuvastatin, registered statins in Lithuania can be prescribed as reimbursed medications by a doctor that works in a health organization that has a contract with the NHIF. Until July 2018 statins had a 20% co-payment in the Lithuanian reimbursement system, then it was reduced to 10%. Since April 2019, statins have a 0% co-payment which allows the drug to be increasingly available to everyone regardless of their financial or employment status [45, 46]. Statins are also available in combinations with several of antihypertensive substances, including rosuvastatin in combination with angiotensin receptor blocker valsartan or atorvastatin together with angiotensin converting enzyme inhibitor perindopril and calcium channel blocker amlodipine [44].

Reimbursed statins are indicated for several different disorders of lipoprotein metabolism and other hyperlipidemias, transient cerebral ischemic attacks and related syndromes, acute, subsequent or old myocardial infarction, some forms of angina pectoris (including unstable angina), cerebral infarction etc. As a part of combination drugs, statins are indicated for primary hypertension and hypertensive heart disease when a patient also has any other statin indications (dyslipidemia, myocardial infarction etc). To get a reimbursed statin prescription for treatment of disorders of lipoprotein metabolism and other hyperlipidemia, the patient needs to comply with the criteria below (Table 3).

Table 3. The criteria for statin prescription reimbursment.

Patients with LDL-C ≥ 3 mmol/l and with high CVD risk factors:	- Moderate CKD (eGFR 30-59 mL/min/ 1.73 m²); - Type 1 or 2 DM without target organ damage; - A calculated SCORE ≥5% and <10% for a 10-year risk of fatal CVD.
Patients with LDL-C ≥ 1,8 mmol/l and with very high CVD risk factors:	- Documented ASCVD including previous ACS (MI or unstable angina), stable angina, coronary revascularization (PCI, CABG, and other arterial revascularization procedures); - Stroke and TIA; - Peripheral arterial disease; - Unequivocally documented ASCVD on imaging (such as significant plaque on coronary or carotid arteries); - Type 1 or 2 DM with target organ damage; - Severe CKD (eGFR <30 mL/min/1,73 m²); - A calculated SCORE ≥10% for a 10-year risk of fatal CVD.
Patients with early detected CVD anamnesis if LDL-C is ≥ 5 mmol/l:	- CVD event happened to first generation male relatives under 55 years old or first generation female relatives under 65 years old.
Patients with LDL-C ≥ 3,0 mmol/l and SCORE risk:	- Patients with a SCORE cardiovascular risk between ≥1% and <5% for a 10-year risk of fatal CVD.

ASCVD = atherosclerotic cardiovascular disease; ACS = acute coronary syndrome; CABG = coronary artery bypass graft surgery; CKD = chronic kidney disease; CVD = cardiovascular disease; DM = diabetes mellitus; eGFR = estimated glomerular filtration rate; LDL-C = low-density lipoprotein cholesterol; MI = myocardial infarction; PCI = percutaneous coronary intervention; SCORE = Systematic Coronary Risk Estimation; TC = total cholesterol; TIA = transient ischemic attack.

2.5. Persistence and Adherence

Adherence is the main challenge with all pharmacological therapies. In the randomized controlled trials CV benefits shown by statin treatment can only be expected to provide similar clinical benefits in patients who follow the prescribed treatment regimen for a prolonged period, possibly even for a lifetime [18]. To achieve the beneficial effects, statins have to be taken continuously. "Taxonomy for describing and defining adherence to medication" introduces three processes that describe actions through established routines to adherence – adherence to medication, management of adherence and adherence-related sciences. Adherence to medication distinguish its three components:

- Initiation (patient takes the first dose of a prescribed medication);
- Implementation (patient's actual dosing corresponds to the prescribed dosing regimen, from initiation until the last dose is taken);
- Discontinuation (end of therapy, when the next dose to be taken is omitted and no more doses are taken thereafter) [56].

Adherence and persistence are both concepts related to the continuous use of chronic treatment. Even though they are two different measures it has been shown that poor adherence and persistence to the medication regimen is a major factor behind the lack of effect [13, 14, 15]. Medication persistence is a medication-taking construct defined as 'the duration of time from initiation to discontinuation of therapy'. By definition, it is expressed solely as a function of time or the number of days (or months) on treatment. Alternatively, persistence can be expressed as a binary variable (persistent or non-persistent), measured at the end of a prespecified period of time. Medication persistence and adherence are similar in that they both measure the extent to which a patient's behaviour agrees with recommendations of a healthcare provider. They differ, however, as they are two different dimensions of the agreed therapy. With regard to taking medications, adherence measures the proportion of times that a patient takes medication as prescribed within a given interval, whereas persistence measures the duration of time that a patient continues to follow a prescribed regimen. In other words, adherence measures 'how often', whereas persistence measures 'for how long.' As such, these constructs are complimentary but distinct [23]. Non-adherence to medications is widely recognized as a major public health concern and contributes to patient morbidity, mortality and healthcare costs [22]. Despite the beneficial effects of statins, the rate of therapy discontinuation is high, both for individuals in primary and secondary prevention [16, 17]. About a half of the patients discontinues statin therapy within the first year, and adherence decreases with time [18]. Observational studies assessing persistence with statins, mainly conducted in elderly subjects, found 1-year persistence rates of 25–85% [19, 20]. A Canadian study among elderly subjects with or without acute coronary syndrome has shown a persistence rate of only 40% at 2 years among patients with acute coronary syndrome, 36% for those with chronic coronary artery disease, and 26% among patients in primary prevention [21]. In particular, high-dose statin therapy is frequently underused and LDL-C goals are not met in a substantial proportion of high CV risk patients. A recent study for underutilized statin therapy for secondary prevention has shown that higher intensity levels of statin therapy are more effective than lower levels in reducing mortality rates. Despite that, some physicians are still avoiding intensive statins therapy and continue treatment at lower doses [63]. Suboptimal adherence to statins therapy is usually advocated as the main barrier to reach and maintain LDL-C targets. Statins discontinuation

occurs more frequently among those patients who did not tolerate the drug, especially after dose escalation. Inappropriate prescribing and poor physicians' attention to the different LDL-C reduction rates provided by different statins and the concomitant presence of some comorbidities limiting the use of high-dose statins in some patients, may also account for failure in reaching LDL-C targets [22]. Nevertheless, the healthcare provider must be willing to ally and dialogue with patients to address concerns and assess the risks and benefits of continued statin therapy. Good compliance with statin therapy in the first 2 years of prescription may reduce hospitalization rates and direct medical costs in the subsequent year [18].

