TALLINN UNIVERSITY OF TECHNOLOGY
School of Information Technologies

Oluwabunmi Temitayo Awe 194263YVEM

THE USE OF LIPID LOWERING DRUGS IN PATIENTS WITH DYSLIPIDEMIA IN NORTH ESTONIA MEDICAL CENTRE

Master's thesis

Supervisor: Margus Viigimaa
MD, PhD
Co-supervisor: Grete Talviste
MSc

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Oluwabunmi Temitayo Awe 194263YVEM

LIPIIDE LANGETAVATE RAVIMITE KASUTAMINE DÜSLIPIDEEMIA PATSIENTIDEL PÕHJA-EESTI REGIONAALHAIGLAS

Magistritöö

Juhendaja: Margus Viigimaa
MD, PhD
Kaasjuhendaja: Grete Talviste
MSc

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Author’s declaration of originality

I hereby certify that I am the sole author of this thesis. All the used materials, references to the literature and the work of others have been referred to. This thesis has not been presented for examination anywhere else.

Author: Oluwabunmi Temitayo Awe

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Abstract

Background: Dyslipidemia, a multifactorial disorder, is an important risk factor for the development of cardiovascular disease. The use of lipid lowering drugs in the treatment of dyslipidemia and in primary and secondary prevention of cardiovascular disease is a key aspect of reducing cardiovascular mortality. Despite the widespread use of lipid lowering drugs, poor compliance to therapy is still a challenge globally. Compliance to lipid lowering drugs is known to be suboptimal, resulting in increased health cost and unfavourable health outcome. Majority of patients with familial hypercholesterolemia (FH) are unable to achieve the low-density lipoprotein cholesterol (LDL-C) target goals, in spite of maximal dose of lipid lowering drugs. In randomized trials, proprotein convertase subtilisin/kexin type 9 inhibitors (PCSK9i) effectively reduce LDL-C and cardiovascular events. However, little research has been done on the efficacy of PCSK9 inhibitors outside of clinical trials. *Aim*: To describe the utilization of lipid lowering drugs and demonstrate treatment compliance of patients with dyslipidemia. Furthermore, to evaluate the efficacy of PCSK9 inhibitors in FH patients in clinical practice. *Method:* Quantitative retrospective research from 01.01.2013–01.01.2020. Study group: A total of 2140 patients with dyslipidemia who were prescribed lipid lowering drugs within the study period and 5 patients who were prescribed PCSK9 inhibitors despite on maximum dose of statin and ezetimibe. Compliance was measured indirectly, based on the pharmacy refill rates and patients were grouped into different compliance groups. Multivariate linear regression analysis was carried out to determine the association between compliance and age, gender, primary diagnosis, co-existing diseases, LDL-C level, active substance prescribed, or department visited. *Result:* Statins were the most prescribed lipid lowering drugs and rosuvastatin (44.6%) and atorvastatin (41.0%) were predominantly used as first line treatment in the study group. The trend in the consumption of statins and average price moved in opposite directions (p=0.0019). Non-compliance was observed in 56.1% and 66.9% of the patients on primary and secondary compliance level, respectively. Young age (20-34 years), diseases of the musculoskeletal system and connective tissue (M00-M99), and visitation to infectious disease department were associated with high compliance, while advanced age (≥65 years) and diseases of

digestive system (K00-K95) were associated with low compliance. Treatment with PCSK9 inhibitors in patients with FH resulted in mean LDL-C reduction of 61.1%. Patients with genetic FH had a greater reduction in LDL-C than those with clinical FH. *Conclusion*: The most frequently used lipid lowering drugs are statins. Patients with dyslipidemia in North Estonia Medical Centre had a low compliance and several factors influencing compliance were identified. Therefore, it is important to identify patients likely to be non-compliance and implement strategies to improve the use of prescribed medications. The use of PCSK9i in FH patients in clinical practice showed similar results to those observed in clinical trials.

This thesis is written in English and is 89 pages long, including 7 chapters, 8 figures and 12 tables.

Annotatsioon

Lipiide langetavate ravimite kasutamine düslipideemia patsientidel Põhja-Eesti Regionaalhaiglas

Taust: Südame-veresoonkonna haiguste kujunemisel on üheks olulisemaks riskiteguriks düslipideemiad. Lipiide alandavate ravimite kasutamist düslipideemiate ravis ning südame-veresoonkonna haiguste esmases ja sekundaarses preventsioonis peetakse üheks tõhusamaks meetodiks, mis aitab vähendada kardiovaskulaarset haigestumust. Vaatamata lipiide alandavate ravimite laialdasele valikule ning nende tõestatud efektiivsusele on ülemaailmseks probleemiks madal ravisoostumus. Lisaks lipiidide ohjamise tõhustamisele ja seeläbi kardiovaskulaarsete komplikatsioonide vähendamisele aitab kõrge ravisoostumus vähendada tervishoiusüsteemi kulusid. Eraldi on autor välja toonud perekondliku hüperkolesteroleemia, kui väga tõsise kuluga düslipideemia, selle ravisoostumuse ja ravieesmärkide saavutamise. Kirjanduse andmetel ei suuda enamus maksimaalsel ravil olevatest perekondliku hüperkolesteroleemia patsientidest saavutada LDL-C eesmärkväärtuseid, kuigi randomiseeritud kliinilised uuringud on tõestanud PCSK9I ravi efektiivsust LDL-C alandamisel ja kardiovaskulaarsete komplikatsioonide vähendamisel. *Eesmärk:* Kirjeldada lipiidide taset alandavate ravimite kasutamist ja hinnata ravisoostumust düslipideemia patsientidel. Lisaks sellele, hinnata PCSK9 inhibiitorite efektiivsust perekondliku hüperkolesteroleemia patsientidel kliinilises praktikas. *Meetodid:* Planeeriti retrospektiivne uurimustöö, mille valim on koostatud Põhja-Eesti Regionaalhaigla patsientidest ajavahemikul 01.01.2013-01.01.2020, kellel on esmaseks või kaasuvaks diagnoosiks düslipideemia (E78.0-E78.9) või kellel ei ole diagnoositud düslipideemia, kuid vere LDL-C väärtused ületavad 5 mmol/L ning kes on 18 – ≤ 70 aastat vanad. Valim: 2140 patsienti, kellele oli antud ajavahemikus kirjutatud vähemalt üks lipiide alandava ravimi retsept ja 5 patsienti, kelle oli kirjutatud PCSK9 inhibiitor lisaks maksimaalsetele statiini ja ezetimiibi doosidele. Ravisoostumust mõõdeti kaudse meetodiga, milleks oli retseptide alusel ravimite väljaostmise määr. Patsiendid jaotati ravisoostumuse järgi erinevatesse gruppidesse. Viidi läbi mitmemõõtmeline lineaarne regressioonanalüüs hindamaks kas ravisoostumust mõjutavad patsiendi vanus, sugu, esmane diagnoos, kaasuvad haigused, LDL-C tase, väljakirjutatud ravimi toimeaine ja osakond, kus patsient viibis. *Tulemused:* Kõige enam kirjutati uuringurühmas lipiidide alandamiseks välja statiine: rosuvastatiini (44,6%) ja atorvastatiini (41,0%). Statiinide

tarbimise trend ja keskmine hind liikusid vastupidises suunas (p=0,0019). Primaarse ravisoostumuse grupis oli mittesoostumus 56.1% ja sekundaarse ravisoostumuse grupis 66.9%. Vanus, diagnoosid ja osakonnad, kus patsient oli viibinud mõjutasid statistilise olulisusega (p) patsientide ravisoostumust. Kõrge ravisoostumus oli seotud vanusevahemikuga 20-34 aastat, skeleti-lihassüsteemi ning sidekoe (M00-M99) diagnoosiga patsientide ja infektsioonhaiguste osakonnas viibimisega. Madal ravisoostumus oli seotud vanuserühmaga ≥65 aasta ja seedesüsteemi diagnoosi (K00-K95) saanud patsientidega. Perekondliku hüperkolesteroleemia patsientidel PCSK9I ravi põhjustas LDL-C keskmise vähenemise 61,1%. Geneetilise perekondliku hüperkolesteroleemia patsientide LDL-C langes rohkem kui ainult kliinilise perekondliku hüperkolesteroleemia patsientidel. *Järeldused***:** Kõige enam kasutatud lipiididesisaldust alandavad ravimid on statiinid. Põhja-Eesti Regionaalhaigla düslipideemia patsientide ravisoostumus oli madal ja uurimistöö leidis mitmed seda mõjustavad faktorid. On oluline välja selgitada potentsiaalselt ravisoostumatud patsiendid ja rakendada ravisoostumust parandavaid strateegiaid. PCSK9 inhibiitorite perekondliku hüperkolesteroleemia patsientide kliinilises praktikas kasutamine andis kliinilistes uuringutega sarnased tulemused.

Lõputöö on kirjutatud inglise keeles ning sisaldab teksti 89 leheküljel, 7 peatükki, 8 joonist ja 12 tabelit.

List of abbreviations and terms

ACC	American College of Cardiology
AHA	American Heart Association
APOA	Apolipoprotein A
APOB	Apolipoprotein B
APOE	Apolipoprotein E
ASCVD	Atherosclerotic Cardiovascular Disease
ATC	Anatomical Therapeutic Chemical
ATP	Adult Treatment Panel
BMI	Body Mass Index
CAD	Coronary Artery Disease
CETP	Cholesteryl Ester Transfer Protein
CHD	Coronary Heart Disease
CKD	Chronic Kidney Disease
CVD	Cardiovascular Disease
DLCN	Dutch Lipid Clinic Network
DM	Diabetes Mellitus
EAC	European Atherosclerosis Society
EHIF	Estonian Health Insurance Fund
EPA	Eicosapentaenoic Acid
ESC	European Society of Cardiology
FCH	Familial Combined Hyperlipidemia
FD	Familial Dysbetalipoproteinemia
FH	Familial Hypercholesterolemia
FHTG	Familial Hypertriglyceridemia
HDL-C	High-Density Lipoprotein Cholesterol
HeFH	Heterozygous Familial Hypercholesterolemia
HoFH	Homozygous Familial Hypercholesterolemia
ICD	International Classification of Disease

MI	Myocardial Infarction
MTP	Microsomal Triglyceride Transport Protein
LDL-C	Low-Density Lipoprotein Cholesterol
LDLR	Low-Density Lipoprotein Receptor
LLD	Lipid lowering drugs
Lp(a)	Lipoprotein (a)
LPL	Lipoprotein Lipase
TC	Total Cholesterol
TG	Triglycerides
PCSK9	Proprotein Convertase Subtilisin/Kexin Type 9
PCSK9I	Proprotein Convertase Subtilisin/Kexin Type 9 Inhibitors
SAM	State Agency of Medicines
SCORE	Systemic Coronary Risk Estimation
VLDL	Very Low-Density Lipoprotein

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1 Introduction

Cardiovascular disease (CVD) is the leading cause of death globally [1], responsible for >4 million deaths in Europe every year [2], and >900,000 deaths in United States of America in 2016 [3], affecting more women than men. Globally, CVD causes more premature deaths than cancer [4]. CVD is a multifactorial disease and to reduce its morbidity and mortality, a comprehensive management of the associated risk factors such as smoking, hypertension, obesity, diabetes mellitus (DM) and dyslipidemia, is pivotal [5].

Dyslipidemia is a major modifiable risk factor in the development of CVD [6]. It accounts for one third of ischemic heart diseases globally, estimated to cause 2.6 million deaths yearly [7], and reported to cause about 4.4 million deaths in 2017 [8]. Therefore, the diagnosis and aggressive treatment of dyslipidemia is essential in decreasing the incidence and mortality of CVD.

Lipid lowering drugs (LLDs), including statins, are used widely in the management of dyslipidemia. However, the use of LLDs is not only indicated for treatment of lipid disorders but also in primary and secondary prevention of CVD [9]. Treatment of familial hypercholesterolemia (FH) with LLDs is highly effective, yet low-density lipoprotein cholesterol (LDL-C) goals are achieved only in minority of patients with FH. A new class of LLD, proprotein convertase subtilisin/kexin 9 inhibitors (PCSK9i) has been shown in randomized trials to effectively reduce low density lipoprotein cholesterol in patients with FH, and allowing the achievement of the LDL-C targets [10].

Despite the well-established and scientific evidence of the benefits of LLDs over the years [11], [12], and its widespread use, compliance to therapy is a major problem worldwide [7]. Poor compliance to therapy not only jeopardizes the effectiveness of the treatment, but also worsens the health outcome and increases health care costs. Compliance is influenced by different factors, not limited to social and economic factors, patients related and health care factors [13]. Therefore, to increase compliance in patients with dyslipidemia, factors influencing compliance needs to be identified and managed.

The aim of this study is to describe the use of lipid lowering drugs in dyslipidemic patients in North Estonia Medical Centre and demonstrate their treatment compliance rates. Furthermore, to determine the efficacy of PCSK9i on FH.

The thesis focuses on the following research questions:

- What are the current lipid lowering drugs used in North Estonia Medical Centre and does the prices of the drugs influence their use?
- What are the treatment compliance rates among patients with dyslipidemia in North Estonia Medical Centre?
- How effective are PCSK9 inhibitors on FH and does treatment efficacy depend on the mutations?

Current thesis consists of seven chapters. Chapter one introduces the topic of the thesis. The second chapter gives an overview of dyslipidemia, the different types of dyslipidemia, guidelines on management of dyslipidemia, treatment strategies and addresses factors influencing compliance in dyslipidemia. The third chapter highlights the aim, objectives, and research questions. Chapter four and five presents the methodology and results of the study. The sixth chapter discusses the result of the research and the final chapter summarizes the study.

2 Background of dyslipidemia, treatment and compliance

This chapter gives an overview of dyslipidemia, different types of dyslipidemia in clinical practice, the recommended guidelines in treating dyslipidemia and current treatment strategies as recommended in the guidelines and other literatures. It also explains the factors influencing compliance in patients with dyslipidemia.

2.1 Dyslipidemia: Definition, etiology, risk factors, symptoms, and treatment

The term 'dyslipidemia' refers to the abnormal levels or disturbance of lipids in the blood, encompassing both hyperlipidemia (high lipid levels in the blood) and hypolipidemia (low lipid levels in the blood). However, the most common and important dyslipidemias are hyperlipidemias [14], and several articles use the term dyslipidemia to describe hyperlipidemia, which is defined as either elevated levels of total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C) or decreased levels of high-density lipoprotein cholesterol (HDL-C) [15], [16]. Increase in LDL-C, TG and TC levels are atherogenic as they are significant risk factors for the development of atherosclerosis, coronary heart disease (CHD) and stroke. In contrast, an opposite effect is derived from high levels of HDL-C as it has been shown to be atheroprotective [17], often referred to as 'good cholesterol'.

Abnormal lipid levels have been associated with different CVDs such as hypertension, stroke, coronary artery disease (CAD) [18], metabolic disorders like DM, obesity. It was attributed to 56% of heart disease, 18% of infarction cases and one third of deaths in the world [19].

According to National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol [20], dyslipidemia is defined as:

- TC: ≥200 mg/dL

- LDL-C: ≥130 mg/dL
- HDL-C: <40 mg/dL
- Serum TG: ≥130 mg/dL

Dyslipidemia can be categorized into primary and secondary dyslipidemia. Primary dyslipidemia, also known as familial or inherited dyslipidemia develops due to a single or multiple genetic defect that causes either an excessive production or decreased clearance of LDL-C and TG, or increased clearance of HDL-C. The most common primary dyslipidemias are FH, familial combined hyperlipidaemia, family hypertriglyceridemia, familial dysbetalipoproteinemia and lipoprotein(a) hyperlipoproteinemia, with prevalence of 1:20 to 1:1000 in the general population [14].

Secondary dyslipidemia, also referred to as acquired dyslipidemia develops as a sequela of other conditions such as DM, obesity, endocrine disorders, chronic renal failure, liver disease and medications [14]. Secondary dyslipidemia is associated with lifestyle factors, for example, eating habits, exercise, smoking etc. Hence, lifestyle modification plays a major role in the treatment and prevention of dyslipidemia.

Generally, dyslipidemia itself does not have a specific symptom that helps in identifying its development, however it results in symptomatic vascular diseases such as atherosclerosis, CHD, stroke, diabetes, etc. High levels of LDL-C, especially in patients with FH, can present with xanthomas, which is the thickening of tendons due to cholesterol deposit, or corneal arcus (deposits of cholesterol in the peripheral cornea) [21]. A significant increase in TG exacerbates the risk of acute pancreatitis and its complications [14].

2.2 Primary and secondary dyslipidemia.

The principal step in the management of lipid disorders is determining the diagnosis and it is important to be able to distinguish primary lipid disorders from secondary dyslipidemia as treatment of underlying conditions can improve the condition. The most common dyslipidemias will be discussed in this review.

