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Ollscoil na hÉireann, Corcaigh
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Patient factors affecting prescribing and outcomes in cardiovascular disease

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LIST OF ABBREVIATIONS

ACC/AHA	American College of Cardiology/ American Heart Association
ACEIs	Angiotensin converting enzyme inhibitors
ARBs	Angiotensin receptor blocker
Apo-B	Apolipoprotein-B
ASCVD	Atherosclerotic cardiovascular disease
ASRQ	Adherence Self-Report Questionnaire
ATC	Anatomical Therapeutic Chemical
PCRS	Primary Care Reimbursement Service
BP	Blood pressure
CCB	Calcium channel blocker
CV	Cardiovascular
CVDs	Cardiovascular diseases
CHD	Coronary Heart disease
CDM	Chronic Disease Management Program
CI	Confidence interval
DALY	Disability-adjusted life years
Diastolic BP	Diastolic blood pressure
ESC	European Society of Cardiology
EAS	European Atherosclerosis Society
ESH	European Society of Hypertension
ES	Effect size
FEC	Free equivalent combination

HDL-C	High density lipo-protein cholesterol
HF	Heart failure
HR	Hazard ratio
IQR	Interquartile range
LDL-C	Low density lipo-protein cholesterol
LLT	Lipid lowering therapy
MMAS	Morisky Medication Adherence Scale
MARS	Medication Adherence Rating Scale
MI	Myocardial infarction
MPR	Medication possession ratio
OPERAM	Optimizing Therapy to Prevent Avoidable Hospital Admissions in Multimorbid Older Adults
OR	Odds ratio
PCSK9i	Monoclonal proprotein-convertase subtilisin/Kexin type-9 inhibitor
PAD	Peripheral artery disease
PDC	Proportion of days covered
QALYs	Quality adjusted life years
RAAS	Renin angiotensin aldosterone system
RR	Risk ratio
SCORE	Systematic Coronary Risk Estimation
Systolic BP	Systolic blood pressure
SPC	Single pill combination
SE	Standard error

SD	Standard deviation
STARS	Screening Tool for AdheRence to medicineS
TC	Total cholesterol
TILDA	The Irish Longitudinal Study on Aging
U.K.	United Kingdom
U.S.	United States
VLDL	Very low density lipo-protein
WHO	World Health Organization

DECLARATION

I declare that this thesis has not been submitted for another degree either at University College Cork or elsewhere. The work, upon which the thesis is based, was carried out in collaboration with a team of supervisors who are duly acknowledged in the text of the thesis. Apart from due acknowledgement, it is entirely my own work. The library may lend or copy this thesis upon request.

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Rehab

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2. Elhiny R, O’Keeffe LM, Bodunde EO, Byrne S, Donovan M, Bermingham M. Goal attainment, medication adherence and guideline adherence in the treatment of hypertension and dyslipidemia in Irish populations: A systematic review and meta-analysis. International Journal of Cardiology Cardiovascular Risk and Prevention. 2025 Mar 1;24:200364. (Chapter 2)

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3. Elhiny R, O’Keeffe LM, Millar SR, Byrne S, Bermingham M, Donovan M. LDL-cholesterol goal achievement and guideline adherence among middle-to older-age Irish adults in a primary care setting. Clinical Epidemiology and Global Health. 2026 Jan 7:102286. (Chapter 3)

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3. Elhiny R, Bermingham M, O'Keeffe L, Byrne S, Donovan M. Cardiovascular risk control in community-based Irish adults with hypertension. *European Journal of Preventive Cardiology*. 2025 May;32 (Supplement_1):zwaf236-129.
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3. Elhiny R, O’Keeffe LM, Byrne S, Donovan M, Bermingham M. Guideline Adherence, Medication Adherence And Goal Attainment In The Treatment Of Hypertension And Dyslipidaemia In Irish Populations: A Systematic Review. EuroCVP 2023 – The annual meeting on advances in cardiovascular pharmacotherapy, Nov 2023, Florence, Italy – Poster presentation
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6. Elhiny R, O'Keeffe LM, Byrne S, Donovan M, Bermingham M. Cardiovascular Risk Control in Community-based Irish Adults with Dyslipidemia. European Society of Clinical Pharmacy, Oct 2024, Krakow, Poland Poster presentation
7. Elhiny R, O'Keeffe LM, Byrne S, Donovan M, Bermingham M. Cardiovascular Risk Control In Community-Based Irish Adults With Dyslipidemia. Dec 2024 College of Medicine and Health Research Conference, UCC, Cork Oral presentation
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CONTRIBUTIONS

1. Dr. Elizabeth O. Bodunde contributed in risk of bias assessment and data extraction in chapter 2 as a second reviewer.
2. Dr Seán R. Millar is the data coordinator of Mitchelstown data, guiding us in interpreting and understanding the data used in chapter 3 and chapter 4.
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4. Dr. Kevin Murphy was in charge of data collection in the Cork setting of the OPERAM data used in chapter 5, he contributed to our understanding of the data.
5. Dr. Lara Brockhus is the data coordinator of the OPERAM data in Switzerland, guiding us in interpreting and understanding the data used in Chapter 5.