2.6. Persistence measurements

There are two main methods to measure persistence – continuous and dichotomous measures. The continuous measures consist of hybrid and refill sequence models. In hybrid model, persistence is measured as the interval between the date of the first prescription and the point at which the patient would have had an insufficient supply of available drug to cover the days between prescription refills. Whereas in refill sequence model persistence is measured as the interval between the date of the first prescription and the point at which an unacceptable gap between prescription refills occurs. Dichotomous measures are easier to measure. For instance, in the minimum's refills measure, a patient is considered persistent with the treatment if she/he was dispensed a specified minimum number of prescriptions per year. No consideration is given to length or dates of prescriptions filled within the 1-year interval. The simplest method of measuring persistence with treatment is the anniversary model in which a patient is deemed persistent for one year if she/he refills a prescription within a specific interval surrounding the anniversary of the first prescription (e.g. -+ 30, 60 or 90 days). This method uses a simple, dichotomous measure of persistence, persistent versus not persistent, with no consideration of prescription refills within the 1-year interval [24] (Figure 4).

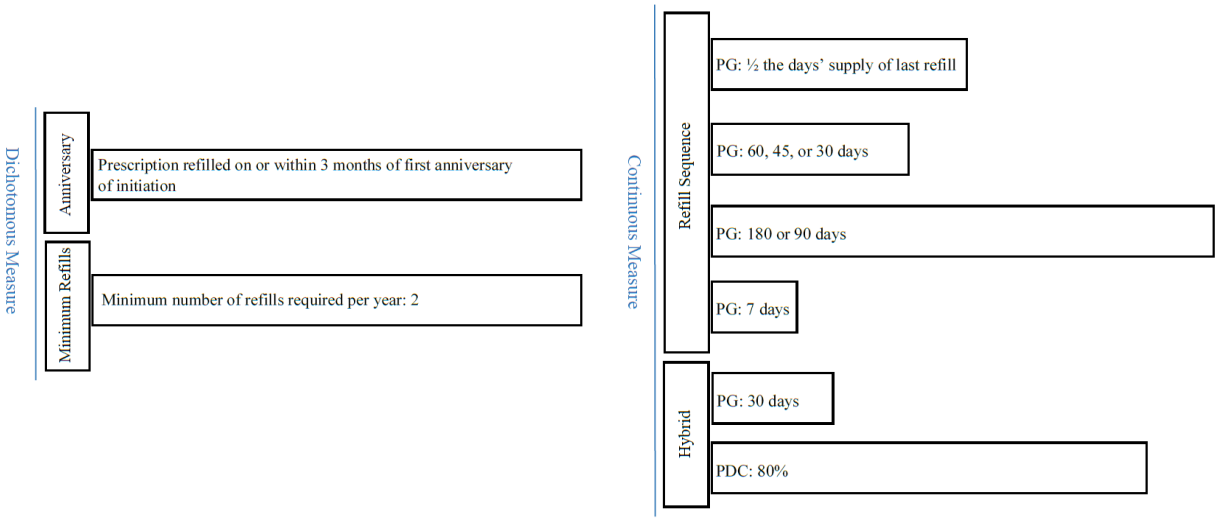

Figure 4. The ways to measure patient's persistence with medication using each method identified in the literature review. PDC- Proportions of days covered; PG- permissable gap (days) [24].

2.6.1. Causes of poor-adherence and poor-persistence

Staying adherent and persistent to medication for treatment of a symptomless condition, such as high LDL-C levels, is a challenge to both, the doctor and the patient. Causes of non-adherence are complex and can be broadly classified into five categories: **patient-related, therapy-related, health system-related, social-economic factors and condition-related factors**. Among these, patient and healtcare-related factors may be the strongest [18].

Patient-related

Physical impairments and cognitive limitations may increase the risk for non-adherence in older adults. Low health literacy, lack of understanding of the disease being treated, educational and ethnicity related background, attitudes concerning the effectiveness of the treatment, negative previous experience with pharmacological therapies, all listed factors contribute to patients non-persistence and non-adherence. Patients forgetfulness plays a role, but underlying reasons often contribute to forgetfulness, including lack of prioritization of the importance of medication intake, medication as a reminder of the patients' condition, the need to take medications make the patients feel old or bad about themselves, or simply not liking the idea of taking a pill [18]. Statin non-persistence has been independently associated with younger patient age, female gender, lower income patients, health condition not considered to be dangerous, medication not considered to be important for health, and taking 2 or more medications ot once [20]. A meta-analysis showed that age as a predictor of non-adherence follows a U shaped curve, with the youngest (< 50 years) and oldest (≥ 70 years) showing lower adherence than those between 50–69 years [20]. Not

surprisingly, adherence to statins is better when patients have a history of CV disease and possess a number of CV risk factors other than elevated LDL-C [20]. Coexisting illnesses such as diabetes and hypertension may predict better adherence. As the patient ultimately makes the decision whether or not to take the medication, it is important to understand their perspectives on non-adherence to statin therapy.

Healthcare-related

The relationship of the doctor-patient is one of the most important health care system-related factors impacting adherence. Complex drug regimens prescribed by physicians, lack of adequate explanation about the disease, about the benefits and about potential adverse events of medications, and inconsistent messages from physicians, all contribute to medication non-adherence. This is true for statins as well. Unfortunately, the economics of the health care market severely limit funding and subsequently the time a physician can spend with one individual patient. This can interfere with adequate patient education about medications, assessment of medication-taking behaviors and encouragement of adherence to prescribed medication regimens. The involvement of several physicians and the necessity of multiple visits to pharmacies to fill or refill different prescriptions, including different refill dates for patients' prescriptions, predict worse medication adherence [22]. The lack of a match between patient readiness and the practitioner's attempts at intervention means that treatments are frequently prescribed to patients who are not ready to follow them. Based on an administrative claims database, certain types of physician prescribers were associated with greater rates of statin adherence among their patients. Initiation of statins by a primary care physician, a cardiologist or a US medical graduate was noted as a predictor of improved adherence [18]. A good relationship between the patient and health care provider, which features encouragement and reinforcement from the provider, has a positive impact on adherence.

Therapy-related

Therapy-related factors leading to non-adherence and non-persistence include complexity of multiple medication regimen - polypharmacy, which includes the number of medications and number of daily doses required, duration of therapy, therapies that are inconvenient or interfere with a person's lifestyle and side effects are also associated with decreased adherence. Non-adherence in therapy related factors is primarily asosciated with patients misunderstanding of the disease. The study of first population-based research in Demnark considers how well patients understand their own disease and their ability to work closely with health care staff. It is also

mentioned that many patients suffering from chronic disease such as CVD do not understand their own illness and possible consequences of not following their treatment regimen [57]. Non-adherence also can be associated with patients exposure or concerns about experiences with adverse events (AEs) [20]. Some patients discontinue treatment when being exposed with severe adverse events while others get concerned or uncertain about the benefits or importance of statins. In other cases it can be the inconvenience of taking a medication and getting laboratory tests done, and preferring to take brand name statins instead of the prescribed generic statin. A recently published study, the Understanding Statin Use in America and Gaps in Patient Education (USAGE), provided further insights into reasons for switching or discontinuing statins through an internet-based survey of 10,138 respondents. At the time of the survey, 88% of respondents were statin users and 12% were former users. The majority patients claimed that they discontinued or stopped using statins (67%) because of adverse events [18].