2.2.1 Familial hypercholesterolemia.

Familial hypercholesterolemia (FH) is an autosomal dominant lipid disorder causing premature CHD due to persistent or lifelong elevation of plasma LDL-C levels [21]. FH is most commonly caused by loss of function mutations in the LDL receptor (LDLR) gene, and less frequently by mutations in apolipoprotein B (apoB) gene and in proprotein convertase subtilisin/kexin type 9 (PCSK9) gene, resulting in either deficient or dysfunctional receptors on the surface of the hepatocytes [14], [22]. Consequently, all the defects lead to decreased cellular uptake and clearance of LDL, and increased plasma TC and LDL-C concentrations.

Heterozygous form of FH (HeFH) is common, with prevalence of 1 per 200-250 of the general population [2], [22]. HeFH is characterized by LDL-C levels >190 mg/dL in untreated adults and LDL-C levels >160 mg/dL in untreated children and adolescents [23]. If left untreated, men and women with HeFH usually develop CAD before 55 and 65 years of age respectively, however if diagnosed and treated early, the risk of developing CAD may be decreased significantly [2].

In contrast, homozygous form of FH (HoFH) is a rare life-threatening disease with estimated frequency of 1 per 160,000-320,000 people. It is characterized by xanthomas, premature atherosclerotic CVD, and TC >13 mmol/L (500 mg/dL). If left untreated, most patients with HoFH develop CAD before the age of 20 years and rarely live beyond 30 years of age [2], [24].

FH is diagnosed based on phenotypic criteria, i.e. elevated LDL-C level, a family history of premature CAD, presence of CAD and physical examinations or positive genetic testing [23]. One of the most common criteria used to establish diagnosis of FH is the Dutch Lipid Clinic Network (DLCN) criteria which prioritizes genetic testing, but also includes non-genetic criteria such as clinical history and laboratory results [14].

All patients with FH are recommended to implement healthy diet and exercise habits, but statin therapy remains the cornerstone of FH treatment. Despite being on statin therapy, many patients with FH will not attain the LDL-C target with statin alone. In this case, ezetimibe is recommended as an add-on to statin regimen [21]. PCSK9 inhibitors can reduce LDL-C level by up to 60%, thereby it is suggested to be considered in FH patients

at a very high risk of atherosclerotic cardiovascular disease (ASCVD), if the treatment target is not achieved despite on maximal tolerated statin and ezetimibe [2].

2.2.2 Familial dysbetalipoproteinemia.

Familial dysbetalipoproteinemia (FD), also known as type III hyperlipoproteinemia is a rare recessive genetic disorder caused mostly by mutation in the apolipoprotein E (apoE) gene, with only 10% of FD due to an autosomal dominant mutation in apoE [25]. ApoE allows for hepatic clearance of chylomicrons remnants and intermediate density lipoprotein (IDL) [2], and as a result of mutations, apoE binds poorly to lipoprotein receptors, leading to defective clearance of chylomicrons, very low-density lipoprotein (VLDL) and their remnants, resulting in an increase in non-HDL-C and reduction in HDL-C [14].

FD primarily affects older people and rarely occurs at a young age or in premenopausal women [26]. It is characterized by elevated serum TC and TG levels before treatment, equally in the range of 7-11 mol/L [2]. Clinically, patients with FD presents with tubero-eruptive xanthomas on the elbow and knees, and palmar xanthomas (orange-yellow discoloration on the palm) in the skin creases of their hand and wrists. FD is associated with increased risk of CVD, premature CVD, and atherosclerosis of femoral and tibial arteries [27], thereby requiring aggressive treatment.

Treatment of FD includes decrease of lipid levels by lifestyle modifications, dietary restrictions, and administration of LLDs [14]. Majority of FD patients can be treated with a statin or fibrate, if there is severe hypertriglyceridemia, however, combination of fibrate and statin may be required [2].

2.2.3 Familial hypertriglyceridemia.

Familial hypertriglyceridemia (FHTG), also known as type IV familial dyslipidemia is a genetic disorder characterized by increased plasma TG due to excessive production of VLDL from the liver [28]. FHTG is a polygenic disorder that is often inherited as autosomal recessive traits and are rare [2]. Typically, the condition develops concomitantly with other comorbidities such as obesity, hypertension, hyperglyceridemia, hyperuricemia [28].

FHTG does not usually present with symptoms, except a secondary factor exacerbates the disease and increases TG production, resulting in the development of pancreatitis and eruptive xanthomas. Acute pancreatitis is the most common complication of FHTG and in a study, 5.4% of patients with severe hypertiglyceridemia developed acute pancreatitis about a year after the initial diagnosis [29].

Management of the disorder is directed mainly on reducing the triglyceride levels with dietary restriction of calories and fat content, avoidance of alcohol and fibrate therapy. In severe cases, lomitapide might be required [2].

2.2.4 Familial combined hyperlipidemia.

Familial combined hyperlipidemia (FCH), an autosomal dominant disorder, is the most common form of genetic dyslipidemia occurring in 1-3% of the population [30]. It is characterized by elevated TG and predominance of LDL-C levels, and it is a principal cause of premature CAD [2]. The metabolic basis of FCH is unclear but increased in apoB production is thought to be a contributing factor to the overproduction of VLDL.

The genetic basis of FCH is complex and determined by interactions of several susceptibility genes and environment. FCH is an oligogenic disorder and is not associated with a single genetic cause, but the lipid phenotype is increased LDL-C and/ or increased TG [2].

The diagnosis of this dyslipidemia is usually based on an increase in TG level >1.5 mmol/ L, combined with apoB levels >120 mg/dL and a family history of premature CVD [2]. Treatment of FCH includes lifestyle interventions and the use of pharmacological agents. The drug of choice for FCH is statin with or without fibrates [14].

2.3 Guidelines on management of dyslipidemia.

Several guidelines have been published over the years by different medical societies to help clinicians in the effective management of dyslipidemia, early prevention of cardiovascular risk and in the use of risk assessment systems. This review will focus on the European Society of Cardiology (ESC) / European Atherosclerosis Society (EAS) and American College of Cardiology/American Heart Association (ACC/AHA) cholesterol management guidelines.

2.3.1 Risk assessment

In ESC/EAS guidelines, the Systemic Coronary Risk Estimation (SCORE) system is used to estimate 10-year cumulative risk of fatal atherosclerotic events. The SCORE system has been recommended by the European Guidelines on CVD prevention because it is based on a large European cohort dataset and it is easy to remodel for individual countries. It has two risk charts for use in patients in high and low risk regions of Europe [2].

The AHA/ACC guidelines use the Pooled cohort Equations (PCEs) which combines age, cigarette smoking, blood pressure, serum TC, HDL-C and presence or absence of DM, to estimate the risk of developing ASCVD (fatal and non-fatal MI and stroke) at 10 years.

2.3.2 Recommended LDL-C target levels and initiation of pharmacological therapy in patients with dyslipidemia.

The ESC/EAS guidelines categorize patients into four different risk groups based on the total cardiovascular risk (Table 1), which was guided by the fact that the higher the risk, the more intense the preventive measures should be. The guidelines use the SCORE system at 10 years to suggest the LDL-C target levels and levels for initiation of pharmacological therapy [2].

It is recommended that very high-risk patients, in primary or secondary prevention should achieve an LDL-C level of <1.4 mmol/L (<55 mg/dL) and ≥50% reduction from baseline. For high-risk patients, the target LDL-C is <1.8 mmol/L (<70 mg/dL) and similarly an LDL-C reduction of ≥50% from baseline is recommended. In moderate risk patients, the LDL-C goal is <2.6 mmol/L (<100 mg/dL), whereas in low risk patients, the LDL-C goal of <3.0 mmol/L (<116 mg/dL) can be considered [2]. It is suggested to achieve at least 50% reduction in LDL-C and the target level, especially in very high risk patients, as there is evidence indicating that decreasing the LDL-C as low as possible results in lesser ASCVD events [31], [32]. Pharmacological therapy is recommended when LDL-C remains higher than the target level despite lifestyle interventions [2].

In AHA/ACC guidelines [33], pharmacological therapy was continually recommended for primary prevention in three major categories: patient with severe hypercholesterolemia, adults with DM and adults 40 to 75 years of age, and PCE 10-year risk score ≥7.5% [34]. For secondary prevention, AHA/ACC guidelines break down their

recommendation on the basis of whether the patients are considered to be at very high risk for future ASCVD events [34].

Table 1. ESC/EAS Cardiovascular risk categories [2].

Very high risk	▪ Documented ASCVD, either clinical or unequivocal on imaging). ▪ DM with target organ damage, or at least three major risk factors, or early onset of type 1 DM (T1DM) of long duration (>20 years). ▪ Severe Chronic Kidney Disease (CKD) (eGFR <30 mL/min/1.73 m2) ▪ Calculated SCORE ≥10% for 10-year risk of fatal CVD. ▪ FH with ASCVD or with another major risk factor.
High risk	▪ Markedly elevated single risk factors, in particular TC >8 mmol/L (>310 mg/dL), LDL-C >4.9 mmol/L (>190 mg/dL), or blood pressure ≥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 m2). ▪ A calculated SCORE ≥5% and <10% for 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

2.4 Treatment strategies

The treatment of dyslipidemia and prevention of CVD risk includes lifestyle modifications, especially healthy diet, and exercise, use of dietary supplements and pharmaceutical treatment.

2.4.1 Lifestyle modifications

Lifestyle modifications have been shown to reduce plasma TC levels and contribute to decreasing CVD risk, with diet and weight loss being the most beneficial approach [35]. As overweight (body mass index (BMI) ≥25-30 kg/m^2), obesity (BMI ≥30 kg/m^2) and adipose usually aid dyslipidemia, reduction in caloric intake and increased energy in patients with excessive body weight and/or abdominal adiposity should be recommended [36].

Dietary strategies to improve plasma lipid profile comprises of avoidance of trans-fat consumption and reduction of intake of saturated fat to <10% of total caloric intake. Dietary fibre and inclusion of dietary supplements and functional foods like phytosterols, soy, monacolin and red yeast have been shown to achieve relevant decrease in LDL-C levels [2], [35].

2.4.2 Statins

Since its introduction in 1980s, statins have become a principal therapy in the treatment of CAD [37] and increased LDL-C levels [35]. Statins decrease the intrahepatic synthesis of cholesterol by blocking the function of the enzyme hydroxymethylysglutaryl CoA reductase, which acts as the rate limiting enzyme in cholesterol biosynthesis. The resultant decrease in cholesterol leads to an enhanced expression of LDL receptor at the surface of the hepatocytes, and increases LDL uptake, thereby decreasing the plasma LDL-C levels [2].

The effect of statins on lipids has been shown to be dose dependent and differs depending on the statin used. Depending on the intensity of the regimen, statins can cause more than 30-50% reduction in the LDL-C, 10-20% reduction in TG levels from the baseline values and 1-10% increase in the HDL-C levels [2].

Multiple studies [32], [38]–[41] have been performed to evaluate the effect of statins in the primary and secondary prevention of cardiovascular events in populations and subgroups. A meta-analysis of individual participant data by the Cholesterol Treatment Trialists' (CTT) Collaboration showed that each 1 mmol/L (39 mg/dL) reduction in LDL-C using statins lead to a decrease in the incidence of major vascular event (myocardial infarction (MI), CAD, stroke, or coronary revascularization) by 22%, in major coronary events by 23%, in incidence of CAD death by 20%, in total stroke by 17% as well as 10% reduction in the total mortality over the period of 5 years, even in patients with no prior history of vascular disease [32].

Despite its benefits, there are limitations and adverse effects to statin therapy. Statins have been found to be ineffective in a few groups of patients such as those with heart failure or receiving haemodialysis [42], [43]. About 5-10% of patients on statin therapy develops myopathy [44], an important clinical adverse effect, however serious effects such as rhabdomyolysis develop rarely with an incidence of about 1-3 cases/100 000 patient-years [2].

2.4.3 Non-Statins

Aside statins, there are other drugs used in the treatment of dyslipidemia and they can be recommended when patients are unable to achieve the target level on statin therapy alone, patients have intolerance to them (e.g., gastrointestinal disorders, myalgia, rhabdomyolysis) or have contraindications such as ongoing liver disease.

- **Cholesterol absorption inhibitors**

Ezetimibe decreases dietary and biliary cholesterol absorption by interacting with Niemann-Pick C1-like protein 1 (NPC1L1), resulting in increased plasma LDL clearance, thereby decreasing the LDL-C and TC levels. Ezetimibe can be used either as a monotherapy or in combination with statins in treatment of disorders associated with elevated cholesterol levels, including LDL-C. In monotherapy, ezetimibe decreases LDL-C by 15-22% in patients with hypercholesterolemia [36].

In several combination therapy trials, the use of ezetimibe with statin has shown greater reduction in LDL-C than ezetimibe monotherapy or statins [45], [46]. A large, pooled analysis showed 15.1% greater reduction in LDL-C with statin and ezetimibe

combination therapy when compared with statin monotherapy in statin naive patients. Additionally, there was a significant reduction in non-HDL-C by 13.5% and decrease in high sensitivity C reactive protein (hs-CRP) by 8.6%. With such great effect on cholesterol level, a higher percentage of patients was shown to attain the ATP (Adult Treatment Panel) III treatment targets with ezetimibe therapy add-on [45].

Although all LLDs have been associated with several side effects, life threatening adverse effects e.g. liver failure in ezetimibe monotherapy or combination therapy with statins are very rare [2].

- **Bile acid sequestrants**

Bile acids are produced in the liver from cholesterol and are transported into the intestinal lumen, however, most of the bile acids are reabsorbed in the terminal ileum via active transport system and returned to the liver. Bile acid sequestrants prevent the reabsorption of cholesterol by binding to bile acids and thereby eradicating a substantial portion of bile acid from the enterohepatic circulation. As a result of depletion of bile, the hepatic demand of cholesterol increases, consequently decreasing the circulating LDL-C [2].

Bile acid sequestrants include two bile acid-binding exchange resins, cholestyramine and colestipol, and a synthetic drug, colesevelam. A daily dose of 24g of cholestyramine, 20g of colestipol, or 4.5g of colesevelam has been observed to cause LDL-C reduction of 18-25% [2]. However, a significant increase in TG has been observed with the use of colesevelam compared with placebo [47], therefore, it is recommended to be avoided in patients with hypertriglyceridemia. Also, colesevelam can cause reduction in glucose levels, which is beneficial in patients with Type 2 diabetes [48]. Due to gastrointestinal side effects, commonly constipation, nausea, and flatulence, present even at a low dose, clinical use of these drugs is limited.

- **Proprotein convertase subtilisin/kexin type 9 inhibitors**

Proprotein convertase subtilisin/kexin type 9 (PCSK9) is a regulatory protein involved in the breakdown of LDL receptor, thereby decreasing LDL hepatic uptake and subsequently, plasma LDL-C level increases. PCSK9 inhibitors lower the concentration and function of the protein, resulting in decreased LDL receptor degradation, increased LDL hepatic uptake and lowers the circulating LDL-C levels [35].

Currently, there are two approved PCSK9 inhibitors, alirocumab and evolocumab (both human monoclonal antibodies), and numerous findings from clinical trials of both monoclonal antibodies have been published. Alirocumab and evolocumab, either alone or in combination with other LLDs have been observed to result in about 60% decrease in LDL-C levels, depending on the dose. When combined with high-intensity or maximally tolerated statins, they decreased LDL-C by 46-73% more than placebo, and 30% greater than ezetimibe. Also, both PCSK9 inhibitors effectively reduced LDL-C levels in high cardiovascular (CV) risk patients [2].

A randomized trial comparing alirocumab with placebo in high risk patients on statin therapy showed that alirocumab reduced LDL-C levels by 62% and the incidence of major adverse cardiovascular events by 48% [49]. These drugs are highly effective in decreasing LDL-C in all patients that can express LDLR in their liver, thereby they are effective in many patients, including those with heterozygous FH. Alirocumab and Evolocumab also decrease TG levels while increasing HDL-C levels, with evolocumab reducing TG levels by 26% and elevating HDL-C by 9% in clinical trials [2].

The potential for PCSK9 inhibitors interactions with orally absorbed drugs is significantly low because they are administered subcutaneously and do not interfere with pharmacokinetics or pharmacodynamics. Both PCSK9 inhibitors have been linked to similar adverse effects, most commonly, itching at the injection site and flu-like symptoms. Although there is a high probability of autoantibodies occurring in long term antibody treatment, very few cases of antidrug antibodies have been reported with their use [2].

- **Fibrates**

Fibrates are agonists of transcription factors, especially peroxisome proliferator-activated receptors (PPARs) that increase hepatic fatty acid oxidation and inhibits synthesis of TG in the liver. They also increase triglyceride catabolism by inducing lipoprotein lipase (LPL), an enzyme which hydrolyzes TG and phospholipids in VLDL and chylomicrons and inhibits apolipoprotein (apo) C-III synthesis, an apolipoprotein that hinders the catabolism of triglyceride-rich lipoproteins. As a result, the use of fibrates reduces plasma TG level by decreasing its synthesis and increasing its hydrolysis. Although the mechanism is not fully understood, fibrates increase HDL-C level and apolipoprotein A

(apoA) I & II synthesis [50]. Clinical use of fibrates has been estimated to cause a 50% reduction in TG level, ≤20% decrease in LDL-C level and up to 20% increase in HDL-C level [2].