THESIS ABSTRACT

Background Cardiovascular diseases (CVDs) are the leading cause of death worldwide. Low density lipoprotein cholesterol (LDL-C) and high blood pressure (BP) are significant risk factors for developing CVDs. Evidence demonstrates a reduction in LDL-C levels and optimal BP control can significantly reduce the incidence of major adverse CV events. However, controlling these critical risk factors remains challenging in clinical practice.

Aims This thesis aims to assess the control of CVD risk factors, in particular dyslipidemia and hypertension control among people treated for primary prevention and people treated for secondary prevention of CVD. In addition, the thesis aims to identify the patient and medication factors that could influence the achievement of recommended LDL-C and BP guideline goals in clinical practice.

Methods In chapter 1, a systematic review and a meta-analysis was conducted to summarise the existing published evidence from Ireland regarding LDL-C and BP control, medication adherence among patients and guideline adherence among prescribers and to identify the gaps in the literature. Chapter 2 used data from the Mitchelstown Cohort Study rescreen dataset of primary care participants aged 51 - 77 years, collected in 2015. The proportion of participants who achieved LDL-C goals in accordance with treatment targets set out in both the 2011 and 2019 European Society of Cardiology (ESC)/ European Atherosclerosis Society (EAS) guidelines for management of dyslipidemia was examined and the prescribing pattern of lipid lowering therapies (LLTs) was assessed. A multivariable logistic regression analysis was conducted to identify the patients' factors that could predict the prescribing of LLTs and LDL-C goal achievements. In chapter 3, using the same Mitchelstown Cohort Study rescreen dataset, multiple imputation by chained equation (MICE) was performed to assess the proportion of people with prescribed antihypertensive medications who achieved systolic BP and diastolic BP goals in accordance with the treatment targets set out in the 2013 and the 2024 ESC/ European

Hypertension Society (EHS) guidelines for management of arterial hypertension, and the prescribing pattern of antihypertensive medications. Medication non-adherence was assessed using a validated self-reported 3-item measure. Multivariable logistic regression analysis was conducted to identify the patients' factors that could predict goal achievements and medication non-adherence in this population. Chapter 4 used the Optimizing Therapy to Prevent Avoidable Hospital Admissions in Multimorbid Older Adults (OPERAM) dataset. OPERAM was a multicenter controlled trial which recruited hospitalised people aged 70 years and older with multimorbidity and polypharmacy. The proportion of people who achieved LDL-C goals in accordance with the treatment targets set out in the 2016 and 2019 ESC/EAS guidelines was assessed. In addition, the prescribing pattern of LLT and the self-reported medication adherence among people with prescribed LLTs was analyzed. A further comparison of LDL-C goal achievements and prescribing pattern of LLTs between clinical trial sites was conducted. In addition, multivariable logistic regression analysis was conducted to identify the patients' factors that could predict LDL-C goal achievements and medication adherence in this population

Results Twenty-three studies were included in the systematic review and 10 studies were included in the proportional meta-analysis. The meta-analysis showed suboptimal control of LDL-C and BP in Ireland. The level of patient adherence to antihypertensive medications varied according to the assessment tools used and adherence to the prescribing guidelines was suboptimal. There was very limited data on adherence to LLTs and the factors associated with LDL-C goal achievement. In the Mitchelstown Cohort Study rescreen dataset, 48.5% of participants were prescribed LLT. However, less than 40% of those prescribed LLT achieved their LDL-C goals, when stratified by their CVD risk category. Diabetes diagnosis and hyper-polypharmacy were predictors of prescribing LLT, while male sex and age ≤ 59 years or 60–64 years were among the predictors of achieving LDL-C goals. In the same cohort, BP control was suboptimal, with 63.8% of participants on antihypertensive medications achieving the recommended 2013 BP goals, falling to 38.4% when applying the stricter 2024 goals. Female sex was a predictor of medication adherence. Being overweight or obese, being non-adherent or

having polypharmacy or hyper-polypharmacy were associated with less likelihood of achieving 2024 goals only. In the OPERAM dataset, 66.5% of participants prescribed LLTs achieved LDL-C goals as recommended in the 2016 ESC/EAS guideline, with just 38.8% achieving LDL-C goal when applying the 2019 ESC/EAS guideline goals. Female sex was a predictor for not achieving LDL-C goals, while people who were treated for primary prevention were more likely to achieve their LDL-C goals than those treated for secondary cardiovascular prevention.

Conclusion The thesis demonstrates suboptimal control of CVD risk factors, in particular dyslipidemia and BP in clinical practice across a wide age range of adults in both Ireland and Europe. Findings demonstrate a significant proportion of people at risk of CVD are not achieving LDL-C and BP goals. Medication adherence is not consistently measured or reported, but where measured, it is suboptimal, potentially limiting goal achievements. Many people with an indication for LLT or antihypertensive medications are not prescribed these therapies when they should be, according to guidelines. Where people are prescribed these medications, they are often not prescribed at the intensity required to meet guideline goals. Some patients' demographic factors including age, sex, body mass index (BMI), and being prescribed polypharmacy may influence LDL-C and BP goal achievements.