Condition - related

Condition-related factors leading to non-adherence and non-persistence include presence of symptoms, disease severity, clinical improvement, psychiatric condition, certain diagnoses/ indications and duration of the disease. Non-adherence in condition related factors is primarily associated with patients misunderstanding of CVD chronic conditions and disease severity. Chronic disease that is persistent or otherwise long-lasting in its effects or a disease comes with time, therefore life-threatening symptoms only become apparent later in life [58]. Long term drugs administration for many chronic illnesses and adherence to such treatment regimens often declines significantly over time. This often happens when patients have few or no symptoms and the absence of the symptoms is a barrier for people to take their medication. It is important for the patient to understand the illness and what will happen if it is not treated [18].

Socioeconomic-related

Socioeconomic-related factors leading to non-adherence and non-persistence include social stigma of disease, costs of drugs and treatments and a lack of social support. There is evidence that people with a lower socioeconomic position are sicker and therefore tend to use comparatively more general health care services, but in contrast they use less specialist services than people in higher socioeconomic position [59]. Although the evidence of a direct association of income and educational achievement with medication adherence is mixed, cost burden is a widely recognized barrier and financial strain has been associated with medication non-adherence among patients with various chronic health conditions [48]. In Lithuania public health policy is based on the

principle of creating societal conditions to promote equality in health and access to health care on equal terms. Since April 2019, statins have no co-payment which allows medicine to be more available to everyone regardless of their financial and employment status [46].

The people who have social support from family, friends, or caregivers to assist with medication regimens have better adherence to treatment. For the effective provision of care for chronic conditions, it is necessary that all, the patient, the family and the community, who support, play an active role. There is substantial evidence that active support among patients can improve adherence to therapy while reducing the amount of time devoted by the healthcare professionals to the care of chronic conditions [18].

The evidence for an impact of education on adherence is uncertain for most diseases and therapies. Some evidence for a positive impact of education on adherence has been found for cardiovascular conditions [49].

3. METHODS

This was a longitudinal observational retrospective cohort study based on the data collected from the National Insurance Fund's database Sveidra.

3.1. Setting

This study was conducted in Lithuania, which is situated in the Baltic region of Europe and is one of three Baltic States on the eastern shore of the Baltic Sea. Lithuania has a population of around 2.8 million people and is ranked 13th in the world by the largest number of older adults [51]. Country holds a total area of 65'300 km^2 and has a density of 43/km^2 (Figure 5).

Figure 5. Map of Europe with Lithuania highlighted and key facts listed (1st of January 2022).

Life expectancy in Lithuania in 2020 was the third lowest in the EU with 5.5 years below the EU average. Although the increase in life expectancy in Lithuania between 2010 and 2019 was the fastest in the EU, the impact of COVID-19 was a major setback. After years of steady gains in population health, the high mortality registered in Lithuania during the COVID-19 pandemic in 2020 temporarily caused a large drop in life expectancy by 1.4 years compared to 2019. On average, Lithuanian women live almost 10 years longer than men do, at around 80 years compared to around 70 years. This gender gap in life expectancy is the largest in the EU. Even though alcohol consumption levels fell by one quarter between 2012 and 2019 due to stricter alcohol control measures targeting younger people. Adolescents in Lithuania are still more frequently exposed to risk factors such as smoking and excessive drinking than the average in the EU. In 2019 in

Lithuania health spending per capital (EUR 1’885) was almost half the EU average (EUR 3’521, adjusted for differences in purchasing power), but is among the highest in central and eastern Europe. The healthcare spending in Lithuania as a share of GDP, remained low at 7.0%, compared to the EU average of 9.9%. About one thirds of it is spent for outpatient care (including home care), pharmaceuticals and medical devices take 28% while prevention equals less than 3% of total expenditures. Only two thirds of health spending were publicly financed in 2019, with the remaining third coming from private sources, mainly out-of-pocket (OOP) payments [60] (Table 4).

Table 4. Comparison of country health profiles in Lithuania and European Union in 2021 [60].

	Lithuania	**European Union average**
GDP in Euros:	55.4 million	14.45 trillions
Health expenditure share of GDP:	7%	9.9%
Life expectancy at birth: Gender gap:	75.1 years 9.9 years	80.6 years 5.4 years
Life expectancy at 65:	17.4 years	17.4 years
Share of population over age 65%:	19.9%	20.6%
Health spending:	Outpatient care – 33% Pharmaceuticals and medical devices – 28% Prevention – 2.7%	Outpatient care – 54.9% Pharmaceuticals and medical devices – 33.6% Prevention – 4.6%

Lithuania by its epidemiological situation had a significant cardiovascular morbidity and mortality for many years. According to the data of the Institute of Hygiene, since 2015 the mortality curve from cardiovascular diseases has started to rise again. During 2020, almost 44 thousand people in Lithuania died from cardio-vascular diseases, comprising 52.7% of all deaths in the same year, ischemic heart diseases (ICD-10: I20-I25) being the leading cause. Comparing 2020 and 2019, almost 10% more people died from CVD’s in 2020 [52]. Covid-19 pandemic might be the main consequence of a vivid CVD’s mortality change due to limited access of other disease treatments.

3.2. Data source

In this cohort study patients data with prescribed statins were extracted from National Health Insurance Fund’s “Sveidra” database. Reimbursed medicines subsystem contains information on

all reimbursed prescriptions and covers up to 100% of the insured population. The medicines that were bought fully out of the pocket are not included in the "Sveidra" dataset.

The extracted data set contains all of the filled prescriptions of reimbursed drugs. It also provides information on prescription and dispensation dates, ICD-10 code, nonproprietary name of the substance, the brand name of the dispensed drug, formulation and strength, ATC code, package size, the number of packages dispensed and the date until the patient is in a possession of drug supply. All ages of adult patients were included. The disease diagnoses were selected using ICD-10 (Table 5) codes below:

Table 5. Disease diagnoses named by ICD-10.

Primary CVD prevention	Secondary CVD prevention
- Diabetes mellitus disease - E10; E11	- Heart attack - I21; I22; I25.2.
- Hypertension - I10; I11	- Stroke and Transient ischemic attack (TIA) - I63.
	- Ischemic coronary heart disease - I20; I25.0; I25.1; I25.5; I25.6; I25.8; I25.9.

3.3. Outcome measure and statistical analysis

For the analyses and comparisons in this study, the ATC index was used for the study period and the ATC code for statins C10AA as well as ATC codes for individual statins – C10AA01 (simvastatin), C10AA04 (fluvastatin), C10AA05 (atorvastatin) and C10AA07 (rosuvastatin). Statins are presented by their available doses in the Lithuanian market (Table 6).