Several randomized clinical trials have illustrated the effects of fibrates on cardiovascular morbidity and mortality; however, their results have varied. A significant reduction in the risk of major CVD with gemfibrozil was observed in primary prevention in Helsinki Heart study (HHS), but fenofibrate did not reduce the rate of cardiovascular events in people with diabetes in the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) and in Action to Control Cardiovascular Risk in Diabetes (ACCORD) studies [2]. Overall, it indicates the clear need for further confirmation of potential cardiovascular benefits of using fibrates.

Fibrates are well tolerated with mild side effects. The most commonly reported adverse effects are myopathy, elevation of hepatic enzymes and cholelithiasis, with myopathy reported to be 5.5 fold more with fibrates monotherapy than with statin therapy [2].

- **Omega-3 Fatty Acids**

Omega 3 fatty acids, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), reduce the synthesis and production of VLDL in the liver. It also diminishes plasma TG concentration by promoting LPL activity and prevents lipogenesis [50].

Omega 3 fatty acids reduce TG at pharmacological doses >2g/day, but their impacts on other lipoproteins are insignificant. Recent studies in people with high level of TG on EPA have shown a decrease of up to 45% depending on the dose and its efficacy has been reported in meta-analyses [2].

Overall, omega 3 fatty acids administration appears to be associated with no significant drug interactions. The prevalent side effect is gastrointestinal disorder and their antithrombotic effect can increase bleeding tendency, especially when co-administered with aspirin or clopidogrel [2].

- **Nicotinic acid**

Nicotinic acid (niacin or vitamin B) reduces LDL-C synthesis through a decrease in hepatic synthesis of VLDL cholesterol, the increase in HDL-C synthesis, inhibition of

lipolysis in adipose and an increase in lipase activity [51]. It mainly increases HDL-C and apoA1 by promoting hepatic apoA1 synthesis [2].

When administered in pharmacological doses, niacin raises HDL-C level by up to 25%, decreases plasma triglyceride levels by ~ 30%, and decreases the level of LDL-C by 10% to 15% [50]. Despite the favorable effect on lipids, two large randomized trials with niacin showed no significant reduction in the risk of major cardiovascular events [52], [53]. There is yet to be any medication containing nicotinic acid approved in Europe [2].

- **Lomitapide and mipomersen**

Lomitapide and mipomersen have been approved as adjunct therapy in patients with HOFH by the Food and Drug administration and both agents target apoB containing lipoproteins' production, rather than increasing their removal from bloodstream [24].

Lomitapide is an inhibitor of microsomal triglyceride transport protein (MTP), that is responsible for transferring triglycerides and phospholipids from endoplasmic reticulum to apoB in the assembly of VLDL. MTP inhibition by lomitapide leads to reduced synthesis of VLDL in the liver and chylomicrons production in the intestine, thereby decreasing plasma levels of all apoB-containing lipoproteins, including chylomicrons, VLDL and LDL [54].

In a single-arm, open label study evaluating the treatment of homozygous FH patients with lomitapide in addition to lipid lowering therapies including LDL apheresis, LDL-C was significantly reduced by approximately 50% from baseline at 26 weeks and resulted in 44% reduction in LDL-C at 56 weeks [55]. The most common adverse effects were gastrointestinal symptoms and due to its mechanism of action, lomitapide has been associated with increased alanine aminotransferase levels and liver fat accumulation [55].

Mipomersen is a second-generation antisense oligonucleotide that binds to the messenger ribonucleic acid (mRNA) of apoB in the liver, inhibiting the translation of apoB protein and ribosomal synthesis of apoB, resulting in decreased secretion of atherogenic lipids i.e. LDL, VLDL, and lipoprotein (a) (Lpa) [56]. In a randomized, double-bind, placebo-controlled trial in HOFH patients, 200 mg of mipomersen assigned randomly to patients weekly resulted in reduction of LDL-C by 25% from baseline, apoB by 27% and Lp(a)

by 31% vs placebo at 26 weeks. The most reported adverse effects observed in patients on mipomersen were injection site reactions [57].

- **Cholesteryl ester transfer protein inhibitors**

These groups of drugs directly inhibit cholesteryl ester transfer protein (CETP), that usually promote cholesterol esters and TG transfer from nonatherogenic HDL fraction to potentially proatherogenic non-HDL fractions. CETP inhibition results in an increase of HDL level by up to 180%, reduces LDL-C level by 0-45% and apoB by 0-34% more than what can be attained with statin therapy [50].

Although, earlier studies of CETP inhibitor has failed to show its clinical benefits on atherosclerotic events, a recent trial involving patients with ASVD receiving intensive atorvastatin therapy showed a reduction in major coronary events by 9% over a median of 4.1 years with use of anacetrapib [58].

2.5 Treatment compliance in dyslipidemia

2.5.1 Terminology

Many studies have been carried out to measure adherence, compliance, or persistence to medications over the years, however, the terminology used to describe how patients comply with their medication regimens varied across literatures and has evolved over the years.

The terminology “Adherence” was defined by World Health Organization as “the extent to which a person’s behavior - taking medication, following a diet, and/or executing lifestyle changes — corresponds with agreed recommendations from a healthcare provider” [59]. Compliance is used to describe “patient’s willingness to follow a prescribed course of treatment” [36], compared to persistence, which defines the “duration of time from initiation to discontinuation of therapy” [60]. Nonetheless, the terms adherence and compliance are used interchangeably in literatures and the term ‘compliance’ is most commonly used [61].

In this thesis, the term compliance has been adopted to describe the extent to which a patient is following a prescribed treatment regimen.

2.5.2 Determinants of treatment compliance.

It is well documented that the use of LLDs is highly potent in decreasing cardiovascular morbidity and mortality, nonetheless, compliance with the drugs has been a significant problem in clinical practice that halts the achievement of the desired therapeutic outcomes.

It is difficult to determine the specific compliance rate in patients with dyslipidemia because it is highly dependent on the study group, setting, data sources and the method used to measure compliance. For instance, a retrospective database analysis carried out in Italy used the proportion of days covered (PDC) by therapy to analyse the patient's compliance to medication [62], while another study used the medication possession ratio (MPR) to measure compliance [63]. Nevertheless, several studies of patients on statin therapy showed differing but notably high rates of non-compliance [60].

Compliance with LLDs is reported to be suboptimal, hindering patients to attain LDL-C targets, but the consequence of non-compliance is not limited to poor clinical outcome. It has been associated with increased medical costs with a resultant cost of about $100 billion to $300 billion a year, and a higher avoidable cost in comparison to those for hypertension and diabetes combined. Poor compliance also increases the cost burden for family caregivers and results in undesired outcome [64]. In contrary, high compliance to statin therapy resulted in lower all cause health care costs [65]

2.5.3 Factors influencing compliance

Multiple studies have been carried out to identify the factors associated with compliance and the impact of compliance with lipid lowering drugs on cardiovascular risk [66]–[68]. The common factors influencing compliance can be aggregated into patient's factor, physician factor and health system factors [13].

- **Patient Factors**

Patient-related factors play a huge role in predicting compliance and it includes patient's resources, knowledge, attitudes, beliefs, perception and expectations of their illness, outcomes of treatment and consequences of poor compliance [60].

Age has been a dominant predictor of compliance to LLDs, particularly with statin. Mann et al found a U shaped association between age and compliance in which both the youngest (<50 years) and the oldest (≥70 years) patients showed lower compliance compared to middle age patients (50-65 years) [68]. According to Reiner et al, elderly patients are less prone to receive lipid lowering drugs or be compliant with the therapy [27].

Several studies showed that men were more likely to be compliant with the prescribed lipid lowering drug than women [68], [13], and according to Lewey et al in their meta-analysis, women are 10 percent more likely to be non-compliant to their medication [69].

Aside demographic factors, others like socioeconomic status have been linked with compliance in the use of lipid lowering drugs [13]. Patients with higher income or residing in higher income neighbourhoods are more likely to be compliant with their therapy [68], [13].

Patient's comorbidities can also play a role in their compliance. In a systematic review and meta-analysis of predictors of nonadherence to statins, patients with a history of CVD or diabetes were more prone to be compliant [68]. Additionally, adverse effects of medication and the quantity of tablets prescribed can reduce compliance in patients [67].

- **Physician factor**

Health care providers play a vital role in determining the overall patient's compliance as they are responsible for adhering to the guidelines on management of dyslipidemias and prescription of LLDs when required.

Physicians are considered the primary source of information, so they can influence the use of drugs by counselling and advising patients as recommended in the national guidelines. As such, if physicians adhere strictly to the guidelines, there might be an increase in the overall population of patients who are able to attain the LDL-C goals [13]. There are numerous reasons why physicians might be non-adherence to the guidelines which includes, but not limited to physicians' perception of patient's compliance to medication, erroneous understanding or use of the guideline, high patient volume or lack of time [13].

A strong physician-patient relationship promotes high compliance in patients, especially if medication is prescribed by their own primary care providers. Chan et al, in their retrospective cohort study, observed that patients who had their prescription written by their own primary care providers were more prone to be compliant with their medication. In addition, expertise of the physician was observed to influence compliance as there was high compliance in patients whose index prescriber was a cardiologist [70].

- **Health system factors**

Compliance to LLDs, like other medications, depends on the cost of the prescribed drug, and any innovations designed to decrease patients' share of the medication cost have been shown to increase compliance [70]. According to Villako et al, the price of drugs is one of the factors that strongly influence the purchase of medication in about 25% of patients [71].

Higher out of pocket costs, low or absence of reimbursement are associated with poor compliance [68], and lower co-payments has been associated with increased compliance with the use of statins [13].

In Estonia, community pharmacists are obliged to recommend the cheapest medicine possible to patients [71], and there is a reimbursement system of medicines to help increase the accessibility of people to affordable drugs and prevent the unavailability of necessary medication due to the high cost of the products.

The reimbursement system of medicines based on the Health Insurance Act of Estonia covers the health care expenses related to the purchase of medicines for insured people. The system allows for partial or complete compensation of medicinal products from the state funds, however only the medicinal product authorized in Estonia and added to the Estonian Health Insurance Fund's (EHIF) list, are covered by the reimbursement system and compensated for in relation to the reference prices (price of the second cheapest drug) and price agreement, if in existent or based on the retail price of the medicinal product [72].

The rates of reimbursement for medicinal products are categorized in accordance with the severity of the disease and are available at 100%, 90%, 75% and 50% discount, with the highest discount rates applied to medicinal products needed in treatment of severe and

chronic disease, old people, or incapacitated pensioners. For each prescription medicine, the buyer is required to pay a prescription fee of 2.5€ and the discount is calculated on the outstanding amount based on the prescribed percentage, which means that the buyer will have to pay any amount exceeding the discount amount [73].

Reimbursement (discount) rates for LLDs varies depending on the active substance (see Table 2). Statins and Ezetimibe are available at 50%, 75%, 90% and 100% discount rate, however fenofibrate and Omega-3 Fatty Acids are only reimbursed at 50% and 100%.

Table 2. Average price of lipid lowering drug and the prices based on reimbursement.

Active substances	**Reference price**	**Price**	**50%**	**75%**	**90%**	**100%**
Statins						
Atorvastatin (20 mg)	2.94 €	2.82 €	2.66 €	2.58 €	2.53 €	2.50 €
Rosuvastatin (20 mg)	4.80 €	10.08 €	8.93 €	8.35 €	8.01 €	7.78 €
Simvastatin (20 mg)	3.40 €	3.46	3.01 €	2.78 €	2.65 €	2.56 €
Pravastatin (20 mg)	10.89 €	10.89 €	6.69 €	4.60 €	3.34 €	2.50 €
Fluvastatin (80 mg)	11.76 €	13.82 €	9.18 €	6.87 €	5.48 €	4.56 €
Fibrates						
Fenofibrate (200 mg)	9.90 €	9.90 €	6.20 €	-	-	2.50 €
Cholesterol absorption inhibitors						
Ezetimibe (10 mg)	17.64 €	19.37 €	11.80 €	8.01 €	5.74 €	4.23 €
Omega-3 Fatty Acids						
Omega-3-acid ethyl esters 90 (1000 mg)	19.55 €	19.55 €	11.02 €	-	-	2.50 €
Proprotein convertase subtilisin/kexin type 9 inhibitors						
Evolocumab (140 mg/mL)	228.99 €	-	-	-	-	-

3 Aim of the study

The aim of this thesis is to describe the use of LLDs in dyslipidemic patients and demonstrate the treatment compliance rate. Furthermore, to determine the efficacy of PCSK9 inhibitors in patients with FH in clinical practice.

Research objectives:

- To study the trend in the use of LLDs in patients with dyslipidemia in North Estonia Medical Centre and in Estonia.
- To study treatment compliance rate and explore factors that influence compliance with LLDs.
- To deeply analyse treatment efficacy in a subgroup of patients with familial hypercholesterolemia on PCSK9 inhibitors.

To address these research aims, it is essential to assess the following research questions:

- What are the current LLDs used in North Estonia Medical Centre and does the prices of the drugs influence their use?
- What are the treatment compliance rates among patients with dyslipidemia in North Estonia Medical Centre?
- How effective are PCSK9 inhibitors on FH and does treatment efficacy depend on the mutations?

4 Materials and methods

This chapter will describe the research methodology, study group, data collection and finally, various steps taken for data analysis.

4.1 Research methodology

A quantitative retrospective research was adopted in this work by analysing and studying North Estonia Medical centre patients with dyslipidemia in the time frame 01.01.2013-01.01.2020. First, to determine the current LLDs used in North Estonia Medical Centre and trend in their use within time frame (01.01.2013-01.01.2020). Second, to evaluate treatment compliance based on the pharmacy refill rates. Third, to determine factors influencing the pharmacy refill or compliance rates among patients with dyslipidemia. Lastly, to evaluate the effect of PCSK9 inhibitors in a subgroup of patients with FH.

This study was approved by the Research Ethics Committee of the University of Tartu as a prerequisite before commencing data gathering as the data included personal information about the study group.

After obtaining the approval, it was possible to request data from the Estonian Health Insurance funds and the North Estonia Medical Centre.

4.2 Study group

The first study group were patients of the North Estonia Medical Centre. The inclusion criteria were patients who were ≥18 years of age in 01.01.2013 and ≤70 years in 01.01.2020. The patients had to either be diagnosed with dyslipidemia (International Classification Code (ICD) E78.0-E78.9), or with LDL-C level ≥5 mmol/L. The exclusion criteria is the lack of prescription of LLDs within the study period (01.01.2013-01.01.2020) as the analysis of the use of LLDs and patient's compliance cannot be carried out.

According to the data obtained from North Estonia Medical Centre, there were 3471 patients within the inclusion criteria. However, after excluding patients without any prescribed LLD, the study group decreased to 2140 patients.

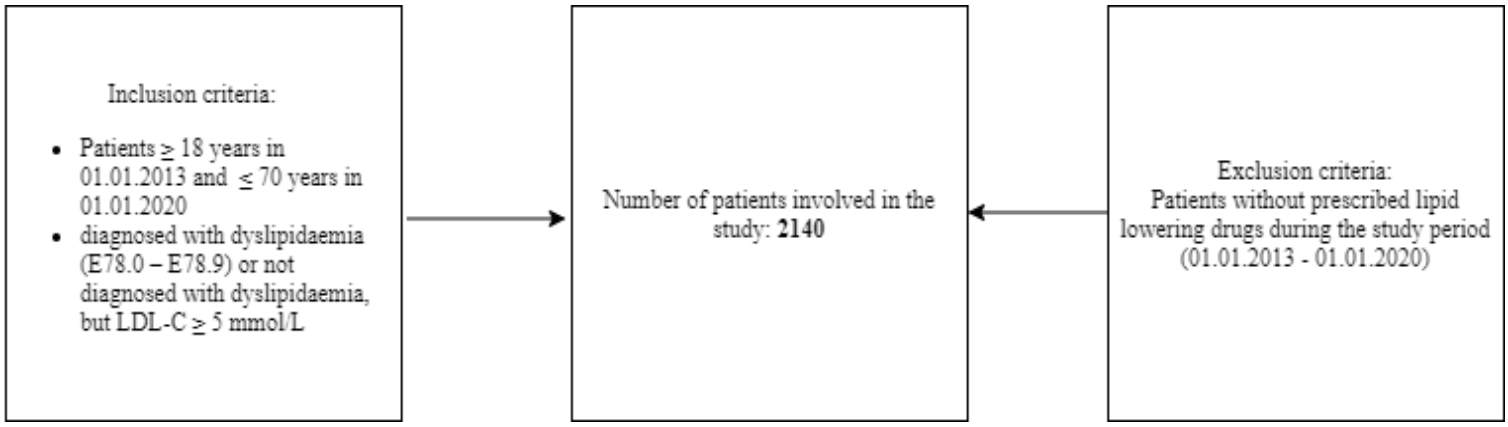

Figure 1. Study group 1.