CHAPTER 1. Introduction

1.1. The global and national burden of cardiovascular diseases

Cardiovascular diseases (CVDs) are the leading cause of deaths worldwide, accounting for approximately 32% of total global deaths in 2022, with 85% of deaths due to heart attack and stroke (1). In Europe, CVDs account for more than four million deaths annually, while in Ireland, CVDs accounted for 26.5% of all deaths in 2021, with 63% of these deaths caused by coronary heart disease (CHD) and stroke (2). CVDs were deemed to be one of the largest drivers of healthcare costs in the United States (U.S.) in 2020, accounting for \$251 billion direct costs as well as \$156 billion indirect costs due to loss of productivity from morbidity and premature mortality (3). In the United Kingdom (U.K.), the estimated CVD-related direct costs was £16.6 billion, comprising 7.3% of the total public U.K. healthcare spending, while the long-term care cost of CVD, £4.65 billion, accounted for 10.7% of the total U.K. spending on long-term care in 2021/2022 (4). In the European Union, the economic burden of CVDs was estimated at €282 billion each year, amounting to 2% of the region's gross domestic product and accounting for 11% of total healthcare spending, with mean annual CVD-related costs of €630 per EU citizen (5). Similarly, CVDs contribute to economic burden in Ireland, with an estimated cost of €1.7 billion each year (2).

These impacts are driven by a mix of modifiable risk factors such as hypertension, diabetes, and obesity, which account for more than three-quarters of CVD-related deaths in the EU (5). Additionally, according to the World Health Organization (WHO), up to

80% of all heart attacks and stroke could be prevented through controlling the major risk factors: high BP, high cholesterol levels, diabetes and obesity (6). To some extent, these modifiable risk factors can be reduced or controlled through lifestyle changes such as physical activity, smoking cessation and eating a healthy diet as a first approach for management (1,2). This is supported by careful monitoring of BP, lipid levels and sugar levels and initiation of pharmacological intervention when required (1,2). In 2023, measured modifiable risk factors were responsible for 347 million CVD disability-adjusted life years (DALY), which represented approximately 80% of all CVD DALY worldwide. Of the top risk factors for CVD DALYs, elevated systolic BP accounted for 223 million DALYs and elevated LDL-C accounted for 90.7 million DALYs (7).

1.2. Modifiable risk factors

1.2.1. Dyslipidemia

1.2.1.1 Pathophysiology and association with CVDs

Cholesterol is a principal component of cell membranes and a precursor of bile acids and steroid hormones. Cholesterol can be obtained endogenously via *de novo* synthesis or exogenously via absorption from diet, and regardless of its origin, it is transported in the bloodstream around the body by LDL-C particles that represent 90% of the circulating apolipoprotein-B (ApoB) in fasting blood along with triglycerides, very low

density lipoprotein (VLDL) cholesterol and high density lipoprotein cholesterol (HDL-C) (8,9). Figure 1.1

Dyslipidemia refers to an abnormal level of lipids in the blood that can result in CVDs (10). There are two types of dyslipidemia: primary dyslipidemia and secondary dyslipidemia. Primary dyslipidemia is caused by a genetic mutation of the lipid metabolism pathway that involves a defect in the synthesis, transport, or degradation of lipoproteins and it can be inherited (10). Examples of primary dyslipidaemia are familial hypercholesterolemia, familial hypertriglyceridemia, and familial combined hyperlipidemia (10). Secondary dyslipidemia is caused by an alteration of lipid levels due to modifiable factors including unhealthy diet, alcohol abuse, smoking and physical inactivity or medical conditions including diabetes, obesity, hypothyroidism and chronic kidney disease (10,11).

Dyslipidemia has a significant association with developing atherosclerosis. Atherosclerosis arises from the invasion of the endothelial layer of the artery wall by oxidized particles of LDL-C. These modified LDL-C particles are captured by monocytes and vascular smooth muscle cells which induce foam cells formation, with activation of several proinflammatory pathways leading to fatty streak formation, the first sign for atherosclerosis (12).