Table 6. Available statin doses in the Lithuanian market [62].

Simvastatin	Fluvastatin	Atorvastatin	Rosuvastatin
10mg; 20mg	80mg	10mg; 20mg; 30mg; 40mg; 60mg; 80mg	5mg; 10mg; 15mg 20mg; 30mg; 40mg

NA – not applicable; LDL-C - low-density lipoprotein cholesterol.

The cohort inclusion period starts from January 2018. The index date is the date of the first dispensed statin prescription in the year 2018. The patient was considered as newly initiated with statin treatment if no statins were dispensed to the patient between 2017.01.01 and 2017.12.31. The year 2017 is used as a run-in period. For a patient to be included in the cohort, it was required to have at least one year of follow-up time after the index date. Baseline patient characteristics were captured at the index date and include sex, age, first statin prescribed (type and intensity), prescriber (GP, cardiologist or other), diagnosis IDC-10 codes, region where the patient got the

prescription filled, which statin substance that was dispensed and latest dispensed strength while staying persistent. Records for the previous use of antihypertensive, antithrombotic or antidiabetic drugs were considered if they were recorded before or at the index date.

Individual patients were followed from the index date to the end of the study period (2020.12.31). Each patient´s dispensing patterns were assessed over time and persistence to statin therapy was calculated within the first year (anniversary method). Persistent patients were defined as patients who did not have statins dispensed at day 365 after the index date, taking into account a permissible gap of 90 days of supply of the last dispensing. Patients remaining on statins treatment, but switching between statin types or doses, were considered as persistent.

Persistence rates were calculated overall for all statins and for each substance and were assessed for the potential predictors of persistence including age, sex, prescriber, first medicine prescribed (type and intensity), year of the treatment initiation, prescriber (GP, cardiologist or other), diagnosis from the ICD-10 code, previous drug use, type of statin used and latest dispensed strength while staying persistent. Crude and adjusted odds ratios were calculated using logistic regression.

Data was analyzed with IBM SPSS statistics 27. Descriptive statistics was used to describe baseline characteristics. Continuous variables were summarized using means and standard variation. A multivariate logistic regression was used to explore factors associated with persistence. Crude and adjusted odds ratios with 95% confidence intervals (CI) were calculated.

3.4. Ethical considerations

Since cardiovascular diseases for many years are the leading cause of death in Lithuania it is important to raise awareness for patients, practicioners and society in order to tackle some of the possible occurring cardiovascular disease events caused by poor-adherence and poor-persistence. Furthermore, study could allow further development of research and dialogue on how to lower the cardiovascular disease mortality. Ethical approval was issued by Vilnius Regional Biomedical Research Ethics Committee in 2021. Permission number - 2021/2-1314-790

4. RESULTS

4.1. Characteristics of patients initiated on the statins treatment

A total of 104’726 patients (41,3% men, 58,7% women) were included in the study (Table 7). The age group of 45-64 years old accounted for the largest proportion of patients initiated on statins treatments. Although women shared a highest percentage for being initiated on stains treatment from the age group of 45-64, men shared a higher percentage of those initiated on the statins treatment from the early age of 18. Men had more cardiovascular comorbidities than women. Other comorbidities such as diabetes mellitus disease and hypertension accounted for small amounts of patients for both genders, however it can be an issue of low disease reporting rate. The proportion of patients with diagnosed disease in the year before statin initiation were relatively low, compared to the previous dispensing of medications such as antidiabetic, antithrombotic and antihypertensives. As shown in the table, women had a larger proportion of previous drugs dispensed, although men had a slightly higher utilization in antithrombotic drugs. The most commonly used drugs were antihypertensive, respectively in men 53,3% and 63,5% women. A majority of all women 78,6% initiated on statin treatment received medication for primary prevention, while the corresponding figure for men was 65,3%. Meanwhile, secondary prevention shared a smaller amount of patients, correspondingly 34,7% of men and 21,4% women, respectively men shared a larger proportion of patients in secondary prevention than women.

Table 7. Characteristics of patients initiated on the statins treatment in Lithuania 2018-2019.

	Women		**Men**	
	Total	**%**	**Total**	**%**
Age group				
Total	61 478	100,0%	43 248	100,0%
Age 18-44	380	0,6%	4 945	11,4%
Age 45-64	37 369	60,8%	24 499	56,7%
Age 65-74	12 056	19,6%	8 128	18,8%
Age 75+	11 673	19,0%	5 676	13,1%
Diagnosis				
Stroke/TIA	1 699	2,8%	1 971	8,1%
Heart attack	3 134	5,1%	6 143	14,2%
Ischemic coronary heart disease	8 337	13,6%	6 883	15,9%
Diabetes mellitus	22	0,0%	16	0,3%
Hypertension	901	1,5%	612	1,4%
Primary prevention	48 308	78,6%	28 251	65,3%
Secondary prevention	13 170	21,4%	14 997	34,7%
Previous use of drugs				
Antidiabetic	7 091	11,5%	4 675	10,8%
Antithrombotic	3 920	6,4%	3 363	7,8%
Antihypertensives	39 054	63,5%	23 041	53,3%

4.2. Types and strenghts of statins used for initiation

Atorvastatin was the leading medication which accounted for 60,2% of all initiated statins, rosuvastatin was the second in order with 39,6%, while fewer than 1% of all patients were initiated on fluvastatin or simvastatin.

The most commonly used strenght at initiation was 20 mg atorvastatin. Other commonly used strenghts were 40 mg atorvastatin and 10 mg rosuvastatin shared a second place of most utilized statins in Lithuania, where rosuvastatin 40 mg respectively. Meanwhile, the least prescribed and utilized stains from atorvastatin and rosuvastatin were the high intensity dosages.