The second study group included 5 patients from the North Estonia Medical centre who were recommended and prescribed PCSK9 inhibitors for a duration of 10 weeks. The treatment with PCSK9 inhibitors is reimbursed by the EHIF provided the patient fulfils the clinical indications:

1) Prior treatment of patient with maximum tolerated dose of statin and ezetimibe has been insufficient or has been contraindicated,

2) The patient's LDL-C level exceeds 200 mg / dL (5.2 mmol / L)

3) The patient has documented atherosclerosis,

4) The service is provided in a regional hospital specified in the list of hospitals based on a decision made by at least two-members expert council consisting of cardiologists from two different regional hospitals

To obtain the reimbursement, the treating physician will have to contact regulatory health authorities (treatment council) in North Estonia Medical Centre or The Heart Clinic of the Tartu University Hospital and provide them with patient’s medical data by e-mail or by e-consultation for the decision to be made.

4.3 Data collection

The patients' medical records were requested from the North Estonia Medical Centre. Data obtained includes the patient's identification code, socio-demographic characteristics like age and gender, clinical data like primary diagnosis and date of diagnosis (ICD code A00-Z99), coexisting diseases, all medical visits in North Estonia Medical Centre with date and the department name, date and values of lipid analysis (LDL-C) and normal values.

Clinical data for patients on PCSK9i such as general characteristics (age, sex), primary diagnosis, coexisting diseases, CVD events, previous and current LLD used, plasma lipid levels (TC, LDL-C, and HDL-C), blood analysis, computed tomography scan results, genetic test (LDLR, APOB, and other gene tested for) were also obtained from North Estonia Medical Centre.

Data about prescribed and refilled lipid lowering medications for patients within the inclusion criteria was requested from the Estonia Health Insurance Funds. Data gathered includes patient's identification code, prescribed lipid lowering drugs' names, date when medication was prescribed, prescription status (whether refilled or not refilled) and the date of refill. The names of the lipid lowering drugs prescribed were according to the Anatomical Therapeutic Chemical Classification System (ATC) in C10 group: C10AA-AC, AX.

The Estonia State Agency of Medicines (SAM) collects drug utilization or sales data from pharmaceutical wholesalers. All wholesalers provide information to SAM quarterly on the amount of each medicine sold and their prices. Lipid lowering drug utilization data from wholesalers was obtained from SAM to analyse the overall consumption and trend in the use of the medication in Estonia during the study period. Data obtained includes active substances, their ATC code, name of medicinal product, concentration, manufacturer, packaging code, quantities sold quarterly, turnover per quarter, packages sold per quarter, and average package price.

4.4 Data analysis

Microsoft excel was used primarily for performing data handling, descriptive analysis, and graph design. An algorithm was created and used to link the data set obtained from North Estonia Medical Centre and Estonia Health Insurance Funds.

Analysis was carried out to evaluate the prevalence of compliance and multivariate linear regression analyses were used to determine the strength and significant of the relationship between different factors (such as age, gender, primary diagnosis, and comorbidities) and compliance. Statistical significance was set at p-value <0.05.

For the analysis of PCSK9 inhibitors, the variables are expressed as mean ± standard deviation (SD).

The data was analysed in three phases:

4.4.1 Phase 1: Assessment of the use of lipid lowering drugs.

The trend in the use of lipid lowering drugs within the study period was explored, determining the most widely used medications in patients with dyslipidemia and their prevalence over the 7-year period. When analysing the consumption of lipid lowering drugs in Estonia, data regarding combined therapy was excluded because patients in the study were on monotherapy. As the information regarding quantities and turnovers of drugs are confidential, only the trends and percentage changes are shown.

4.4.2 Phase 2: Treatment compliance evaluation.

Compliance rate for individual patient is often reported as the percentage of prescribed doses of medication over a specific period [74].

In this study, compliance was evaluated based on the rate at which patients refill prescriptions, that is, the rate at which they purchase the prescribed medication from the pharmacy. Compliance to medication was divided into primary and secondary compliance. Primary treatment compliance describes whether patients purchased their prescribed medication in the first place, using the percentage of refilled prescriptions over the treatment duration.

Secondary compliance describes the behaviour of patients from the first prescription until the discontinuation of treatment. Based on the refills, we evaluate the rate at which patients refill their medication, putting into the consideration the required refills over the course of the treatment with lipid lowering drugs.

A. Primary treatment compliance

In this phase, compliance was determined based on whether the patients refill their medication once it was prescribed and started the treatment. To start analysing the data, the compliance group was defined.

As prescriptions are generally valid for 180 days in Estonia, then 100% compliance is defined as compliance when all the prescriptions during the course of treatment were refilled within 180 days.

The compliance rate for each patient was measured using the equation (1) adopted from [61]:

$$p\% = \frac{a}{A} \times 100\% \quad (1)$$

Where *p*% represents the compliance rate per patient, *a* represents refilled prescriptions and *A* is all the prescribed lipid lowering drugs.

Case Sample: 8 lipid lowering drug prescriptions were prescribed in total for patient "X", and patient refilled 6 out of 8 prescriptions within 180 days. In this case, the compliance is calculated with equation (1), where:

a = 6 prescriptions

A = 8 prescriptions

$$p\% = \frac{6}{8} \times 100\%$$

Therefore, the overall compliance (p%) for patient X is 75%.

Based on the compliance, each patient was categorized into one of three compliance groups:

- High treatment compliance: Defined as patients adhering to the treatment regimen as prescribed at least 80%.

- Intermediate treatment compliance: Defined as patients adhering to the treatment regimen as prescribed 40-79%.
- Low treatment compliance: Defined as patients adhering to the treatment regimen as prescribed less than 40%.

Compliance in each group was then further classified by:

- Gender: male, female
- Age: 20-34 years, 35-49 years, 50-64 years, ≥65 years
- Primary diagnosis: ICD code (A00-Z99)
- Coexisting diseases (secondary diagnosis): yes, no
- LDL-C level: ≥5 to <5.5 mmol/L, ≥5.5 to <7 mmol/L, ≥7 mmol/L
- Active substance: statins, fibrates, cholesterol absorption inhibitors, omega-3 Fatty Acids, PCSK9i.
- Department visited: cardiology, internal medicine, gynaecology, haematology, nephrology, neurology etc.

B. Secondary treatment compliance

In this phase, the average of the yearly prescription refill rates over the course of treatment was used to evaluate compliance in patients, putting into consideration the required prescription refills for the course of treatment.

As one prescription of lipid lowering drug contains doses for 2 months, patients will require 6 prescriptions (containing doses for 12 months) in a calendar year to be compliant with the treatment regimen. For patients prescribed medication for more than one year, the average of each year's compliance is calculated.

The compliance rate for each patient in a year was measured using equation (1):

$$p\% = \frac{a}{A} \times 100\%$$

Where *p%* represents the compliance rate per patient, *a* represents the refilled prescriptions and *A* is the expected number of prescribed lipid lowering medications (6 prescriptions per year).

Then, the yearly compliance was summed up and divided by the total number of years the patient was prescribed medications.

Case sample: 8 lipid lowering drug prescriptions for patient "X" were prescribed in 2013, 6 prescriptions in 2014 and 2015. Patient X refilled 6 out of 8 prescriptions in 2013, 4 prescriptions in 2014 and 3 prescriptions in 2015.

The yearly compliance for each year is calculated using equation (1):

In 2013: $\frac{6}{6} \times 100 = 100\%$

In 2014: $\frac{4}{6} \times 100 = 66.6\%$

In 2015: $\frac{3}{6} \times 100 = 50\%$

Therefore, the overall compliance for the duration of treatment is 72.2%.

Based on the compliance, each patient was categorized into one of four compliance groups:

- High treatment compliance: Defined as patients adhering to the treatment regimen within the duration of treatment at least 75%.
- Intermediate treatment compliance: Defined as patients adhering to the treatment regimen within the duration of treatment in 50-74%.
- Low treatment compliance: Defined as patients adhering to the treatment regimen within the duration of treatment in 25-49%.
- Very low treatment compliance: Defined as patients adhering to the treatment regimen within the duration of treatment in less than 25%.

Compliance in groups was then further classified by:

- Gender: male, female

- Age: 20-34 years, 35-49 years, 50-64 years, ≥65 years
- Primary diagnosis: ICD code (A00-Z99)
- Coexisting diseases (secondary diagnosis): yes, no
- LDL-C level: ≥5 to <5.5 mmol/L, ≥5.5 to <7 mmol/L, ≥7 mmol/L
- Active substance: statins, fibrates, cholesterol absorption inhibitors, omega-3 Fatty Acids, PCSK9i.

4.4.3 Phase 3: Assessment of the effect of PCSK9 inhibitors in patients with familial hypercholesterolemia

In this study, patients were considered to be diagnosed with FH if they had a documented pathogenetic mutation in LDL receptor, APOB, or PCSK9 gene, or if they had a DCLN score ≥6.

The efficacy of PCSK9 inhibitors was assessed based on the percentage reduction in LDL-C levels compared to the pre-treatment or baseline levels, and the attainment of LDL-C target levels according to the European Atherosclerosis Society/European Society of Cardiology guideline [2]. It is recommended to aim to achieve LDL-C <2.6 mmol/L (<100 mg/dL) in primary prevention or LDL-C <1.8 mmol/L (<70 mg/dL) in secondary prevention (in the presence of CVD). Secondary effect was evaluated by the influence of PCSK9 inhibitors on TC and HDL-C levels.

A separate analysis was carried out for patients with genetic FH and patients with clinically diagnosed FH to evaluate the effect of mutations on PCSK9 inhibitors.

4.5 Ethical considerations

Prior to data collection, ethics approval for this study was obtained from the Research Ethics Committee of the University of Tartu as the data required for the study contains patient's personal information. Identification codes for each patient was required to link the data obtained from North Estonia Medical Centre with the prescription data, and therefore included into data collection. As a result, a data exchange contract was concluded.

All personal data collected for the research were pseudonymized. Each patient was assigned a unique code, so they will not be identified and none of the patient's data will be reported in this work.

5 Results

Current chapter describes the results of the data analysis in accordance with the research questions and discusses the important findings**.**

Retrospective study was conducted, and the study group was chosen from the North Estonia Medical Centre database within the inclusion criteria within the study period 01.01.2013-01.01.2020. Subjects were ≥18 years of age at the start of the study period (01.01.2013) and ≤70 years in 01.01.2020 and either diagnosed with dyslipidemia or with LDL-C level ≥5 mmol/L. 3471 patients were selected based on the criteria and the prescription data was asked from the EHIF. 1331 individuals had to be excluded due to lack of data about prescription, therefore data for 2140 patients were analysed. Additionally, 5 patients with FH on PCSK9 inhibitors were included in the study.

5.1 Use of lipid lowering drugs in patients with dyslipidemia

In the analysis of the use of LLDs in the study group, it was observed that statins were the drug of choice in 96.4% of patients. The most frequently prescribed statins were rosuvastatin (44.6% of patients), atorvastatin (41.0% of patients) and simvastatin (8.5%). Omega-3 fatty acids were used in 2.2% of patients and both ezetimibe and fenofibrate were used only in 0.6% of the study group (see Table 3).

The trend in the consumption of LLDs in the study group from 2013 to 2019 was observed to decrease yearly with a slight peak in 2019 (see Appendix 1, Figure 2). In 2013, rosuvastatin was the most frequently used medication in patients (52.2%) but was overtaken by atorvastatin in 2015 when 47.6% of patients were prescribed the medication and rosuvastatin was prescribed in only 38.0%. Thereafter, atorvastatin remained the most prescribed LLD till the end of the study period (see Appendix 1, Figure 3). In comparison, the use of ciprofibrate, ezetimibe and fenofibrate gradually declined over the study period. Ciprofibrate was last prescribed in patients in 2014, ezetimibe in 2016 and fenofibrate in 2017, while evolocumab emerges among the prescribed medications in 2019.

Table 3. The use of lipid lowering drugs as first line of treatment in patients with dyslipidemia.

Medication	ATC	Number of patients	%
Statins			
Atorvastatin	C10AA05	877	41.0
Fluvastatin	C10AA04	34	1.6
Rosuvastatin	C10AA07	955	44.6
Pravastatin	C10AA03	16	0.7
Simvastatin	C10AA01	181	8.5
Cholesterol absorption inhibitors			
Ezetimibe	C10AX09	12	0.6
Fibrate			
Fenofibrate	C10AB05	13	0.6
Ciprofibrate	C10AB08	3	0.1
Bile acid sequestrants			
Cholestyramine	C10AC01	1	0.05
Omega-3 Fatty Acids			
Omega-3-acid ethyl esters 90	C10AX80	47	2.2
Proprotein convertase subtilisin/kexin type 9 inhibitors			
Evolocumab	C10AX13	1	0.05

5.1.1 The price and consumption of statins in Estonia

The average package price of statins was observed to move in an inverse direction to the consumption from 2013 to 2019 (see Appendix 1, Figure 4). The average price remained almost the same from 2013 to 2015 and from 2015 to 2019, the price decreased by about 11.6%. In contrast, the total consumption of statins was progressively increasing over the study period, with ≈20.0% increase in consumption from 2013 to 2019. A statistical association was found between the consumption of statins and the average price ($p=0.0019$), indicating that the lower the price, the higher the consumption.

Within the study period, the use of the most prescribed statins, rosuvastatin and atorvastatin in Estonia was evaluated. The consumption of rosuvastatin was 21.0% higher than artovastatin in 2013, but from 2017 to 2019, the overall consumption of artovastatin surpassed that of rosuvastatin (see Appendix 1, Figure 5). This is similar to the trend observed in the use of statins in the study group (see Appendix 1, Figure 3).

The average price of atorvastatin was significantly cheaper than rosuvastatin over the period of 2013 to 2017. Although the price of rosuvastatin progressively declined within the period, it was still more expensive than atorvastatin. From 2017 to 2019, the average price of both drugs plateaued, with little changes observed (see Appendix 1, Figure 5).

5.2 Treatment compliance

Study group

From the 2140 patients with prescription for lipid lowering medications, 950 (44.4%) were male and 1190 (55.6%) female, aged from 20-69 years with a mean age of 54.8 years. 3.7% of the patients were 20-34 years old, 19.4% were 35-49 years old, 66.5% were 50-64 years old and 10.3% were ≥65 years old. From the study group, the primary diagnosis was diverse with 982 (45.9%) of the patients diagnosed with diseases of the circulatory system (I00-I99) and only 68 patients (3.2%) had been diagnosed with dyslipidemia (E78-E78.9). 1384 (64.7%) patients had coexisting (secondary) diseases and 756 (35.3%) subjects had no coexisting diseases. LDL-C levels in 1062 (49.6%) patients were between 5 to 5.4 mmol/L, 969 (45.3%) patients had LDL-C levels within the range of 5.5 to 6.9 mmol/L and 109 patients (5.1%) had LDL-C levels ≥7 mmol/L. The most prevalent medications used in treatment of dyslipidemia in the study group are statins, with atorvastatin used in 877 (41.0%) of the patients and rosuvastatin was prescribed medication in 955 (44.6%) patients (see Appendix 2, Table 9).

5.3 Primary treatment compliance

From the study group, 938 (43.8%) patients were considered highly compliant as they were following the treatment regimen as prescribed at least 80%. Majority of the study group, 949 (44.3%) patients, were following the prescribed treatment regimen in 40-79%, therefore, considered intermediate compliant and only 253 patients were considered to be low compliant by following the treatment regimen as prescribed less than 40% (see Table 4).

Table 4. Primary treatment compliance in dyslipidemic patients between 01.01.2013-01.01.2020.

Compliance group	**N**	**%**
High compliance (≥80%)	938	43.8
Intermediate compliance (40-79%)	949	44.3
Low compliance (≤39%)	253	11.8

45.3% of the males in the study group were highly compliant (≥80%), 45.2% had intermediate compliance (40-79%) and just 9.6% had low compliance (≤39%). In

comparison to the females in the study group, the compliance groups were 42.8%, 43.6% and 13.6% respectively. Despite the higher proportion of men in high compliance groups, there was no significant statistical association between gender and the compliance groups ($p>0.05$) (see Appendix 2, Table 10).

There was a notable outcome in the comparison between patients within age group 50-64 and patients ≥65 years. Although compliance was highest within 50-64 age group with a total of 1424 out of 2140 patients, of which 175 of them were categorized under low compliance and only 18 out of 220 patients in the ≥65 age group were categorized under low compliance, the result showed statistical association ($p=0.013$) between these age groups in the low compliance group (see Appendix 2, Table 10). Therefore, patient's age is considered to be an influential factor to compliance. Conclusively and statistically, patients ≥65 years will most likely have low compliance to their treatment.