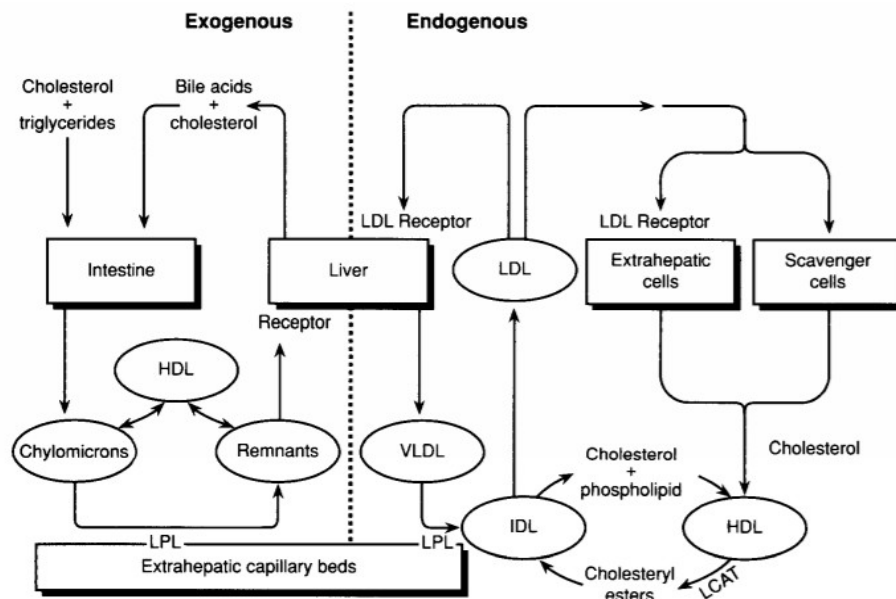


Figure 1.1 Exogenous and endogenous cholesterol uptake pathway. The cycles start with the secretion of triglyceride-rich particles, chylomicrons and very-low-density lipoprotein, (VLDL), which are converted to cholesterol-ester-rich particles, chylomicron remnants, intermediate-density lipoprotein (IDL), low-density lipoprotein (LDL), and high-density lipoprotein (HDL). Abbreviations LCAT, lecithin-cholesterol acyltransferase; LPL, lipoprotein lipase. **(13)**

Several studies have examined the association between cholesterol level, overall mortality, and CVD-related mortality (14–16). A meta-analysis of 60 randomized controlled trials has shown that every 1 mmol/L reduction in LDL-C was associated with 22% reduction in major vascular events (hazard ratio, HR 0.78, 95% confidence interval 0.75, 0.81), with relative risk reductions slightly more favorable in people with no existing CVD (HR 0.74, 95% CI 0.68, 0.81) than in people with existing CVD (HR 0.86, 95% CI 0.77, 0.83) (15).

A meta-analysis of cohort studies demonstrated the relationship between serum cholesterol including total cholesterol (TC), LDL-C and HDL-C with CVD mortality, whereby elevated TC and LDL-C are associated with an increased risk of CVD mortality (HR 1.24; 95% confidence interval, CI 1.16, 1.32, and HR 1.21; 95% CI 1.09, 1.35, respectively) while decreasing HDL-C level is inversely associated with the risk of CVD mortality (HR 0.6; 95% CI 1.19, 1.36) (14).

1.2.1.2 Prevalence

The global prevalence trend of dyslipidemia has shown considerable heterogeneity in recent years; in high-income western countries, there was a reduction of more than 1.0 mmol/L in the mean non-HDL-C between 1980 and 2018 (17). According to the National Health and Nutrition Examination Survey 2003-2006, an estimated 53% (105.3 million) of U.S. adults had lipid abnormalities including 27% (53.5 million) with high LDL-C, 23% (46.4 million) with low HDL-C and 30% (58.9 million) with high triglyceride. Additionally, 21% (42 million) of U.S. adults have mixed dyslipidemia including high

LDL-C with either low HDL-C or high triglyceride, with nearly 6% (11.6 million) with all three lipid abnormalities (18). A recent meta-analysis reported the global prevalence of high LDL-C was (18.93%, 95% CI 15.42, 23.03), with a higher prevalence among women (21.03%, 95% CI 16.24, 26.78) than men (19.57%, 95% CI 14.93, 25.23)(19).

1.2.1.3 Cardiovascular risk and treatment targets

Evidence has shown that prevention of CVDs results in reducing CHD mortality, with more than 50% of the reduction in mortality attributable to modifying CVD risk factors and 40% attributed to improving treatment (20). Due to the burden of high lipid levels, the Taskforce on Management of Dyslipidemia in the ESC and EAS and the Taskforce on Clinical Practice Guidelines in the American College of Cardiology (ACC)/American Heart Association (AHA) have established an evidence-based approach for dyslipidemia management that has been evolving over the past decades (21–27). This approach mainly focuses on stratifying treatment based on a CVD risk estimation system. The CVD risk means the individual likelihood of developing an atherosclerotic cardiovascular event over a defined period of time (21). There are different CVD risk assessment systems, but the most commonly in Europe are the Framingham models (10-year risk of CHD events) and the Systematic Coronary Risk Estimation (SCORE) which assesses an individual's 10-year risk of CVD mortality (28). **Appendix 1**

This CVD risk SCORE is based on the combined CVD risk effect of age, sex, TC, systolic BP and smoking status. Individuals are classified according to their risk into three groups: very high risk, high risk and low-moderate risk. However, CVD risk score

estimation is intended for people who have no previous CVDs (primary prevention), not for those with established CVD (secondary prevention) who are at very high risk of cardiovascular event without needing risk scoring (20,21). The treatment goals recommended in early guidelines were relatively moderate, focusing on TC <5mmol/L and LDL-C <3mmol/L for high-risk people (29). Consequently, with the evolving evidence that confirmed the key role of LDL-C and other cholesterol-rich ApoB-containing lipoproteins in causing atherogenesis, guidelines were revised to intensify treatment and reduce LDL-C. In 2011 and 2016, the ESC Taskforce recommended LDL-C targets <1.8 mmol/L for very high risk people including people treated for secondary prevention, LDL-C <2.5 mmol/L for high risk, and LDL-C <3 mmol/L for low-moderate risk people. In 2019, the treatment targets were refined again, and stricter goals were recommended with LDL-C <1.4 mmol/L for very high risk people, including people treated for secondary prevention and LDL-C <1.8 mmol/L for high risk people. The 2025 ESC/EAS guidelines included a novel, stricter LDL-C cutoff level of <1.0 mmol/L for people who have experienced recurrent cardiovascular events (21,22,26,27).