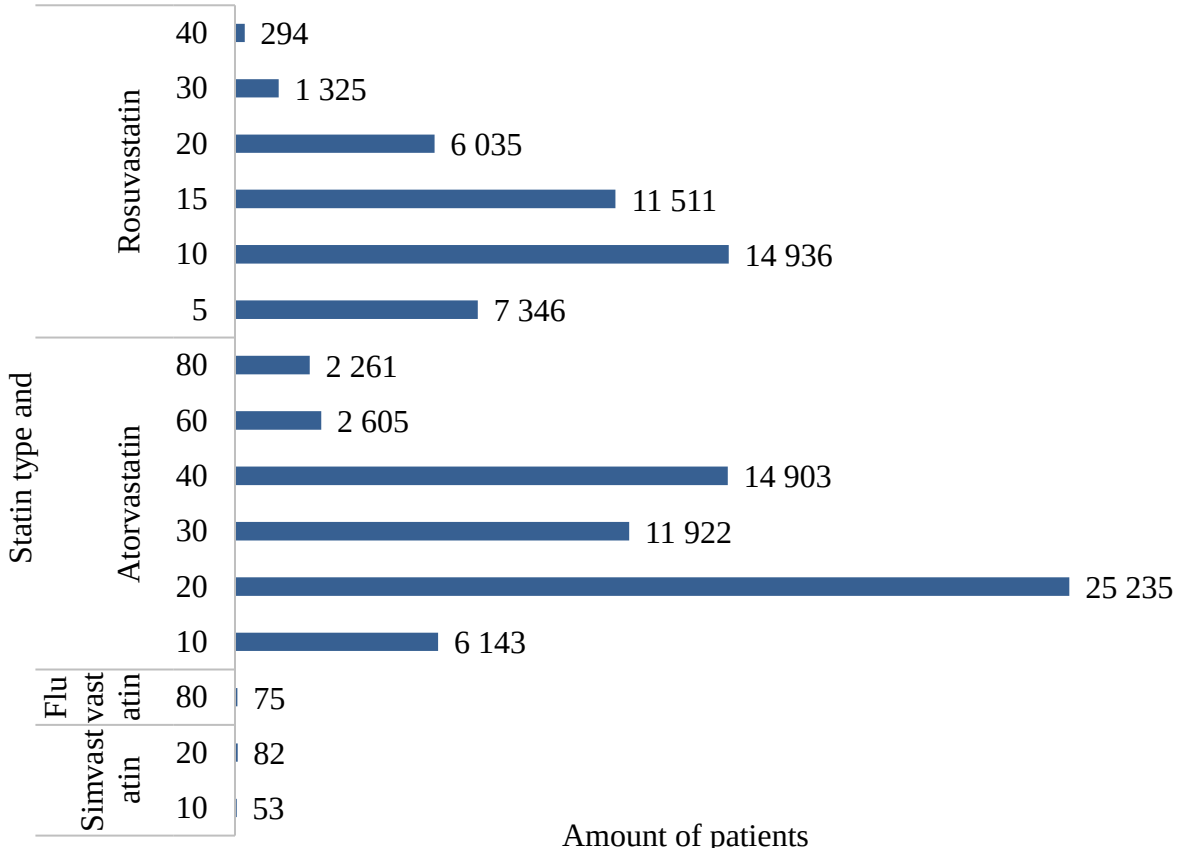

Figure 6. Statins types and strengths prescribed in Lithuania reflected with count of patients. Statins strengths defined represented in mg.

The least prescribed statins in Lithuania appeared to be simvastatin and fluvastatin. In total 10mg and 20 mg of simvastatin together with 80 mg of fluvastatin were prescribed to 210 patients (Figure 6).

4.2.1. Initiation trends of atorvastatin and rosuvastatin by gender

Women had a larger proportion being initiated on lower strengths of statins and men held a higher proportion initiated on intensity statins. From all six different available streghts of atorvastatin in Lithuania, females had a predominance in four statins strengts from 10 mg dose to 40 mg dose. Meanwhile, males by the porportion were leading only in two strengts 60 mg and 80 mg of atorvastatin. The largest diference by gender for patients initiated on atorvastatin, was captured with 20 mg dose, which consider 5% (Figure 7).

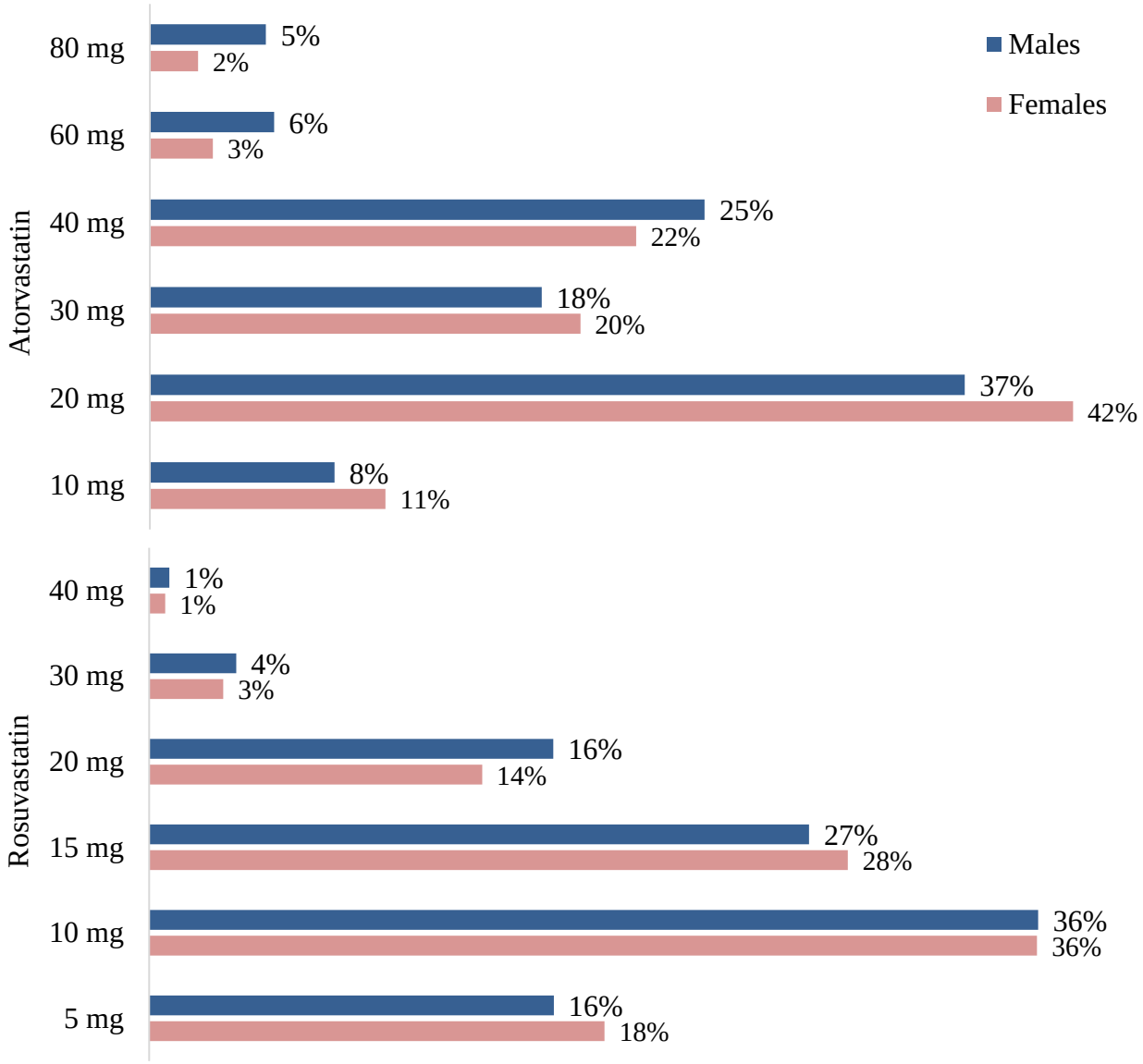

Figure 7. Proportion of patients initiated on different statin type and strength split by gender.