Based on the results, 45.6% of patients diagnosed with other endocrine, nutritional and metabolic diseases (E00-E77, E79-E89), and 44.3% of patients diagnosed with diseases of circulatory system (I00-I99) were intermediate in their compliance. The result of the comparison between these two diagnoses was close to being statistically relevant ($p=0.07$) which would highlight the theory that patients with any of these diagnoses will most likely be compliant on an intermediate level (see Appendix 2, Table 10).

In the comparison between patients diagnosed with mental, behavioral, and neurodevelopmental disorders (F01-F99), diseases of the nervous system (G00-G99) and diseases of circulatory system (I00-I99) each respectively, results showed statistical relevance at the intermediate compliance level for these diagnoses (see Appendix 2, Table 10). This clearly prove that patients diagnosed with mental, behavioral, and neurodevelopmental disorders, diseases of the nervous system and diseases of circulatory system are more likely to be compliant to their treatment on an intermediate level.

The result showed that 10.0% of patients with coexisting diseases and 15.1% of patients without coexisting diseases were low compliant. The author observed that more patients in this category could potentially result in a profound statistical relevance, however, p-value being 0.06 means that comorbidities could influence the compliance level of the patients (see Appendix 2, Table 10).

Similar to the observation in comorbidities, patient's LDL-C level could potentially impact their compliance. There were significantly higher patients with LDL-C level ≥5 to <5.5 (1062 patients) and ≥5.5 to <7 (969 patients) in comparison to patients with LDL-C level ≥7 (109 patients). However, 57.8% of the patients with LDL-C level ≥7 mmol/L as opposed to 43.6% each of patients with other LDL-C levels, were compliant at intermediate level, and resulted into the exact threshold (p=0.05) for statistical relevance (see Appendix 2, Table 10).

The author found no significant statistical association between the active substances and patients' compliance to treatment. Although, in the comparison between the use of ezetimibe and fenofibrate, there was a close possibility of these substances influencing the compliance rate (p=0.09). The possibility of statistical relevance based on the use of these active substances would be more pronounced if more patients were recorded under these drugs (see Appendix 2, Table 10).

From the category based on the doctor's specialty (see Appendix 2, Table 11), the cardiology department had the most patients by number in each compliance category. 235 patients (39.0%) who were highly compliant, 291 (48.3%) intermediate and 77 (12.8%) low compliant patients. However, further statistical analysis showed that although patients who visited doctors in the infectious disease department are significantly lesser than the population of patients who visited doctors in the cardiology department, patients who visited doctors in the infectious disease department are more inclined to be highly compliant (p=0.049) to their treatment. Furthermore, 10 (13.2%) out of 76 patients who visited the doctors in the oncology department were low in compliance. The statistical relevance (p=0.009) points to the conclusion that patients who visit doctors in the oncology department will most likely be low in compliance to their treatment.

The author further analysed the overall compliance per year from 2013 to 2019 in the study group and the result showed that the overall average compliance was 62.8% in 2013 and decreased to 57.1% in 2016, but thereafter, there was a rise in the compliance rate reaching 65.1% at 2019 (see Appendix 1, Figure 6).

5.4 Secondary treatment compliance

From the study group, 709 (33.1%) patients were considered highly compliant, meaning they were following the regimen during the duration of treatment at least 75%. 562 (26.2%) patients were following the treatment regimen in 50-74%, and there were 493 (23.0%) patients following prescribed regimen as required in 25-49%, while 376 (17.6%) were considered as very low compliant as they followed the treatment regimen less than 25% (see Table 5).

Table 5. Secondary treatment compliance in dyslipidemic patients between 01.01.2013-01.01.2020.

Compliance group	**N**	**%**
High compliance (≥75%)	709	33.1
Intermediate compliance (50-74%)	562	26.3
Low compliance (25-49%)	493	23.0
Very low compliance (<25%)	376	17.6

38.5% of the males in the study group had high compliance during the treatment duration (≥75%), 27.2% had intermediate compliance (50-74%), 20.5% had low compliance (25-49%) and 13.8% had very low compliance (<25%). In females, the compliance groups were 26.8%, 25.5%, 25.0% and 20.6% respectively (see Appendix 2, Table 12).

Patients within the age range 50-64 years were significantly populated on every compliance level. However, when compared to patients in the age range 20-34 years, with a statistical relevance of p=0.006, it can be concluded that patients within this age range are highly compliant to their treatment (see Appendix 2, Table 12). This observation further supports the conclusion in section 5.3 that age contributes to the compliance level of patients.

Patients diagnosed with diseases of circulatory system are numerically more than the population of other patients with other diagnoses. The statistical relevance of the impact of this diagnosis on compliance was a near-miss (p=0.06) when compared with patients diagnosed with other endocrine, nutritional and metabolic diseases. However, patients diagnosed with diseases of the digestive system (K00-K95) are more likely to be low or very low in their compliance as observed with the statistical relevance p=0.0015 and 0.051, respectively (see Appendix 2, Table 12). This result implies that certain diagnoses

influence the compliant level of patients and the conclusion is explored further in the subsequent analysis of diagnoses.

The author observed that diseases of the skin and subcutaneous tissue (L00-L99) and diseases of the musculoskeletal system and connective tissue (M00-M99), when compared to the diseases of circulatory system (I00-I99), are statistically relevant (see Appendix 2, Table 12). Patients diagnosed with diseases of the skin and subcutaneous tissue are more likely to be compliant on an intermediate level while patients diagnosed with musculoskeletal system and connective tissue disorders are more likely to be highly compliant.

The author found no significant statistical association between LDL-C levels and the compliance of patients to their treatment. Although, in the comparison between LDL-C level ≥5 to <5.5 and ≥5.5 to <7, a close possibility of these substances influencing the compliance rate (p=0.09) was observed (see Appendix 2, Table 12).

In the analysis of the active substances used in treatment of dyslipidemia, atorvastatin and rosuvastatin were highly used. The numerical value was observed to influence the statistical relevance of these substances. The compliance of patients who used these substances were compared, hereby resulting into a statistical relevance of 0.024 (see Appendix 2, Table 12). Although this relevance was observed at the intermediate compliance level, it can also be speculated that the active substances, especially atorvastatin and rosuvastatin, used in the treatment of dyslipidemia can influence the compliance level of patients.

The use of simvastatin showed a close potential to being statistically relevant. When compared to the use of rosuvastatin, it resulted into a p-value of 0.08 at an intermediate compliance level. On the other hand, the presence of comorbidities has no effect on the compliance level of the patients (see Appendix 2, Table 12).

It was observed that within the treatment duration, some patients were not prescribed medications within a specific period. For example, a patient got prescriptions for 2013, 2014 and 2016 but none was prescribed in 2015. Taking into account the missing prescriptions within the treatment duration, when compliance is measured, there is an observable decrease in the overall compliance of the patient. However, if the patient was

prescribed medication as required within the treatment duration, then compliance is only affected by the patient's prescription refill rates.

In the study group, patients were randomly selected to observe these differences. In Appendix 1, Figure 8, patient A, B, C, and G had no prescription in at least a year within the treatment duration and as a result, the compliance reduced. Whereas, for patient D, E and F, the overall compliance remained unchanged because they did not miss any year's prescription within the treatment duration.

Based on the analysis, it was observed that 616 (28.8%) patients missed their prescription for at least a one-year period. Prescription was mostly missed in 2016 and 2017 (see Table 6).

Table 6. Statistics of patients that missed at least one prescription per year.

Year missed	Number of patients
2014	158
2015	259
2016	304
2017	287
2018	185
2019	9

When comparing primary and secondary treatment compliance within the treatment duration, patients were categorized into one of three compliance groups:

- High treatment compliance (80-100%)
- Intermediate treatment compliance (40-79%)
- Low treatment compliance (≤39%).

The proportion of patients in the secondary treatment compliance group were 602 (28.1%), 844 (39.4%) and 694 (32.4%) respectively. In comparison to the primary compliance group (see Table 4), less patients were highly compliant, and a significant proportion of patients were in the low compliance group (see Appendix 1, Figure 7).

5.5 Efficacy of PCSK9 inhibitors in patients with familial hypercholesterolemia

The study group consisted of 5 patients, 3 males and 2 females who initiated treatment with PCSK9 inhibitors (evolocumab and alirocumab), aged 50-67 years. Three patients were primarily diagnosed with FH. The remaining patients had chronic ischemic heart disease as the primary diagnosis but had FH as a concomitant disease. All the patients in the study had CAD, resulting in stenoses of up to ≥50%.

Genetic testing was carried out prior to the study to confirm the diagnosis of FH by analysing DNA isolated from the patient's whole blood. In 3 patients, the result of the analysis confirms the diagnosis of FH as mutation of the genes encoding LDL receptor was found, while in one patient, the analysis revealed no disease-related variants in the gene studies and one patient had no genetic test result at the time of the study. Both patients without confirmed genetic testing had DLCN scores of 6 and 7, indicating probable FH.

The main reason (80%) for PCSK9i prescription was the failure to achieve LDL-C targets despite maximum lipid lowering treatment, while statin intolerance was the indication for PCSK9i in 1(20%) patients.

Table 7. Clinical characteristics of patients treated with PCSK9i.

Characteristics	**N**	**%**
Primary disease		
E78.0	3	60
I25.0	2	40
Genetic test		
Confirmed	3	60
Non-confirmed	2	40
DLCN	6, 7	
LLD prior to initiation of PCSK9i		
Statin only	1	20
Low statin + ezetimibe	2	40
High statin does +ezetimibe	2	40

Initiation of PCSK9i resulted in mean reduction of TC by 50.0%, of LDL-C by 61.1% and mean increase of 14.4% in HDL-C (see Table 8).

The effect of PCSK9 inhibitors on lipid levels was compared in patients with genetic FH (i.e., their diagnosis had been confirmed by molecular testing) and patients with clinical FH (DLCN ≥ 6). There was a greater reduction in TC and LDL-C in patients with genetic confirmation than those without (52.67% vs 44.3% and 63.49% vs 56.9% respectively), whereas there was a greater increase in HDL-C in patients without genetic confirmation of FH compared to those with molecular diagnosis of FH (21.5% vs 10.6%).

The overall percentage of patients who achieved the guideline recommended LDL-C target level <2.5 mmol/L (100 mg/dL) after initiation of PCSK9i was 60.0% (3 patients). All patients had a history of CVD mainly coronary artery disease and only 2 (40.0%) patients with CVD attained the secondary prevention LDL-C target of <1.8 mmol/L.

Table 8. Percent lipid changes after administration of proprotein convertase subtilisin/kexin type 9 inhibitors.

Lipids	**Baseline**	**After PCSK9i**	**P value**	**% change**
Total cholesterol (mmol/L)	8.7 ± 1.4*	4.4 ± 1.2	0.5625	50.0 ± 12.7
LDL cholesterol (mmol/L)	7.1 ± 1.0	2.8 ± 1.4	0.4064	61.1 ± 30.8
HDL cholesterol (mmol/L)	1.1 ± 0.3	1.3 ± 0.2	0.8796	14.4 ± 19.5

*mean ± SD

6 Discussion

This retrospective study assessed the utilization of lipid lowering drugs in 2140 patients with dyslipidemia. It also evaluated the compliance rate to lipid lowering drugs and assessed the efficacy of PCSK9 inhibitors in FH patients in clinical practice.

The most commonly used LLDs were statins, encompassing 96.4% of the overall prescriptions in the study group, while fenofibrate accounted for only 0.6%. This is expected because statin is the first line treatment for LDL-C lowering and CVD burden reduction [2]. The most prescribed statins were rosuvastatin (44.6%) and atorvastatin (41.0%). Up until 2014, rosuvastatin was the dominant statin, but was overthrown by atorvastatin in 2015. The change in the prescription pattern to atorvastatin till the end of the study period is most likely due to the well-documented efficacy of atorvastatin in lowering LDL-C. Atorvastatin when compared with other statins in patients with dyslipidemia has been shown to be more effective and significantly decrease lipid levels and mortality [75], [76].

Another factor that could have contributed to the preferred prescription of atorvastatin is the price. Atorvastatin has been identified to be the most cost effective medication in patients with dyslipidemia and relatively cheaper [77], [78]. The total consumption of statins in Estonia was observed to be influenced by the average price ($p=0.0019$), that is, the lower the average price, the higher the total consumption of statin. Moreover, we observed that the price of atorvastatin is cheaper than that of rosuvastatin (see Table 2 and Appendix 1, Figure 5), therefore, it is plausible that the cost effectiveness of the medication and its efficacy influenced the decision to opt for atorvastatin as the first-line medication in dyslipidemia.

When comparing these results with studies carried out in other countries, atorvastatin is the most prescribed medication in Poland at 47.8% [9], in Saudi Arabia at 62.36% [79], in Columbia at 78% [77], and in China [78], whereas a study conducted in eight Asian countries found a predominance of simvastatin [80]. The cross sectional observational studies carried out in 11 European countries and Canada by Gitt et al also found

simvastatin to be the most frequently used medication in statin-treated patients with dyslipidemia [81].

Despite the extensive use and effectiveness of lipid-lowering medications, multiple studies documented high rates of non-compliance [68]. Compliance is a key factor associated with the efficacy of all pharmacological therapies, including LLDs [82], and consequently, low compliance limits the benefits of the drugs. Although, measurement of compliance is challenging [82], interventions to enhance compliance can only be developed if the nature and magnitude of the problem is measured [83]. Therefore, compliance rate to LLDs was measured in this research.

Among the 2140 patients prescribed LLDs in the study, overall compliance to LLDs was low as 56.1% had compliance level less than 80% for primary compliance, and 66.9% had compliance level less than 75% for secondary compliance. Contrary to the findings in this research, Xie et al in their study reported a higher compliance rate of 80.8%, 64.9% and 57.0% in patients on lipid lowering treatment at year 1, year 2 and year 3 of treatment respectively [84]. However, in a retrospective cohort study of 14,257 patients, only 36.4% of the patients were fully compliant to their medication [70]. The possible reasons for non-compliance varies and can include factors from the five groups: patient, disease, therapy, healthcare and social factors [85]. The most common reasons reported for non-compliance such as fear or presence of adverse effects especially in long term use, general concerns about medication, decision to opt for lifestyle modifications instead and low perceived illness severity might have contributed to low compliance in this study.

In addition, other factors that might be associated with compliance were evaluated namely age, gender, primary diagnosis, comorbidities, LDL-C level, prescribed medication, and department visited. Older patients (≥65 years) were more likely to be non-compliance to LLDs, while younger patients (20-34 years) were found to be highly compliant. There are opposing data in literatures regarding the association between age and compliance. The conclusion that compliance to lipid modifying agents is lower in older patients was confirmed by Agarwal et al in their study, indicating that patients ≥65 years were less prone to be compliant in comparison to younger patients aged 20-44 years [86], which corroborates the outcome in this work. Reasons for poor compliance in elderly patients have been attributed to problems with vision, hearing and memory, difficulties with following instructions owing to cognitive impairment or other physical problems. It is

plausible that older patients in this study had experienced more side effects with the use of the medications. Socioeconomic factors have also been observed to affect compliance in elderly patients as they might not have sufficient money to refill their prescriptions due to poverty, family issues, education level or cultural factors [87]. In another study, elderly patients over the age of 75 years showed lower compliance rates to statin therapy and possible confounding reasons postulated by the author includes concomitant dementia or poor access to health care [13]. On the contrary, other studies have found older patients to be more compliant to lipid lowering agents than younger patients [88], [89], whereas a study in Indonesia observed no association between age and compliance rates in patients treated with LLDs [90].

Previous studies have shown association between gender and compliance, identifying gender as a predictor of compliance. Many studies have concluded that women are more likely to be non-compliance to LLDs than men [13], [68], [69], [84], [90], [91]. In a meta-analysis, women were observed to be 10% percent less likely to be compliant to their prescribed medication (OR 1.10, 95% CI 1.07-1.13) [69]. Majority of the studies reviewed by Mann et al supported this hypothesis and when comparing women to men, the relative risk values for low compliance was 1.07 (95% CI 1.02 to 1.12) [68]. Similarly, Agarwal et al reported that men were 1.161 times more prone to be compliant than women, and other studies have found akin result [86]. Low compliance may be due to greater number of comorbidities in women and therefore higher requirement for medications, or that women and their health providers might underestimate their cardiovascular risk and thus, query the importance of the medication, or have more concerns regarding side effects than men [91]. On the contrary, no association was found between gender and compliance to LLDs in this research. This is aligned with the mixed results in previous studies [68]. It is likely that both men and women in the current study perceived their cardiovascular risk and importance of LLDs to the same extent. Overall, gender does not appear to be a significant factor influencing compliance.