1.2.1.4 Types of lipid lowering therapies

The initial management of dyslipidemia focused on lifestyle modifications, including weight loss and exercise. However, current guidelines from both ESC/EAS and ACC/AHA recommend the early introduction of LLT for people who fail to achieve the recommended LDL-C goals with lifestyle changes and those at high risk of CVD, with a follow-up recommended 6 - 8 months after therapy initiation (21,30). 3-hydroxy-3-methyl

glutaryl-coenzyme A (HMG-CoA) reductase inhibitors, also known as statins, are the first line (Class I evidence) and most widely prescribed LLT (31). These agents work by inhibiting the HMG-CoA reductase enzyme, a rate-limiting step in cholesterol synthesis in the liver, that directly reduces the blood cholesterol level (32). In addition, low intrahepatic concentrations of cholesterol leads to upregulation of LDL-C receptors in hepatocytes, thus increasing the uptake of LDL-C from the circulation leading to a further reduction in blood cholesterol levels (32). Figure 1.2

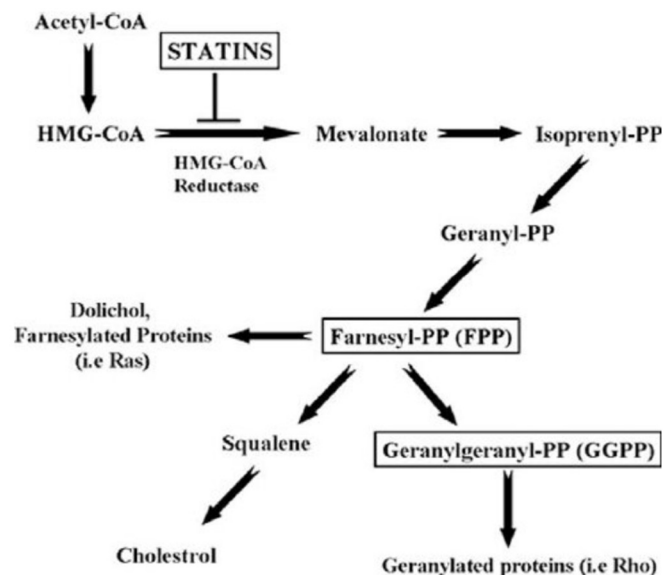


Figure 1.2 Statins' mechanism of action. Statins inhibit HMG-CoA reductase to block the synthesis of mevalonic acid, and consequently the cholesterol synthesis (33)

Statin efficacy has been proven in several studies, with a reduction in LDL-C of 30% among people treated for primary prevention and 50% for people treated for secondary prevention in cumulative randomized trial experience (34–38). The degree of LDL-C reduction is dose-dependent and varies between different statins (27). Lovastatin, pravastatin and fluvastatin are first generation statins and are generally less potent compared to simvastatin, atorvastatin and rosuvastatin (39). The variation in statin intensity is directly reflected in the percentage of LDL-C reduction achieved, with high intensity therapy equating to a reduction in LDL-C of $\geq 50\%$ and moderate intensity therapy defined as reduction in LDL-C of 30%–50% (27,40) (**Table 1.1**).

A systematic review and a meta-analysis of 26 studies showed that statin treatment for primary prevention was associated with lowering the risk of all-cause mortality (risk ratio (RR) 0.92; 95% CI 0.87, 0.98), stroke (RR 0.78; 95% CI 0.68, 0.90) and myocardial infarction (MI) (RR 0.67; 95% CI 0.60, 0.75) (41).

Table 1.1. Reduction in the plasma LDL-C levels associated with statin treatment **(42,43)**

Statin	5mg	10mg	20mg	40mg	80mg
Fluvastatin	–	–	21%	27%	33%
Pravastatin	–	20%	24%	29%	–
Lovastatin	–	–	25%	31%	45%
Simvastatin	–	27%	32%	37%	42%
Atorvastatin	–	37%	43%	49%	55%
Rosuvastatin	38%	43%	48%	53%	–

Several non-statin LLTs are available including ezetimibe, bile acid sequestrants, fibrates, nicotinic acid, and omega-3 fatty acids, and newer agents such as bempedoic acid, monoclonal proprotein-convertase subtilisin/Kexin type-9 inhibitors (PCSK9i), and small interfering RNA agent inclisiran (27,44). Nicotinic acid is no longer routinely prescribed due to safety concerns and the efficacy of omega-3 fatty acids in preventing ASCVD has been questioned (44). Non-statin LLT are recommended as an add-on therapy among patients who do not tolerate high intensity statin therapy or among patients who do not achieve their LDL-C goals while prescribed statin, in particular among very high risk and high risk people who are treated for primary prevention or people who are treated for secondary prevention (27,44).