There was a less pronounced gender difference for rosuvastatin than atorvastatin. However, with rosuvastatin it was also observed a tendency to initiate males on higher strenghts. Respectively males were more likely to be initiated on statins from 20 mg of rosuvastatin to 40 mg (Figure 7).

4.3. Patients persistence to the treatment

In the study 41% of all patients remained on the statin therapy after one year. Persistence was similar between genders with 40,3% of women and 41,3% of men being considered as persistent to the statin treatment (Table 8). The proportion of patients staying persistent to the treatment in Lithuania increased by age, except for in the oldest age group. Less persistent patients were found in the age group of 45-64 years old for both genders, respectively males 39,7% and 37,0% females. The lowest persistence rate was discovered in the youngest age group of 18-44 years old patients. The age group of 18-44 years old patients was the only group were males shared a lower persistence rate than females, respectively 31,6% for males and 35,8% for females patients (Table 8).

Table 8. Patients persistent to statin treatment by gender, age group and prevention type.

		Total	Persistent	Persistent %
Female		61 478	24 751	40,3%
	18-44	380	136	35,8%
	45-64	37 369	13 828	37,0%
	65-74	12 056	5 542	46,0%
	75+	11 673	5 245	44,9%
Male		43 248	17 872	41,3%
	18-44	4 945	1 563	31,6%
	45-64	24 499	9 733	39,7%
	65-74	8 128	3 932	48,4%
	75+	5 676	2 644	46,6%
Primary prevention		76 559	29 014	37,9%
	Female	48 308	18 689	38,7%
	Male	28 251	10 325	36,5%
Secondary prevention		28 167	13 609	48,3%
	Female	13 170	6 062	46,0%
	Male	14 997	7 547	50,3%

Patients initiated on statins for secondary prevention were more likely to stay persistent to the statin treatment than patients initiated for the statins on the primary prevention. Furthermore, men who recieved statins for secondary prevention were more persistent to statin treatment than women. The opposite gender difference was observed for primary prevention – where a larger proportion of females were staying persistent to the therapy (Table 8).

4.3.1. Patients persistence to statin substance and strength

There was a trend towards more patients beeing persistent on higher doses of statins both in women and men, an exception was observed only in women taking rosuvastatin, where the persistence rate was more or less similar between doses (Table 9).

Table 9. Patient's persistence rates for different atorvastatin and rosuvastatin doses and previous use of antidiabetic, antithrombotic and antihypertensive medications.

	Women			Men		
	Total	**Persistent**	**Persistent %**	**Total**	**Persistent**	**Persistent %**
Statin						
Atorvastatin	35 014	13 952	39,8%	28 055	11 928	42,5%
10	3 773	1 449	38,4%	2 370	914	38,6%
20	14 781	5 796	39,2%	10 454	4 105	39,3%
30	6 894	2 653	38,5%	5 028	1 983	39,4%
40	7 786	3 200	41,1%	7 117	3 147	44,2%
60	1 009	494	49,0%	1 596	919	57,6%
80	771	360	46,7%	1 490	860	57,7%
Rosuvastatin	26 346	10 758	40,8%	15 101	5 905	39,1%
5	4 867	1 948	40,0%	2 479	946	38,2%
10	9 490	3 946	41,6%	5 446	2 159	39,6%
15	7 468	2 903	38,9%	4 043	1 511	37,4%
20	3 559	1 558	43,8%	2 476	997	40,3%
30	792	335	42,3%	533	234	43,9%
40	170	68	40,0%	124	58	46,8%
Previous use of medications						
Antidiabetic	7 091	3 644	51,4%	4 675	2 526	54,0%
Antithrombotic	3 920	1 955	49,9%	3 363	1 713	50,9%
Antihypertensive	39 054	17 666	45,2%	23 041	11 146	48,4%

During the study women were found to have highest persistence rate for higher doses of atorvastatin such as 60 mg and 80 mg. Meanwhile, women shared a higher persistence rate proportion for rosuvastatin than men. The highest persistence rate 43,8% was found for women for 20 mg rosuvastatin. While, for men persistence rate was found higher than women when different atorvastatin strenghts were directly compared. There was also a tendency towards higher persistence rates in men for the higher doses of atorvastatin and rosuvastatin respectively (Table 9).

Men were found to be relativly more persistent for previouse use of other medications such as antidiabetic, antithromotic and antyhypertensives. Patients with previous use of medications shared the largest proportion for being persistent to antidiabetic drugs, for both

men and women. Men shared the highest persistence rate for antidiabetic medications of 54%, while women shared the lowest for previous use of antihypertensives 45,2% (Table 9).

4.3.2. Specialist qualification influence to patients persistence

Family doctors and cardiologist had the highest number of statins initiated patients, respectively 55‘041 patients in total for family doctors with persistence rate of 41% and 22‘710 patients in total for cardiologists doctors with persistence rate of 39%.

Table 10. Type of specialist initiating statins treatment.

Specialty	Total	Persistent	Persistent %
Family doctor	55 041	22 710	41%
Doctor cardiologist	20 491	7 984	39%
Internal medicine physician	12 382	4 971	40%
Medical doctor	9 934	4 120	41%
Doctor neurologist	2 855	1 167	41%
Pediatrician	1 330	519	39%
Physician of Physical Medicine and Rehabilitation	663	337	51%
General Practitioner	392	164	42%
Endocrinologist	275	122	44%
Echoscope Doctor	195	83	43%
Pulmonologist	174	71	41%
Doctor anesthesiologist resuscitator	145	58	40%
Rheumatologist	119	49	41%
Doctor nephrologist	109	47	43%
Other	598	221	37%

** specialists initiated up to 100 treatments were assigned to „other“*

Among these two type of specialist, although the difference was small, patients initiated on statins by family doctors were found to have a slightly higher persistence. It was observed that patients who were initiated on statins treatment from physicians of physical Medicine and Rehabilitation had the highest persistence rate for initiated statins treatment in Lithuania (Table 10).

4.4. Factors associated with persistence to statins

Characterstics for patients having a high persistence were assessed with multivariate logistic regression adjusting for all covariates presented above. Patient in the age group of 65-74 years were more likely to stay persistent to the statin treatment (OR 1,28 (1,19-1,37)). It was also oserved, that patietnts on secondary prevention were more likely to stay persistent to the treatment than the patients on primary prevention (OR 1,49 (1,43-1,56)). Patients diagnosed with stroke,

TIA and heart attack had higher chances to stay persistent to statin treatment (OR 1,55 (1.45-1.66) and OR 1,95 (1,86-2,05)) respectively. In the study we have also observed that patients with previous use of other drugs were more persistent (OR 1,73 (1,68-1,78)) than those who had no previous use of these drugs (table 11).