It was also observed that a patient's diagnosis can contribute to both compliance and non-compliance to LLDs. This finding corroborates previous studies by showing that compliance level varies, depending on the patient's condition. Patients diagnosed with diseases of circulatory system, diseases of nervous system, mental, behavioral, and neurodevelopmental disorders or diseases of the skin and subcutaneous tissue were averagely compliant to their prescription. Low compliance was observed to be more likely

in those with digestive system disorders, whereas diseases of the musculoskeletal system and connective tissue increases the likelihood of high compliance. On the other hand, presence of comorbidities did not have any association with compliance in this study, but it is worth noting that the association was a near miss (p=0.06).

Despite the heterogeneity in studies, diseases and comorbidities were consistently associated with differences in compliance [68], [91]–[93]. Diseases that contributes to high compliance includes diabetes [68], [92], hypertension [68], [92], presence of renal diseases [91], history of CVD (MI or stroke) [68], [91], [93]. By contrast, depression [91], [92], and respiratory diseases such as chronic obstructive pulmonary disease or asthma [91], contribute to non-compliance. Mental health disorder was observed in a study to increase the odds of being compliant and there is evidence that suggests that patients with this disorder tend to have higher cardiovascular risk and they are most likely aware of the predisposition, therefore they are compliant [92]. Patients with higher number of comorbidities are significantly most likely to be compliant to the medication [108].

The association between certain diseases, comorbidities and compliance can be explained by the health belief model which suggests that the perceived risk of a disease does affect behaviors [68], that is, sicker patients or those with severe diseases might be more deliberate with taking their medication or adhering to their prescription. Increase in awareness of the severity of disease can allow patients to acknowledge the importance of adhering to medications. Although the precise interaction between disease and compliance is unclear, measures to manage these conditions in patients with dyslipidemia might positively influence the use of LLDs.

In contrast to the findings of one large general population study [94], the current retrospective study found no association between patient's LDL-C level and their compliance. Braamskamp et al found non-compliance to be accompanied by significantly elevated LDL-C in young adults with FH. A cross-sectional study also found low compliance to statins to be associated with higher LDL-C level for both men and women ($p<0.001$) [89]. These findings, as opposed to the result of this study, reflects the potential clinical importance of LDL-C level in the use of LLDs among patients, and therefore future studies need to explore the relationship between compliance and lipid levels.

Another factor suggested to be predictive of compliance is the type of LLDs prescribed [84], [92]. Patients on statins tend to be more compliant than those on other LLDs [84]. Statins have been shown to not only effectively reduce LDL-C, but improve other lipid levels, reduce cardiovascular events and generally a safe medication to prescribe [13]. Xie et al also attributed their findings to the efficacy of statins on dyslipidemia as shown in their previous study to have an attainment rate for a cholesterol target level of 35%, compared to 23% for patients using fibrates, 24% when using niacin and 28% when using other LLDs [84].

In Hope et al's review, one included study observed that patients were more likely to be compliant to fluvastatin and rosuvastatin than to simvastatin, and less likely to be compliant to lovastatin compared to simvastatin [92]. Although, only on an intermediate compliance level, the present study supports this hypothesis as atorvastatin and rosuvastatin were observed to influence compliance. This might be due to the high potency of these drugs on dyslipidemia. Atorvastatin and rosuvastatin are highly effective as monotherapy to achieve a greater degree of LDL-C reduction compared to other LLDs [95]. It is also plausible that patients experienced lesser side effects with these agents, or they are relatively cheaper than other LLDs.

Patients treated in the infectious disease department were highly compliant than those in other departments, while patients who visited the oncology department were poorly compliant to their treatment. This could be due to the difference in the characteristics of patients treated in these departments, severity of the disease or drug interactions. Therapeutic complexity and polypharmacy negatively influence compliance [96], and patients with oncology diseases or other chronic diseases are likely to be on multiple medications. Also, poor patient-physician relationship and medical distrust can result in low compliance [7]. However, the information about patient's additional prescriptions and their relationship with physicians was not available in this study, so the impact of the department, physician or polypharmacy on compliance could not be fully explained or ascertained.

Overall, based on the result of the current thesis, age, presence of certain diseases, the type of medication prescribed, and departments visited are factors affecting compliance in dyslipidemia patients. Nonetheless, there are other factors, although not included in the

present study that might influence compliance such as duration of prescription, number of pills prescribed, co-prescription or polypharmacy etc.

Within the treatment duration, it was observed that there was a gap in the treatment regimen. 28.8% of patients were not prescribed medication for at least one year during the treatment duration, this therefore decreased their overall compliance level. However, possible reasons for discontinuation of medication could not be deduced as the information was not available due to the nature of the study.

This study is one of the few studies that examined the real-world indication and efficacy of PCSK9 inhibitors in patients with genetic dyslipidemia [10], [97]–[99]. Despite the use of established LLDs and combination therapy, most patients with FH fail to achieve the LDL-C treatment targets and therefore, the introduction of PCSK9 inhibitor with its significant potency for lowering LDL-C is an effective additional treatment option for these patients**.**

The predominant reason for PCSK9i prescription was the failure to achieve LDL-C targets despite maximum lipid lowering treatment. This is expected as a pre-requisite for obtaining an approval for PCSK9i in Estonia requires the patient's LDL-C level to be >200 mg / dL despite prior treatment with maximum LLD.

The addition of PCSK9i to the treatment of FH patients resulted in a mean LDL-C reduction of 61.1% with relatively higher proportion of patients attaining the lipid treatment target. These findings are comparable to those reported in other real-world settings and randomized trials [10], [97]–[100] In a recent real-world cohort, PCSK9i resulted in a mean LDL-C reduction of 56.2% at 3 months and the LDL-C lowering effect remained persistent at 12 months [10]. The Reduction of LDL-C With PCSK9 Inhibition in Heterozygous Familial Hypercholesterolemia Disorder (RUTHERFORD) randomized patients with heterozygous FH on statin therapy to evolocumab 350 mg, 420 mg vs placebo and observed a 43% to 55% reduction in LDL-C at 12 week [101]. Stoekenbroek et al in their cohort demonstrated a mean LDL-C reduction of 55% from a baseline of 4.4 mmol/L [98].

In this study, LDL-C reduction was greater in FH patients with genetic mutation than those without genetic mutation. This is contrary to Galema-Boers et al's findings where patients with heterozygous FH with genetic mutation had lesser LDL-C reduction

compared to patients with clinical HeFH [97]. Although these findings cannot be explained in both studies, there seems to be a relationship between the presence or absence of mutations in FH patients and LDL-C lowering effect of PCSK9 inhibitors. Notably, treatment with PCSK9i resulted in mean HDL-C increase of 14.4% similar to that observed in Stoekenbroek et al's study [98].

Furthermore, the proportion of patients who achieved the guideline recommended LDL-C target are in line with those observed in randomized clinical trials. Overall, 60.0% of patients achieved the treatment target for primary prevention of LDL-C ≤2.6 mmol/L (≤100 mg/dL), and the secondary prevention target of LDL-C ≤1.8 mmol/L (≤70 mg/dL) was attained in 40.0% of the patients. In the study from Netherlands on 83 FH patients (79 HeFH and 4 HoFH) treated with PCSK9i, LDL-C goals for primary and secondary prevention were attained in 55% and 60% of patients, respectively [97]. Another study from the Netherlands which comprised of 238 patients (67% had FH and 43% were statin intolerant) reported that 54.5% of patients achieved the primary prevention LDL-C target of <2.5 mmol/L (<100 mg/dL) and 67.1% reached the secondary prevention LDL-C goal of <1.8 mmol/L (<70 mg/dL) [98]. A cohort comprising of 141 patients treated with PCSK9i from Greece showed LDL-C goal attainment of <100 mg/dL in 71.4% of patients without CVD and LDL-C goal of <70 mg/dL was achieved in 67% of patients with CVD [10]. Although high attainment rates have been observed across several studies, it can be influenced by the study group, the baseline LDL-C levels and the duration of treatment. The present study alongside previous studies confirm the efficacy of the PCSK9 inhibitors and thereby suggest that they are of beneficial use in patients with FH.

6.1 Study limitations

The utilization study showing the total consumption of LLDs was based on the wholesale data and does not show the exact amount of drug used by patients. It only gives the overall trend in consumption and does not allow assessment of the real prescription or recommendation in patients with dyslipidemia.

Evaluation of treatment compliance in the current study was based on pharmacy refill rates and although this is an objective method of assessing compliance, it can be subjected to patient manipulation (purchasing pills but still not taking them, pill dumping, pill

sharing) [61]. Treatment compliance in patients can easily be overestimated as there is no way to know for certain whether patients did take the medication as recommended or not, despite refilling their prescription. Additionally, the rate of discontinuation of medication and the reason why patients stopped their medicines could not be evaluated. Therefore, a combination of methods is recommended to accurately assess patients' compliance to prescribed medication, for example using self-reported questionnaires, pharmacy refill rates, and electronic monitors.

The study considered whether patients refilled any LLD prescribed and did not consider whether the patient switched medications. For example, a patient might be prescribed rosuvastatin in the beginning of the study and later prescribed atorvastatin. The limitation of this is that patients might switch to another high potency medication that may be associated with a different outcome or effect and as a result, different compliance level. Future studies may evaluate changes in compliance with a switch in the drugs prescribed.

Due to the retrospective nature of the study, certain variables such as patient's race, socioeconomic status, lifestyle-related risk factors, severity of disease, polypharmacy, side effects and medication costs, which might have influenced treatment compliance could not be obtained for the study group, and therefore their impact on compliance could not be assessed. Also, there is no information regarding the interaction or relationship between patients and physicians, an important predictor of compliance. Physicians' approach usually contributes to patient's compliance. If physicians adequately explain the advantages and side effects of medication to the patients, and encourage them to effectively use their drug, compliance may improve. However, there is no way of obtaining such information in this type of study and thus, unable to clearly explain the association between compliance and patient-physicians' relationship or the department visited.

The main limitation of the PCSK9i study is the relatively small study group. Therefore, further investigation in a larger population of FH patients is required to provide further insight on the use of PCSK9i in real life settings in Estonia. Furthermore, this study reported short-term results and as such, the side effects and discontinuation rate were not assessed. A larger population of patients prescribed PCSK9i for a prolonged treatment period is required to establish side effects and discontinuation rates.

6.2 Future perspectives and recommendations

While several factors influencing compliance were identified, a multi-method compliance measurement technique should be used in future research to identify other predictors of compliance and obtain more accurate results. A better understanding of the association between these predictors and compliance, and their impact on health outcomes of dyslipidemia in Estonia is required.

The current predictors of compliance identified in the study should be used to identify patients with dyslipidemia who are less likely to be compliant to their treatment regimen and design intervention aimed at improving compliance and enhancing optimal clinical outcomes.

Although the result of use of PCSK9 inhibitor is promising with LDL-C targets now achievable, future studies in a larger treated population will be required to establish its efficacy and safety in Estonian population. Also, there are still aspects of PCSK9 inhibitors yet to be explored. There seems to be an association between mutations found in FH patients and LDL-C lowering effects of PCSK9 inhibitors, hence, further research is necessary to provide definitive evidence of the association and help maximize effects of the drugs in sub-groups of patients with FH.

7 Summary

Cardiovascular disease is the leading cause of death worldwide. Dyslipidemia is a major cardiovascular risk factor accounting for 2.6 million death per year, demonstrating the need for an effective treatment regimen to reduce CVD mortality and morbidity.

Even though the benefits of LLDs are well-documented and there is evidence of their effect in preventing cardiovascular events in randomised controlled trials, compliance to LLD is poor. The effectiveness of a drug is dependent on the compliance of the individual patient [84], thereby poor compliance halts the achievement of the optimal effect of prescribed medication and increases economic burden due to the associated increased health care cost. It is important to measure compliance and identify the factors influencing compliance, in order for interventions to improve compliance and consequently enhance quality of care to be implemented.

The management of FH with LLDs is challenging, as the control of lipid levels and attainment of LDL-C targets in FH patients is often difficult. A new class of LLDs, proprotein convertase subtilisin/kexin type 9 inhibitors (PCSK9i) has recently emerged as a promising alternative for patients unable to adequately decrease LDL-C level, despite maximum tolerated LLDs. Evolocumab and alirocumab have been observed in randomised controlled trials to achieve LDL-C reduction of ≈60% in FH patients and well tolerated. However, it is important to establish the efficacy of PCSK9i in FH patients in real life settings.

The aim of this thesis was to describe the use of lipid lowering drugs and demonstrate treatment compliance of patients with dyslipidemia. Also, to evaluate the efficacy of PCSK9i in FH patients in real-life settings. Therefore, patients' data was obtained from North Estonia Medical Centre, data about patients' prescription was obtained from Estonia Health Insurance Funds and drug utilization data was asked from the Estonia State Agency of Medicines.

Based on the findings of the research, the main outcome and conclusion of the thesis are following:

- The most used LLDs are statins, with atorvastatin and rosuvastatin predominantly used in patients with dyslipidemia. Atorvastatin is cheaper than rosuvastatin, suggesting that this might have influenced the prevalent use of atorvastatin.

- The trend in the overall consumption of LLDs in Estonia and the average package price of the drugs moved in opposite directions, that is, consumption is influenced to an extent by the price of the medication.

- Treatment compliance rates in patients with dyslipidemia in North Estonia Medical Centre is low. Only 43.8% from the study group were in the high primary compliance group, meaning they were following the treatment regimen as prescribed at least 80%, and only 33.1% of the patients were in the high secondary compliance group, meaning they were following the regimen during the duration of treatment at least 75%.

- Many factors affect compliance to LLDs. Age, presence of certain diseases, type of medication and department visited by patients influences compliance. Factors that contribute to high compliance are young age (20-34 years), diseases of the musculoskeletal system and connective tissue and visitation to infectious disease department. Advanced age (≥65 years) and diseases of the digestive system are associated with low compliance in patients with dyslipidemia.

- The use of PCSK9 inhibitors in FH patients on maximum LLD resulted in significant reduction of LDL-C and attainment of LDL-C targets according to international guidelines. PCSK9i also improves other lipid profiles, decreasing TC, increasing HDL-C, and reducing cardiovascular risk in FH patients.

Effective treatment of dyslipidemia is necessary to reduce cardiovascular risk, mortality morbidity and health care cost, therefore there is a need to improve patient's compliance to LLDs. This study has highlighted few factors associated with compliance to LLDs in clinical practice, which may be useful for professionals and health care providers to recognize group of patients less likely to be compliant and implement strategies to enhance compliance. Interventions such as telephone reminders, calendar reminders, patient's education in the form of text messages or information booklets, and pharmacist review have been identified as effective methods to improve compliance to LLDs [102].

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Appendix 1

Figures for results

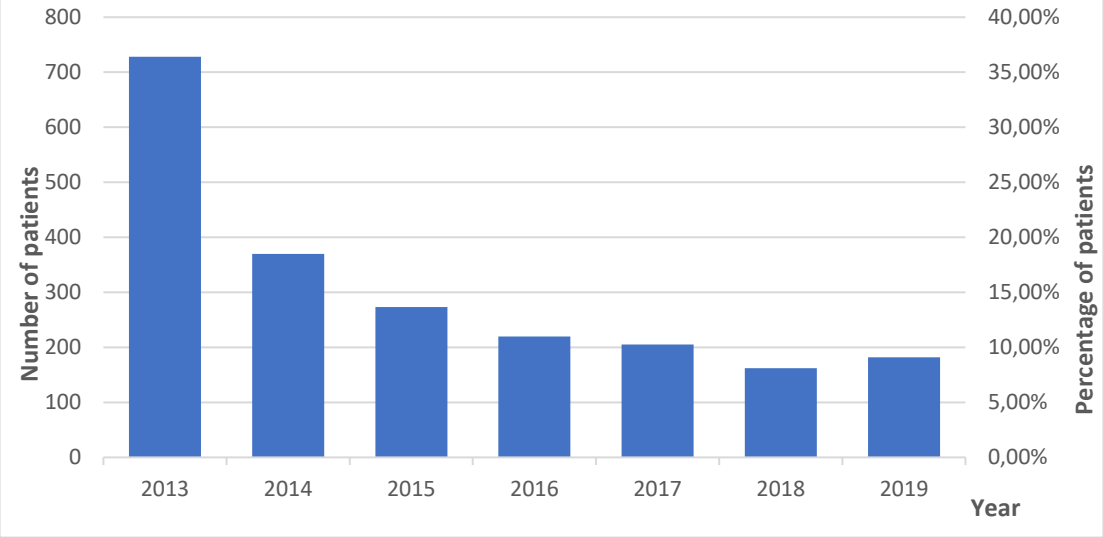

Figure 2. The yearly number of patients who started treatment with lipid lowering drug from 01.01.2013 to 01.01.2020.