1.2.1.5 Prescribing pattern of lipid lowering therapy

Initiation of LLT, in particular statin therapy, is essential for people with ASCVD, those who are treated for primary prevention with high LDL-C, and those at high risk of developing CVD, including people with diabetes. The selection of LLT and intensity of LLT prescribed, is based on the percentage LDL-C reduction required for each individual (21,23). Despite the proven efficacy of statin therapy, prescribing of LLT, in particular statins, remains inadequate in real world studies (34,36,45,46). In addition, achieving LDL-C goals remains suboptimal among people treated for primary prevention or secondary prevention (34,47–52). Findings from U.S. national outpatient retail prescription data showed that the number of patients filling prescriptions for statins, either as monotherapy or in combination with other add-on LLT increased by 25%, from 27 to 34 million, in the period 2017–2022. This increase was 14.9% among patients filling prescriptions for

moderate intensity statins and 64.1% among patients filling prescriptions for high intensity statins as monotherapy. In addition, findings showed an increase of 117.8% (from 772,533 to 1.7 million) and 1,533.1% (from 16,707 to 272,838) in patients filling prescriptions for ezetimibe or PCSK9i, respectively in the same time period (53).

A real-world descriptive study from the PaTH Clinical Research Network, focused on three cohorts, found that statin therapy was prescribed for 59% of 240,625 patients in the ASCVD cohort, 54% of 113,662 patients in the diabetes cohort and 44% of 11,276 patients in the high LDL-C cohort (54). High intensity statin therapy was prescribed for 29% of the entire cohort, with the use varying between cohorts; 34% among patients with ASCVD, 19% among patients with diabetes and 16% among patients in elevated LDL-C cohort. Ezetimibe was the most prescribed non-statin LLT, with 2% – 5% of people prescribed it across the three cohorts. Combination therapy of statin and ezetimibe was prescribed for 4% of ASCVD cohort, 1% of the diabetes cohort and 2% of the LDL-C cohort (54). Similarly, findings from a review of 50 studies conducted in European countries showed that patients at very high risk/high risk CVD received high intensity statin or moderate intensity statin (range 1% to 97% and 3% to 77%), while the proportion of very high risk and high risk people who received a combination of statin and ezetimibe ranged from 1% to 22% (55). This indicates the underutilization of high intensity statin and combination therapy in high risk and very high risk people (55).

1.2.2. Hypertension

1.2.2.1 *Definition and types of hypertension*

Hypertension is the leading modifiable risk factor for CVDs (56). In 2015, the global proportion of mortalities associated with systolic BP ≥ 140 mmHg were 40% of ischemic heart disease deaths, 38% of ischemic stroke deaths and 43% of hemorrhagic stroke deaths (57). Hypertension or high BP is defined as having an office systolic BP ≥ 140 mmHg and/or diastolic BP ≥ 90 mmHg, which is equivalent to a mean 24-hour ambulatory BP monitoring of $\geq 130/80$ mmHg, or mean home BP monitoring of $\geq 135/85$ mmHg (58). In the 2024 ESC guidelines for management of elevated BP and hypertension, while they retain the previous definition, a new category termed “*Elevated BP*” was introduced and defined as BP of 120-139/70-89 mmHg in patients at risk of heart attack and stroke (59,60). However, the 2017 ACC/AHA guidelines for the prevention, detection, evaluation and management of high BP in adults are more stringent and define hypertension as having an office blood pressure of $\geq 130/80$ mmHg (61). Hypertension is classified into primary hypertension and secondary hypertension. Primary hypertension is an elevated BP of unknown cause, resulting from environmental and lifestyle factors, while secondary hypertension is caused by toxicities, iatrogenic and congenital diseases (62).

1.2.2.2 *Prevalence of hypertension and association with CVDs*

A pooled analysis of 1201 population-representative studies including 104 million people showed that the global prevalence of hypertension among people aged between 30-79 years has doubled from 1990 to 2019, from 331 (95% CI 306 – 359) million women and 317 (292 – 344) million men in 1990 to 626 (584 – 668) million women and 652 (604 – 698) million men in 2019 (63). Using data from an ageing and retirement survey of health in Europe between 2021–2022 including 68,047 adults aged ≥ 50 years across 27 countries, results showed a higher prevalence of hypertension diagnosis among adult men aged 50 – 64 years compared to women in the same age group (39.4% vs 33.5%), while the prevalence was comparable among adults aged 65 – 79 years (63.1% vs 62.6%) and women had a higher prevalence than men among adults aged ≥ 80 years (78.0% vs 71.8%) (64).

According to the WHO, 1.4 billion people lived with hypertension in 2024, with one in five of them having uncontrolled hypertension (65) .