Table 11. Factors associated with persistence to statins

Characteristics		Persistent		Crude Odds Ratio* for persistence	95 CI lower	95 CI upper	Adjusted Odds Ratio*** for persistence	95 CI lower	95 CI upper
Age, years	18-44	1 699	31,9%	Reference					
	45-64	23 561	38,1%	1,31	1,24	1,39	**1,12**	1,05	1,19
	65-74	9 474	46,9%	1,89	1,77	2,01	**1,28**	1,19	1,37
	75+	7 889	45,5%	1,78	1,67	1,90	**1,16**	1,08	1,25
Gender	Women	24 751	40,3%	Reference					
	Men	17 872	41,3%	1,05	1,02	1,07	**1, 07**	1,04	1,10
Area of primary care registration	Rural	20 849	41,1%	Reference					
	Urban	21 774	40,4%	1,03	1,00	1,06	**1,03**	1,00	1,05
Type of prevention	Primary	29 014	37,9%	Reference					
	Secondary	13 609	48,3%	1,53	1,49	1,57	**1,49**	1,43	1,56
Diagnosis ****	No Diagnosis	28 373	37,8%	Reference					
	Stroke/TIA	1 780	48,5%	1,55	1,45	1,65	**1,55**	1,45	1,66
	Heart attack	5 166	55,7%	2,07	1,98	2,16	**1,95**	1,86	2,05
	IHD	6 663	43,8%	1,28	1,24	1,33	**1,11**	1,07	1,16
	DM	21	55,3%	2,03	1,07	3,85	**1,77**	0,93	3,34
	Hypertension	621	41,0%	1,14	1,03	1,27	**0.99**	0,90	1,10
Prescriber qualification	Family doctor	22 710	41,3%	Reference					
	Doctor cardiologist	7 984	39,0%	0,88	0,85	0,91	**0,75**	0,73	0,78
	Other	11 929	40,9%	0,97	0,95	1,00	**0,91**	0,88	0,94
Previous use of medications	No previous use	13 245	32,0%	Reference					
	Yes previous use***	29 378	46,4%	1,84	1,78	1,89	**1,73**	1,68	1,78
Initiated with	Atorvastatin	25 880	41,0%	Reference					
	Rosuvastatin	16 663	40,2%	0,97	0,94	0,99	**1,06**	1,03	1,09
	Other	80	38,1%	0,88	0,88	1,17	**0,81**	0,61	1,07

** Calculated with 95% confidence interval*

** *Previous use of anti-diabetic, antithrombotic and antihypertensive (at least one or all of them)*

**** Multivariate stepwise regression model including all covariates studied: age in years, gender, area of primary care registration, prescriber qualification, type of prevention, diagnosis, previous use of drugs and initiated statin type*
***** IHD - Ischemic coronary heart disease; DM - Diabetes mellitus disease, TIA - Transient ischemic attack.*

4.4.1. Previous use of medication influence to statin treatment

In the study, patients with a previous use of other medications such as antidiabetic, antithrombotic and antihypertensives were more persistent to statin treatment than those patients with no previouse use (Table 12).

Table 12. Comparison of different previously used medications influence for persistency to statin treatment

Characteristics		Persistent		Crude Odds Ratio* for persistence	95 CI lower	95 CI upper	Adjusted Odds Ratio** for persistence	95 CI lower	95 CI upper
Previous use of medications	Antidiabetic no	36 453	39,2%	Reference					
	Antidiabetic yes	6 170	52,4%	1,70	1,65	1,78	**1,61**	1,55	1,68
	Antithrombotic no	38 955	40,0%	Reference					
	Antithrombotic yes	3 668	50,4%	1,52	1,45	1,60	**1,34**	1,28	1,41
	Antihypertensives no	13 811	32,4%	Reference					
	Antihypertensives yes	28 812	46,4%	1,80	1,76	1,85	**1,70**	1,65	1,74

** Calculated with 95% confidence interval*
*** Multivariate stepwise regression model including all covariates studied: age in years, gender, area of primary care registration, prescriber qualification, type of prevention, diagnosis, previous use of drugs and initiated statin type*

4.4.2. Patients persistence to statin doses

Adjusted all the covariates during the study it was discovered that the likelyhood of beeing was higher for 60 mg and 80 mg of atorvastatin doses compared to the lowest doses. The same tendence was observed for rosuvastatin, but it was not as pronounced and the higest strength showed no significang difference (Table 13).

Table 13. Comaparison between different Statins used for treatment initiation

Characteristics			Persistent		Crude Odds Ratio* for persistence	95 CI lower	95 CI upper	Adjusted Odds Ratio** for persistence	95 CI lower	95 CI upper
Initiated with	Atorvastatin	10mg	2 363	38,5%	Reference					
		20mg	9 901	39,2%	1,03	0,98	1,09	**1,01**	0,95	1,07
		30mg	4 636	38,9%	1,02	0,96	1,08	**0,99**	0,93	1,06
		40mg	6 347	42,6%	1,19	1,12	1,26	**1,10**	1,04	1,17
		60mg	1 413	54,2%	1,90	1,73	2,08	**1,62**	1,48	1,79
		80mg	1 220	54,0%	1,87	1,70	2,07	**1,55**	1,41	1,72
	Rosuvastatin	5mg	2 894	39,4%	Reference					
		10mg	6 105	40,9%	1,06	1,01	1,13	**1,06**	1,00	1,13
		15mg	4 414	38,3%	0,96	0,90	1,02	**0,96**	0,91	1,03
		20mg	2 555	42,3%	1,13	1,05	1,21	**1,14**	1,07	1,23
		30mg	569	42,9%	1,16	1,03	1,30	**1,17**	1,04	1,32
		40mg	126	42,9%	1,15	0,91	1,46	**1,19**	0,94	1,51
	Other***		80	33,3%	-	-	-	-	-	-

** Calculated with 95% confidence interval*
*** Multivariate stepwise regression model including all covariates studied: age in years, gender, area of primary care registration, prescriber qualification, type of prevention,, previous use of drugs (Table 11)*
**** Simavastatin and Fluvastatin were relatively insignificant*

4.5. Discussion

Over 3,7% of the adult population of Lithuania were initiated with statin treatment in 2018-2019. One year later 41% were persistent to the statin treatment. The age group of 45-64 years old accounted for the largest part of patients initiated on statins treatments, with 61% in both genders. Predictors behind high persistence were being male, elderly, receiving high-dose statins for secondary prevention. However, the persistence of patients in the 75+ age group was slightly lower than the patients group of 65-74 years. This finding might be explained due to the fact that in Lithuania the life expectancy at birth is 75.1 years and the study data did not contain mortality linked to drug dispensing and consequently, some of patients not purchasing the drugs might have died.