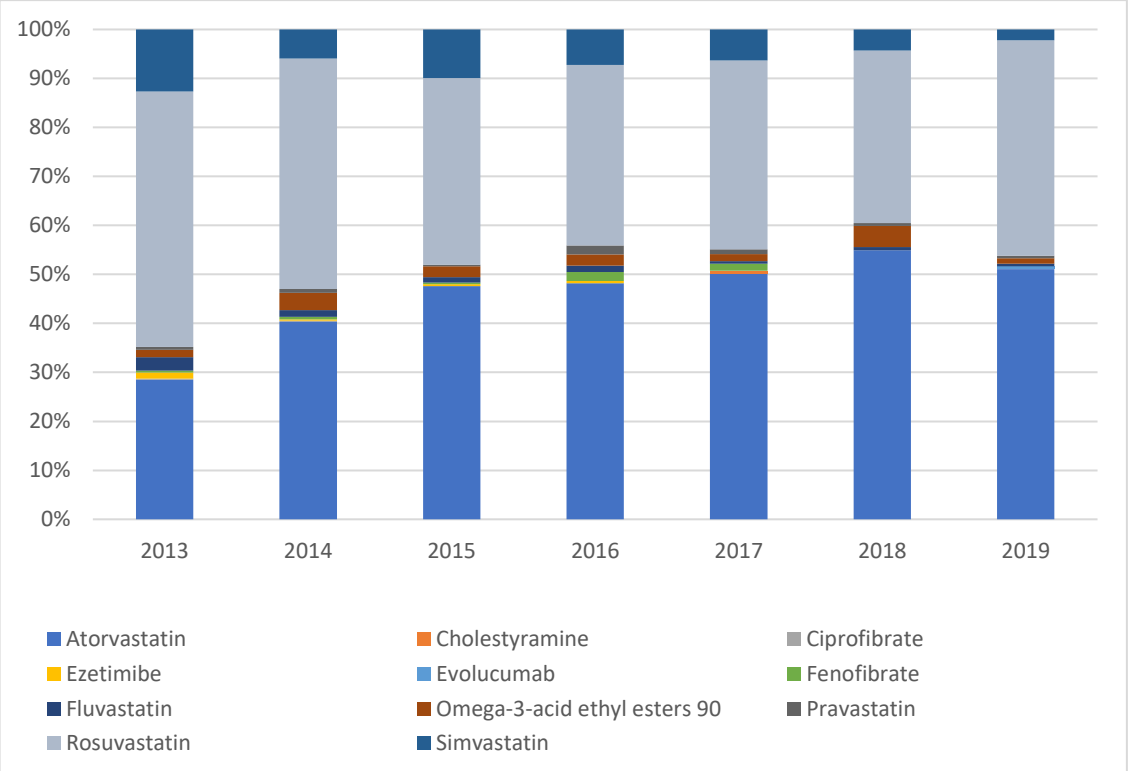

Figure 3. The use of lipid lowering drugs from 01.01.2013 to 01.01.2020, expressed as the proportion of different active substances.

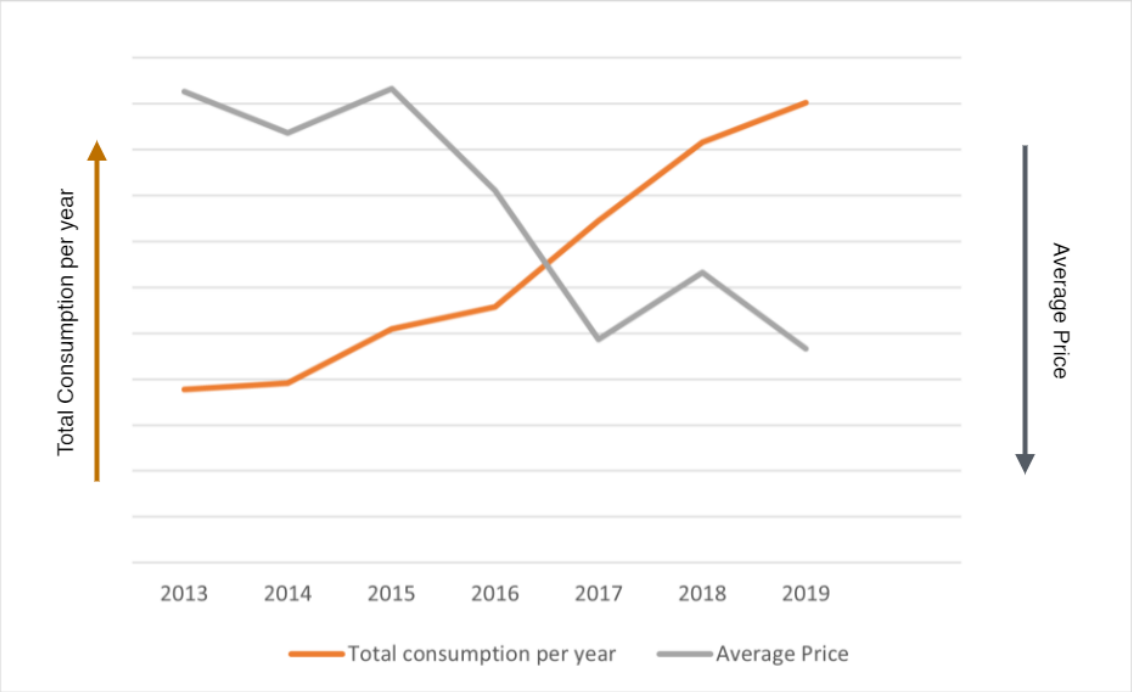

Figure 4. The trend in consumption and average price of statin in Estonia from 01.01.2013 to 01.01.2020.

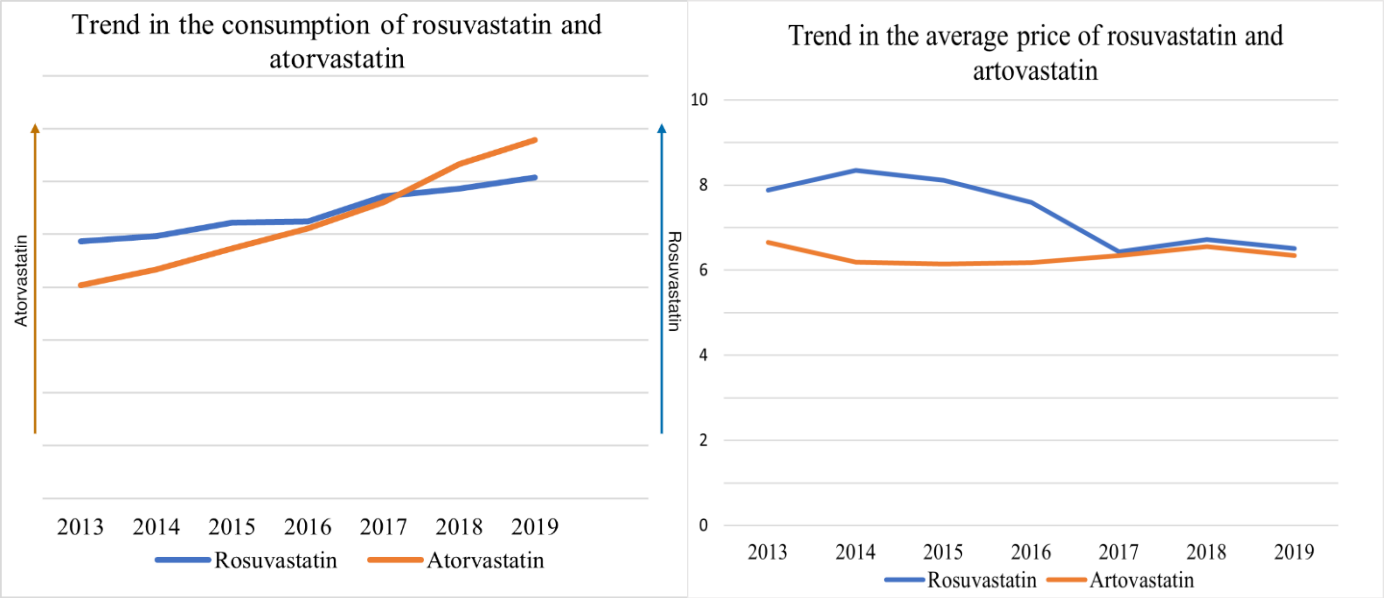

Figure 5. Trend in consumption and average price of rosuvastatin and atorvastatin from 01.01.2013 to 01.01.2020.

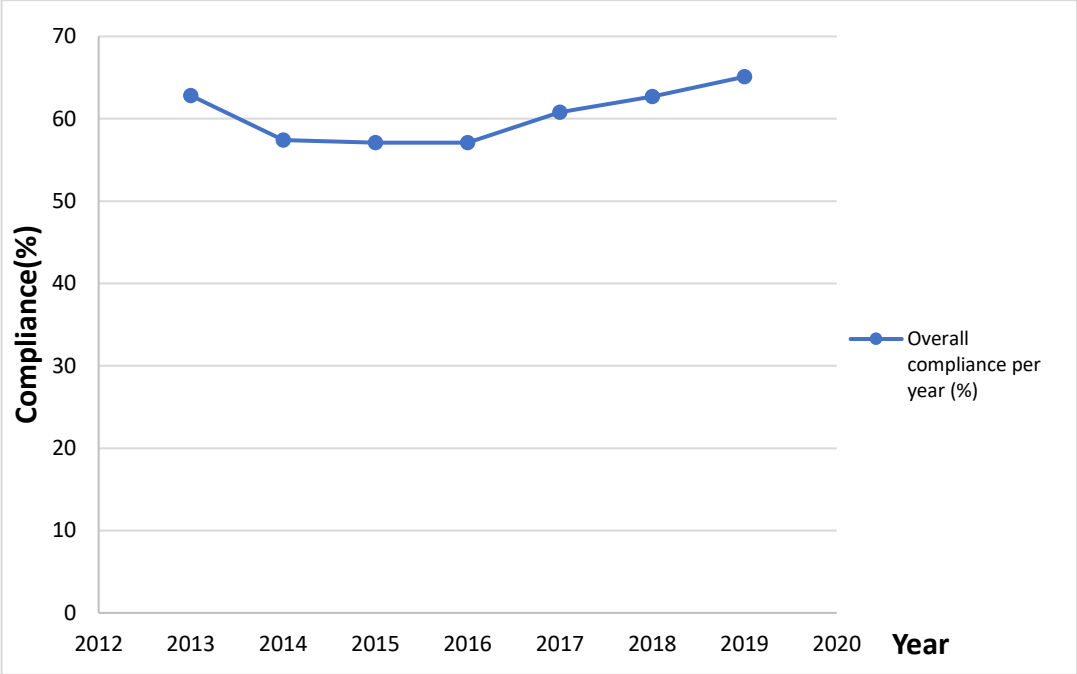

Figure 6. Overall primary treatment compliance in patients with dyslipidemia between 01.01.2013 to 01.01.2020.

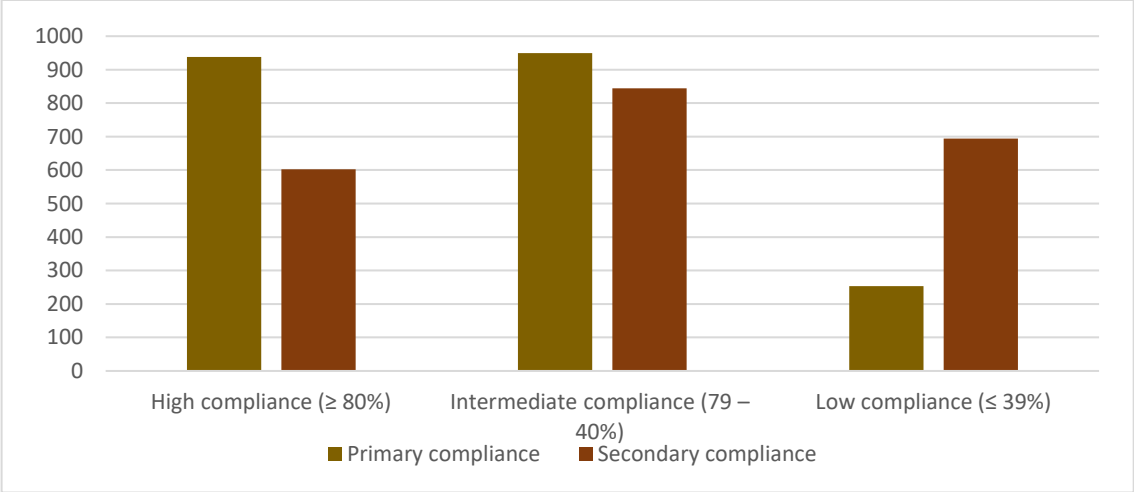

Figure 7. Comparison of the primary treatment compliance and secondary treatment compliance

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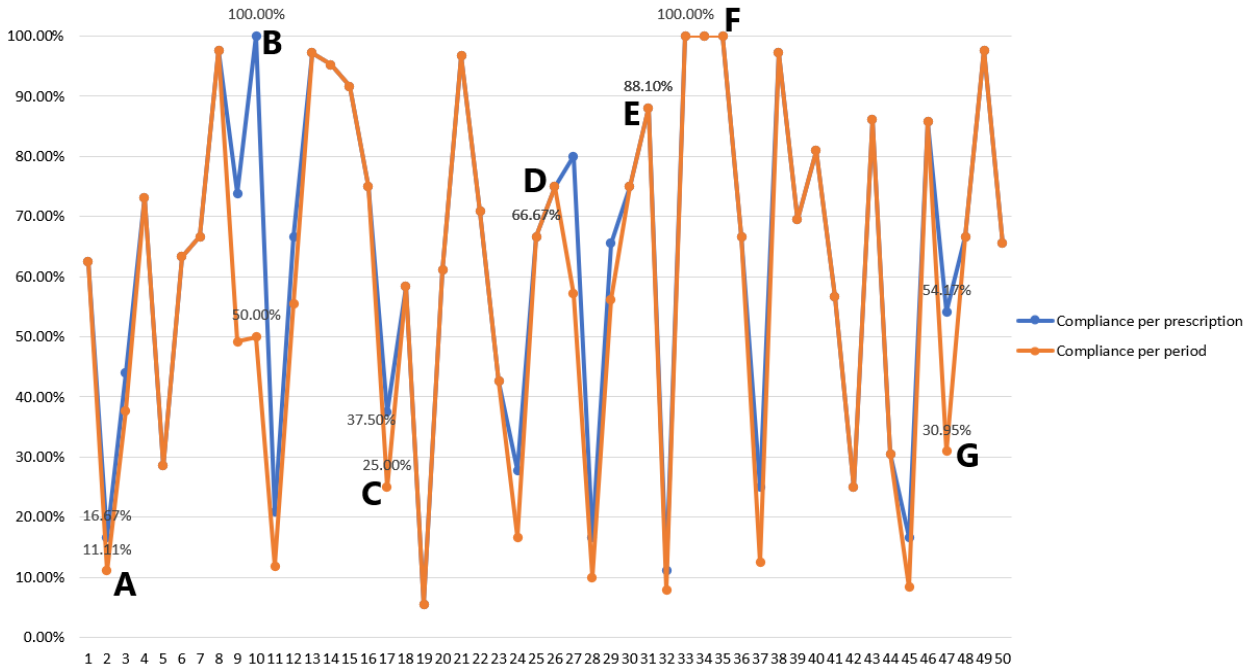

Figure 8. Change in compliance based on missing prescription year.

Appendix 2

Explicit tables for result

Table 9. Characteristics (profile) of selected patients (n=2140) with prescription.

Variables	**Number of patients (n)**	**Percentage (%)**
Male	950	44.4
Females	1190	55.6
20-34 years	80	3.7
35-49 years	416	19.4
50-64 years	1424	66.5
≥65 years	220	10.3
Primary diagnosis		
Disorders of lipoprotein metabolism and other lipidemias (E78-E78.9)	68	3.2
Other endocrine, nutritional and metabolic diseases (E00-E77, E79-E89)	180	8.4
Diseases of circulatory system (I00-I99)	982	45.9
Infectious and parasitic diseases (A00-B99)	15	0.7
Neoplasms (C00-D48)	135	6.3
Diseases of the blood (D50-D89)	13	0.6
Mental, Behavioural and Neurodevelopmental disorders (F01-F99)	148	6.9
Diseases of the nervous system(G00-G99)	39	1.8
Diseases of ear and mastoid process (H60-H95)	7	0.3
Diseases of the respiratory system(J00-J99)	37	1.7
Diseases of the digestive system(K00-K95)	63	2.9
Diseases of the skin and subcutaneous tissue(L00-L99)	23	1.1
Diseases of the musculoskeletal system and connective tissue(M00-M99)	92	4.3
Diseases of the genitourinary system (N00-N99)	99	4.6
Congenital malformations, deformations, and chromosomal abnormalities(Q00-Q99)	12	0.6

Variables	Number of patients (n)	Percentage (%)
Symptoms, signs, and abnormal clinical and laboratory findings, not elsewhere classified (R00-R99)	27	1.3
Injuries, poisoning and certain other consequences of external causes (S00-T88)	8	0.4
Factors influencing health status and contact with health services (Z00-Z99)	192	9.0
Coexisting diseases (secondary diagnosis)		
Yes	1384	64.7
No	756	35.3
LDL-C level (mmol/L)		
≥5 to <5.5	1062	49.6
≥5.5 to <7	969	45.3
≥7	109	5.1
Medication		
Atorvastatin	877	41.0
Cholestyramine	1	0.0
Ciprofibrate	3	0.1
Ezetimibe	12	0.6
Evolocumab	1	0.0
Fenofibrate	13	0.6
Fluvastatin	34	1.6
Omega-3-acid ethyl esters 90	47	2.2
Pravastatin	16	0.7
Rosuvastatin	955	44.6
Simvastatin	181	8.5

Table 10. Influence of different variables on primary treatment compliance.