In 2019, the Global Burden of Disease study estimated that high systolic BP was the leading risk factor for mortalities worldwide, accounting for 19.2% of all deaths. In the EU, it accounted for one million deaths and 15.6 million DALYs, mainly linked with CVDs and kidney diseases (66).

1.2.2.3 Guideline recommended treatment targets

A meta-analysis which included 123 studies of 613,815 participants showed that a 10 mmHg reduction in systolic BP can reduce the risk of major cardiovascular events by 20%, CHD by 17%, stroke by 27%, heart failure (HF) by 28% and all cause of mortality

by 13% (67). The European guidelines have progressively modified the systolic BP and diastolic BP treatment targets across the last decade. The ESC/ESH Taskforce for management of hypertension in 2007 recommended BP targets based on the total cardiovascular risk. A relaxed BP goal of <140/90 mmHg was recommended for people at low-moderate risk of CVDs while a strict goal of <130/80 mmHg was recommended for people at high risk of CVDs including those with diabetes, cerebrovascular events, CVDs and renal diseases (68). In 2013, a unified systolic BP goal of <140 mmHg was recommended for all hypertensive patients including people with diabetes, and a diastolic BP of <90 mmHg was recommended for all except for people with diabetes who were recommended to achieve a value of <85 mmHg (69). In 2018, the ESC/ESH guideline was updated, with a primary cutoff of <140/90 mmHg recommended for all patients, and if treatment was tolerated, a secondary cutoff level of <130/80 mmHg was recommended (58). In addition, in 2018, an age-stratified approach was established, with patients <65 years recommended a systolic BP goal ranging from 120–129 mmHg and patients aged 65–80 years recommended a systolic BP goal between 130–139 mmHg. A diastolic BP goal of <80 mmHg was set for all patients treated for hypertension (58). The 2024 ESC/ESH guidelines shifted toward more intensive BP control, with a strict systolic BP of 120–129 mmHg recommended for all patients unless it is not tolerated (58,60,69,70). However, the ACC/AHA guidelines for management of hypertension favors the strict BP goal of <130/80 mmHg for most adults with or without established CVDs (25,61,71).

1.2.2.4 Hypertension management

Lifestyle modifications are the first fundamental approach in preventing hypertension and in managing high BP, alone in mild cases of hypertension, or in combination with pharmacological therapy otherwise (72,73). Several classes of antihypertensives are available treat high BP, with many of them reported to reduce cardiovascular events. The recommended primary antihypertensives are medications that act directly or indirectly on the renin-angiotensin aldosterone system (RAAS), including angiotensin–converting enzyme inhibitors (ACEIs), angiotensin receptor blocker (ARBs), and direct renin inhibitors (72,73). ACEIs and ARBs are the antihypertensive of choice for people with chronic kidney diseases with evidence of proteinuria and for people with HF(74). Irrespective of their antihypertensive effects, both classes are proven to have a cardioprotective effect, particularly among people at high risk of CVD (74). Thiazides and thiazides like diuretics are mainly act on increasing the water and sodium excretion either by reducing the intravascular volume, and it is proved in decreasing CVDs(73). This class is used as monotherapy or in combination with other antihypertensive medication and is recommended in all age groups unless there is evidence for chronic kidney diseases (74). Calcium channel blockers (CCB) are first line of treatment as monotherapy or in combination with other antihypertensive treatments, with a proven evidence to decrease CVDs and HF (74). CCBs may be dihydropyridines (potent vasodilators) or non-dihydropyridines (less potent vasodilators which improve cardiac contractility and conduction) (74). Beta-blockers are no longer considered first-line agents but are prescribed as antihypertensives among patients with other indications for that class such as

atrial fibrillation, MI and HF(75). Beta-blockers are not inferior to other BP lowering medications in as antihypertensive agents, however they are less efficacious than other classes in the prevention of major cardiovascular events (RR 1.17, 95% CI 1.11, 1.24), stroke (RR 1.24, 95% CI 1.14, 1.35), all cause of mortalities (RR 1.06, 95% CI 1.01, 1.12) (71). Novel therapeutic approaches targeting the RAAS, endothelin receptors and natriuretic peptide signaling and using innovative strategies for drug delivery such as RNA interference-based therapies have progressed into clinical developments. Zilebesiran is the first-in-class trivalent N-acetylgalactosamine ligand-conjugated siRNA targeting hepatic angiotensinogen production (76). It is administered via subcutaneous injection, and it is released slowly from the hepatic endosomes providing a sustained suppression of angiotensin production. Aldosterone-targeted therapies which developed to selectively target aldosterone synthase (CYP11B2) over cortisol synthase (CYP11B1) (76). Non-steroidal mineralocorticoid receptor antagonists are formulated with an enhanced benefit-to-risk profile compared to steroidal mineralocorticoid receptor antagonists (spironolactone and eplerenone) (76,77). Novel non steroidal MRAs posses anti-inflammatory and antifibrotic effect with cardiorenal benefits (76,77). Ocedurenone and esaxerenone and finerenone are members of this class that posses high affinity and selectivity in binding to receptors and longer half-life that facilitate improved 24-hrs BP control respectively (76,77). Dual endothelin A and B antagonists endothelin-targeted therapy (Aprocitentan) is approved in the U.S., Europe, and the U.K. for the treatment of resistant hypertension and in those who are not tolerating combination therapy with ACEI/ARB and mineralocorticoid receptor antagonists (77). In the setting of hypertension and chronic kidney disease, endothelin-1 expression is upregulated, which provides a

strong rationale for blockade of endothelin-1 signaling to reduce BP and slow chronic kidney disease progression (76).