Lithuania belongs to the countires with the lowest lipid-modifying medication consumption in European countries. A cross-sectional study measuring lipid-modifying agent use in 83 countries assessed drugs utilization trends over a decade from January 2008 to December 2018. Despite the fact that CVD has been the main cause of mortality in Lithuania for many years, consumption of lipid-modifying agents has changed insignificantly from 5’000-10’000 standard

units per 1’000 inhibits (per year) to 10’000-20’000 standard units per 1’000 inhibits (per year) [61]. The low utilization may either be explained by the fact that few patients are initiated on the drug or the low persistence. Rior studies have shown a large difference in persistence between different studies were variation in one-year persistence between studies was found from around 30-85% for lipid lowering agents (LLA) [71]. A better persistence rate with 90-days permissible gap to the statins treatment was captured in a nationally representative pharmacy claims database representing one hundred US health care plans, where persistence rate was found to be 62%. This persistence rate in US might be explained by the big increase of statins reported between 2002 and 2005, annual statin prescriptions increased from 134 million to 221 million (64.9% increase) over this period [65, 66].

In Lithuania, atorvastatin and rosuvastatin were found to be the leading statins for patients initiated on the treatment. Patients on secondary prevention were found more likely to be initiated on higher atorvastatin and rosuvastatin doses. While Lithuania few patients initiaded on simvastatin, a recent study shown that simvastatin was reported as the second leading statin in Sweden [67]. The most commobly used statins in Sweden was atorvastatin. It was also observed that higher doses of statins were used in Sweden, although previous studies has shown that many patients still receive too low doses of statins [72]. Moreover, the Swedish data on statin utilization and ischemic heart disease mortality indicated that the decline in ischemic heart disease mortality in reacent years is inversely related to the increased utilization of statins and the correlation was found to be very strong [67]. Such a correlation was not observed for Lithuania, indicating room for improvement in, e.g. persistence to the treatment.

In this study it was discovered that in Lithuania there were relatively more men on secondary prevention than women while women, for primary prevention. The tendency for women generally to experience onset of CVD 10 years later then men is notable, though the risk for CVD such as ischemic heart disease rised in parallel after age 55 years for women and 45 years for men. In clinical trials, women experience the same low-density lipoprotein (LDL) reductions on statins and possibly greater atherosclerotic regression on statins per unit LDL reduction. However, in practice, it has been shown that women taking statins are less likely to achieve desired LDL goals [68]

After the adjustment of different covariates it was discovered that patients on the secondary prevention were more likely to stay persistent on the treatment, than patient on the primary prevention. This is positive given the higher risk these patients have. A systematic review to asses effects of adherence and persistence on clinical outcomes in patients treated with statins has shown that good adherence and longer durations of persistence with statins was associated with progressively increasing clinical benefits in secondary prevention and reduction of CVD events

[69]. It was also discovered in our study that patients who had a record of previous use of other medications were more persistent to statin treatment than those who had no previous use of medications which may indicate that people have a better understanding of possible disease risk and knows about the importance of staying persistent to the treatment.

Interestingly it was found that patients who were initiated with statins by family doctors had higher persistence rates than patients initiated with statins treatment by cardiologist. Better persistence initiated by family doctors might be explained with patients follow-up visits to measure cholesterol and renew prescriptions. Surprisingly, the highest persistence rate was captured with Physician of physical medicine and rehabilitation what could be the indication that in rehabilitation specialist are more focused on patient's well-being and might have more time to educate patients on the importance of drug persistence and adherence. However, it is also important to recognize that reletaively few patients were initiated by this type of doctor and that there may be other potential patient characteristics, not adjusted for in the study, explaining these differences.

Comparing patient's persistency with adjusted covariates to different doses of atorvastatin and rosuvastatin the tendency staying persistent to higher atorvastatin doses was vividly visible in Lithuania. It is similar to findings in a Danish study where statins discontinuation where elderly people prescribed with higher statins doses were less likely to discontinue treatment with statins compared to patients on primary prevention [70]. Regardless of highest persistence to high statins doses the main reason for discontinuing therapy are adverse effects such as muscle pain, but these related side effects appear rarely.

The main strength of this study is the large number of included patients with nationwide coverage of all patients in Lithuania initiated on statin treatment. Furthermore, important covariates such as previous cardiovascular diagnoses to distinguish between secondary and primary prevention as well as previous use of other medications were also assessed.

In the study there were also some limitations. As in all database studies using information on dispensed medicines, it was not known whether patients take their medicines as prescribed. Furthermore, there is no information about initiations, i.e. those patients who were prescribed with statins medication, were dispensed with medication that never claimed their prescription at a pharmacy. We used the anniversary method to assess persistence. It is simple and easy to operate, but it is rather unspecific, it only provides the information of patients who has purchased drugs one year later, but does not defines if patients took the medication correctly. We may have also missed statins which were completely paid out of pocket, but this is unlikely to be a big concern in chronic diseases like hyperlipidemia.

Despite methodological limitations of the study, this investigation of statins persistence in Lithuania, should raise concerns among clinicians, patients and society about the clinical problem.

Poor medication adherence has been a healthcare issue for several decades, very few countries measure and report on rates of adherence and persistence at the health system level. Cardiovascular diseases could be preventable with initiation and continuation of statins treatment being one of the most critical interventions to decrease cardiovascular morbidity and mortality [3]. Poor-persistence with therapy has been linked with five main factors introduced by the WHO: patient-related, therapy-related, health system-related, social-economic factors and condition-related factors [18] and further studies should be done in Lithuania to assess which factors are most important to address the problem.

Interventions to increase therapy persistence could be done. In particular, given the high mortality rate due to cardiovascular diseases in Lithuania. The interventions to improve adherence could be divided into three groups focused on: the patient, health professionals and the health delivery system. Multifaceted combinations of patient education, patient-physician communication enhancement, extended care through ancillary health care providers, simplification of drug regimens, increased patient monitoring and additional follow-ups. Although listed interventions could help increase persistence to statin treatment, this would require relatively high investments into health labor by the government.

5. CONCLUSIONS

In this comprehensive study on all patients initiated on statin treatment in Lithuania during 2018 and 2019, following observations were made:

1. Persistence on statin treatment in Lithuania can be considered as low, only 40% continued to purchase their medicine one year after initiation.

2. Patients treated for secondary prevention were more likely to be persistent to statins treatment than those who were treated for primary prevention.

3. There was no sex difference in statin persistence, the finding was that the age group of 65-74 years was the most persistent to statins treatment.

4. The highest persistence was observed for patients taking higher doses of atorvastatin. The same tendency was shown for rosuvastatin, however, no significant differences between doses were observed.

5. Specialist qualification did not have a major influence to patients persistent. Patients with the highest persistence rate were found to be prescribed by family doctors.

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