Variables		High compliance (≥80%) (n=938)			Intermediate compliance (40-79%) (n=949)			Low compliance (≤39%) (n=253)		
		N	%	P-value	N	%	P-value	N	%	P-value
Gender	Male (n=950)	430	45.3	0.43	429	45.2	0.58	91	9.6	0.28
	Female (n=1190)	509	42.8		519	43.6		162	13.6	
Age	20-34 years (n=80)	32	40.0	0.99	39	48.8	0.53	9	11.3	0.20
	35-49 years (n=416)	184	44.2		181	43.5		51	12.3	
	50-64 years(n=1424)	621	43.6	0.61	628	44.1	0.744	175	12.3	0.17
	≥65 years (n=220)	101	45.9	0.22	101	45.9	0.84	18	8.2	0.013[1]
Diagnosis	Disorders of lipoprotein metabolism and other lipidemias (E78-E78.9) (n=68)	29	42.6	0.82	29	42.6	0.41	10	14.7	0.80
	Other endocrine, nutritional and metabolic diseases (E00-E77, E79-E89) (n=180)	71	39.4	0.92	82	45.6	0.07[2]	27	15.0	0.28
	Diseases of circulatory system (I00-I99) (n=982)	459	46.7		435	44.3		88	9.0	
	Infectious and parasitic diseases (A00-B99) (n=15)	5	33.3	0.43	4	26.7	0.93	6	40.0	0.29
	Neoplasms(C00-D48) (n=135)	64	47.4	0.38	51	37.8	0.93	20	14.8	0.86
	Diseases of the blood (D50-D89) (n=13)	7	53.8	0.40	4	30.8	0.88	2	15.4	-
	Mental, Behavioral and Neurodevelopmental disorders (F01-F99) (n=148)	73	49.3	0.77	59	39.9	0.015[3]	16	10.8	0.57

Variables		High compliance (≥80%) (n=938)			Intermediate compliance (40-79%) (n=949)			Low compliance (≤39%) (n=253)		
		N	%	p-value	N	%	p-value	N	%	p-value
	Diseases of the nervous system(G00-G99) (n=39)	13	33.3	0.09	22	56.4	0.04[4]	4	10.3	0.26
	Diseases of ear and mastoid process (H60-H95) (n=7)	2	28.6	-	4	57.1	0.17	1	14.3	-
	Diseases of the respiratory system(J00-J99) (n=37)	19	51.4	0.68	14	37.8	0.12	4	10.8	0.82
	Diseases of the digestive system(K00-K95) (n=63)	18	28.6	0.91	34	53.9	0.92	11	17.5	0.39
	Diseases of the skin and subcutaneous tissue(L00-L99) (n=23)	7	30.4	0.35	14	60.9	0.17	2	8.7	-
	Diseases of the musculoskeletal system and connective tissue(M00-M99) (n=92)	27	29.3	0.72	47	51.1	0.15	18	19.6	0.08
	Diseases of the genitourinary system (N00-N99) (n=99)	45	45.5	0.18	47	47.5	0.76	7	7.1	0.48
	Congenital malformations, deformations, and chromosomal abnormalities(Q00-Q99) (n=12)	6	50.0	0.77	3	25	0.78	3	25	0.77
	Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified (R00-R99) (n=27)	13	48.1	0.57	13	48.1	0.69	1	3.7	-

Variables		High compliance (≥ 80%) (n=938)			Intermediate compliance (40-79%) (n=949)			Low compliance (≤39%) (n=253)		
		N	%	P-value	N	%	P-value	N	%	P-value
	Injuries, poisoning and certain other consequences of external causes (S00-T88) (n=8)	3	37.5	0.50	4	50.0	0.72	1	12.5	-
	Factors influencing health status and contact with health services (Z00-Z99) (n=192)	77	40.1	0.125	83	43.2	0.38	32	16.7	0.64
Coexisting diseases (secondary diagnosis)	Yes (n=1384)	623	45.0	0.33	621	44.9	0.14	139	10.0	0.06
	No (n=756)	315	41.7		328	43.4		114	15.1	
LDL-C level (mmol/L)	≥5 to <5.5 (n=1062)	461	43.4	0.38	463	43.6	0.36	137	13.0	0.06
	≥5.5 to <7 (n=969)	439	45.3		422	43.6		108	11.1	
	≥7 (n=109)	38	34.9	0.06	63	57.8	0.05	8	7.3	0.32
Active substance	Atorvastatin (n=877)	429	48.9	0.54	362	41.3	0.88	86	9.8	0.62
	Cholestyramine (n=1)	-			-			1	100	
	Ciprofibrate (n=3)	1	33.3	-	1	33.3	-	1	33.3	-
	Ezetimibe (n=12)	4	33.3	0.75	4	33.3	0.09	4	33.3	
	Evolocumab (n=1)	-			-			1	100	-

Variables		High compliance (≥80%) (n=938)			Intermediate compliance (40-79%) (n=949)			Low compliance (≤39%) (n=253)		
		N	%	P-value	N	%	P-value	N	%	P-value
	Fenofibrate (n=13)	6	46.1	0.75	6	46,1	0.09	1	7.7	-
	Fluvastatin (n=34)	11	32.4	0.47	18	52.9	0.25	5	14.7	0.49
	Omega-3-acid ethyl esters 90 (n=47)	19	40.4	0.94	20	42.6	0.13	8	17.0	0.33
				0.37			0.76			0.57
	Pravastatin (n=16)	6	37.5		8	50		2	12.5	
	Rosuvastatin (n=955)	381	40.0	0.54	449	47	0.88	125	13.1	0.62
	Simvastatin (n=181)	81	44.8	0.96	81	44.8	0.78	19	10.5	0.82
				0.60			0.30			0.36

[1]for p-value calculation where patients 50-64 years were compared with patients ≥65 years
[2]for p-value calculation where diagnosed with diseases with ICD codes E00-E77 and E79-E89 were compared with disease of circulatory system (I00-I99)
[3]for p-value calculation where diagnosed with diseases with ICD codes F01-F99 were compared with disease of circulatory system (I00-I99)
[4]for p-value calculation where diagnosed with diseases with ICD codes G00-G99 were compared with disease of circulatory system (I00-I99)

Table 11. Influence of doctor's department on primary treatment compliance.

Doctor's department	High compliance			Intermediate compliance			Low compliance		
	N	%	p	N	%	p	N	%	p
Cardiology (n=603)	235	39.0	0.22	291	48.3	0.93	77	12.8	0.90
Dermatologist (n=26)	10	38.5	0.37	13	50.0	0.38	3	11.5	-
Emergency room (n=120)	60	50.0	0.22	52	43.3	0.93	8	6.7	0.90
Endocrinology (n=149)	64	43.0	0.28	62	41.6	0.29	23	15.4	0.54
Gastroenterology (n=32)	11	34.4	0.59	17	53.1	0.74	4	12.5	-
Gynecology (n=2)	-	0.0	-	1	50.0	-	1	50.0	-
Hematology (n=29)	13	44.8	0.94	13	44.8	0.62	3	10.3	-
Infectious disease (n=24)	7	29.2	0.049[1]	10	41.7	0.33	7	29.2	0.73
Internal medicine (n=113)	40	35.4	0.12	57	50.4	0.52	16	14.2	0.13
Intensive care (emergency and cardio-intensive care unit) (n=221)	130	58.8	0.49	81	36.7	0.68	10	4.5	0.40
Nephrology (n=184)	80	43.5	0.85	83	45.1	0.98	21	11.4	0.38
Neurology (n=132)	67	50.8	0.31	59	44.7	0.93	6	4.5	0.12
Occupational health and safety (n=36)	13	36.1	0.86	19	52.8	0.53	4	11.1	-
Oncology (including chemotherapy, radiotherapy treatment) (n=76)	39	51.3	0.48	27	35.5	0.26	10	13.2	0.009[2]
Orthopedics (n=8)	4	50.0	-	2	25.0	-	2	25.0	-
Otorhinolaryngology (n=4)	3	75.0	-	-	-	-	1	25.0	-
Psychiatry (n=137)	68	49.6	0.63	53	38.7	0.29	16	11.7	0.11
Pulmonology (n=23)	11	47.8	0.34	9	39.1	0.73	3	13.0	-
Rheumatology (n=38)	13	34.2	0.78	16	42.1	0.93	9	23.7	0.83
Surgery (general surgery, facial and maxillofacial, head and neck, thoracic, vascular, cardiac, or oncological) (n=84)	32	38.1	0.54	41	48.8	0.19	11	13.1	0.28
Urology (n=8)	1	12.5	-	6	75.0	0.16	1	12.5	-
Un-specific department (health check cabinet, palliative care room, health check, nursing, or isotope treatment cabinet) (n=91)	37	40.7	0.88	37	40.7	0.47	17	18.7	0.61

[1]for p-value calculation for patients who visited a doctor from the infectious disease department compared to the department of cardiology

[2]for p-value calculation for patients who visited a doctor from the oncology department compared to the department of cardiology

Table 12. Influence of different variables on Secondary treatment compliance.

Variables		High compliance (≥75%) (n=709)			Intermediate compliance (50-74%) (n=562)			Low compliance (25-49%) (n=493)			Very low compliance (<25%) (n=376)		
		N	%	p-value	N	%	p-value	N	%	p-value	N	%	p-value
Gender	Male (n=950)	366	38.5	0.94	258	27.2	0.75	195	20.5	0.99	131	13.8	0.37
	Female (n=1190)	343	28.8		304	25.5		298	25.0		245	20.6	
Age	20-34 years (n=80)	28	35.0	0.006[1]	24	30.0	0.96	17	21.3	0.22	11	13.8	0.50
	35-49 years (n=416)	132	31.7	0.68	115	27.6	0.50	98	23.6	0.73	71	17.1	0.40
	50-64 years (n=1424)	470	33.0		370	26.0		321	22.5		263	18.5	
	≥65 years (n=220)	79	35.9	0.45	53	24.1	0.54	57	25.9	0.63	31	14.1	0.86
Diagnosis	Disorders of lipoprotein metabolism and other lipidemias (E78-E78.9) (n=68)	22	32.4	0.09	18	26.5	0.19	11	16.2	0.18	17	25.0	0.42
	Other endocrine, nutritional and metabolic diseases (E00-E77, E79-E89) (n=180)	48	26.7	0.09	50	27.8	0.11	47	26.1	0.35	35	19.4	0.06[2]
	Diseases of circulatory system (I00-I99) (n=982)	375	38.2		264	26.9		210	21.4		133	13.5	
	Infectious and parasitic diseases (A00-B99) (n=15)	2	13.3	-	3	20.0	-	6	40.0	0.32	4	26.7	0.60
	Neoplasms (C00-D48) (n=135)	40	29.6	0.64	31	23.0	0.24	33	24.4	0.40	31	23.0	0.69
	Diseases of the blood (D50-D89) (n=13)	4	30.8	0.46	3	23.1	0.62	2	15.4	-	4	30.8	0.52

Variables		High compliance (≥75%) (n=709)			Intermediate compliance (50-74%) (n=562)			Low compliance (25-49%) (n=493)			Very low compliance (<25%) (n=376)		
		N	%	p-value	N	%	p-value	N	%	p-value	N	%	p-value
	Mental, Behavioural and Neurodevelopmental disorders (F01-F99) (n=148)	50	33.8	0.51	34	23.0	0.88	37	25.0	0.13	27	18.2	0.11
	Diseases of the nervous system(G00-G99) (n=39)	9	23.1	0.39	10	25.6	0.07	12	30.8	0.61	8	20.5	0.41
	Diseases of ear and mastoid process (H60-H95) (n=7)	2	28.6	-	2	28.6	-	3	42.9	-	-		
	Diseases of the respiratory system(J00-J99) (n=37)	11	29.7	0.69	12	32.4	0.31	8	21.6	0.70	6	16.2	0.97
	Diseases of the digestive system(K00-K95) (n=63)	11	17.5	0.59	15	23.8	0.46	17	27.0	0.0015[3]	20	31.7	0.051[3]
	Diseases of the skin and subcutaneous tissue(L00-L99) (n=23)	6	26.1	0.86	8	34.8	0.03[4]	5	21.7	0.95	4	17.4	0.67
	Diseases of the musculoskeletal system and connective tissue(M00-M99) (n=92)	16	17.4	0.017[5]	24	26.1	0.99	27	29.3	0.49	25	27.2	0.11
	Diseases of the genitourinary system (N00-N99) (n=99)	37	37.4	0.98	30	30.3	0.56	22	22.2	0.97	10	10.1	0.43
	Congenital malformations, deformations, and chromosomal abnormalities(Q00-Q99) (n=12)	2	16.7	-	5	41.7	0.55	1	8.3	-	4	33.3	0.6

Variables		High compliance (≥75%) (n=709)			Intermediate compliance (50-74%) (n=562)			Low compliance (25-49%) (n=493)			Very low compliance (<25%) (n=376)		
		N	%	p-value	N	%	p-value	N	%	p-value	N	%	p-value
	Symptoms, signs, and abnormal clinical and laboratory findings, not elsewhere classified (R00-R99) (n=27)	9	33.3	0.72	8	29.6	0.29	6	22.2	0.36	4	14.8	0.95
	Injuries, poisoning and certain other consequences of external causes (S00-T88) (n=8)	2	25.0	-	-	-	-	4	50.0	-	2	25	-
	Factors influencing health status and contact with health services (Z00-Z99) (n=192)	63	32.8	0.52	45	23.4	0.12	42	21.9	0.26	42	21.9	0.83
Coexisting diseases (secondary diagnosis)	Yes (n=1384)	491	35.5	0.10	373	27	0.32	308	22.3	0.26	212	15.3	0.55
	No (n=756)	218	28.8		189	25		185	24.5		164	21.7	
LDL-C level (mmol/L)	≥5 to <5.5 (n=1062)	361	34.0	0.09	287	27	0.66	225	21.2	0.39	189	17.8	0.45
	≥5.5 to <7 (n=969)	310	32.0		248	25.6		238	24.6		173	17.9	
	≥7 (n=109)	38	34.9	0.13	27	24.8	0.65	30	27.5	0.31	14	12.8	0.36
Active substance	Atorvastatin (n=877)	360	41.0	0.74	210	23.9	0.024	181	20.6	0.31	126	14.4	0.18
	Cholestyramine (n=1)	-	-		-	-		--	-		1	100	
	Ciprofibrate (n=3)	1	33.3		1	33.3					1	33.3	
	Ezetimibe (n=12)	4	33.3	0.49	3	25	0.29	1	8.3		4	33.3	

Variables		High compliance (≥75%) (n=709)			Intermediate compliance (50-74%) n=562			Low compliance (25-49%) (n=493)			Very low compliance (<25%) (n=376)		
		N	%	p-value	N	%	p-value	N	%	p-value	N	%	p-value
	Evolocumab (n=1)	-	-		-	-		-	-		1	100	
	Fenofibrate (n=13)	3	23.1	0.49	8	61.5	0.29	-	-		2	15.4	
	Fluvastatin (n=34)	8	23.5	0.65	14	41.2	0.13	6	17.6	0.87	6	17.6	0.20
	Omega-3-acid ethyl esters 90 (n=47)	7	14.9	0.88	14	29.8	0.34	14	29.8	0.95	12	25.5	0.61
				0.43			0.10			0.35			0.46
	Pravastatin (n=16)	3	18.8		4	25		4	25		5	31.3	
	Rosuvastatin (n=955)	270	28.3	0.74	261	27.3	0.024	241	25.2	0.31	183	19.2	0.18
	Simvastatin (n=181)	53	29.3	0.66	47	26	0.38	46	25.4	0.89	35	19.3	0.5
				0.17			0.08[6]			0.99			0.64

[1]for p-value calculation where patients 50-64 years were compared with patients who are 20-34 years

[2]for p-value calculation where diagnosed with diseases with ICD codes E00-E77 and E79-E89 were compared with disease of circulatory system (I00-I99)

[3]for p-value calculation where diagnosed with diseases with ICD codes K00-K95 were compared with disease of circulatory system (I00-I99)

[4]for p-value calculation where diagnosed with diseases with ICD codes L00-L99 were compared with disease of circulatory system (I00-I99)

[5]for p-value calculation where diagnosed with diseases with ICD codes M00-M99 were compared with disease of circulatory system (I00-I99)

[6]for p-value calculation where the active substance for medication is simvastatin, compared with rosuvastatin.