The approaches for treating hypertension have evolved over several iterations of European guidelines (60,69,78). In the 2003 ESC/ESH guidelines, initiation of antihypertensive medications was mainly based on CVD risk and level of systolic BP and diastolic BP, irrespective of the patients' age. The 2018 ESC/ESH guidelines recommended initiation of antihypertensives for people at stage 2 or stage 3 hypertension and people at stage 1 if there are at very high risk or high risk, or low-moderate risk with organ damage (79). In addition, people with chronic kidney disease, diabetes or stroke should initiate treatment if their BP $\geq 140/90$ mmHg (79). Findings from several studies showed a consistent increase in the use of antihypertensive medications, in particular ACEIs, ARBs and CCBs (79–81).

A population-based cohort study over 31 years including 2.7 million primary care patients in the U.K. showed that the prevalence of patients with prescribed antihypertensive medications has increased from 7.8% in 1998 to 21.9% in 2018, with 51.0% of patients being prescribed two or more antihypertensive medications (81). The prescribing pattern of antihypertensive medications in the U.S. between 2008 and 2017 showed an increase in the incident use of ACEIs/ARBs and CCBs among people with hypertension; however inconsistent with guidelines, beta-blocker use remains prevalent with only a modest decrease over the study period (81,82). Despite the increase in prescribing antihypertensive medications, the reliance on monotherapy remains predominant, with underutilization of combination therapy (83,84).

1.3. Current evidence of CVD risk factors control in dyslipidemia and hypertension

Despite the evidence demonstrating the importance of controlling CVD risk factors, in particular LDL-C and BP, to reduce the risk of cardiovascular events among people treated for primary prevention or people treated for secondary prevention, optimal control of LDL-C and BP still presents a major challenge (85–87). Approximately 120 million adults in the U.S. have hypertension (48.1% of total population). Of those, 92.9 million (77.4%) were uncontrolled (88). Studies in the U.S. have also shown that between 72 and 84% of adults who were treated for secondary prevention had an LDL-C level >70 mg/dl (1.8 mmol/L), while among patients prescribed LLT, only 21% achieved LDL-C <70 mg/dl (1.8 mmol/L) (47). Across real-world European studies including high risk and/very high risk patients, the overall achievement of LDL-C goals among people on oral LLT ranged from 2% - 73% (55). Likewise, in 24 European countries included in EUROSPIRE IV (2013-2015), among 7653 people with CHD, 42.4% had uncontrolled BP (89). Taken together, these studies suggest that one of the contributing factors to this challenge is patients' medication adherence, which significantly affects treatment outcomes.

1.4. Medication adherence and controlling CVD risk factors: dyslipidemia and hypertension

Medication non-adherence is a serious challenge and the most significant modifiable factor that undermines treatment outcomes across a diverse array of medical

conditions (90). The WHO defines adherence as “*the extent to which the person’s behavior (including medication taking) corresponds with the agreed recommendations from a healthcare provider*” (90,91). This includes medication initiation, implementation of the prescribed regime and discontinuation of pharmacotherapy (90). An adherence level of 80% is needed for antihypertensive treatment and LLT to be effective (92,93). However, it is reported that only half of patients with chronic illness are adherent to their long-term medications (90). Poor adherence to LLT is a barrier to control of LDL-C and is associated with increased risk of adverse outcomes (93,94). There are several reliable and valid tools for assessing medication adherence. These tools are classified into direct measures and indirect measures (91,95). Direct measures include measuring the drug and its metabolite concentration in the body fluids such as blood and urine through evaluation of a biological marker given with drugs (91,95). Despite the advantages of this measure, it has some drawbacks that include being expensive, difficult to conduct, and could be affected by drug-drug interaction and drug-food interaction that may affect the accuracy of the assay (91,95). Another direct measure is observing patient’s medication-taking behavior (91,95). Indirect measures include electronic medication packaging, pharmacy refills and prescription claims database, pill count, and self-reported measures (91,95).

In outpatients post cardiovascular event using the fill frequency assessment, patients who were adherent to statin therapy were half as likely to experience a subsequent MI compared to non-adherent patients (HR 0.45, 95% CI 0.20,0.99) (96). Likewise, poor adherence to antihypertensive medications is associated with suboptimal BP control, accounting for approximately 75% of hypertensive patients who did not achieve treatment

targets (97). In the U.S., a study found that 100% adherence to antihypertensive medication could result in a reduction in the CVD risk by 32%, with 8.5 million fewer events over 10 years (92,98).

Findings from European studies show that <60% of people with hypertension have an 80% adherence to their medications (92,99,100). Similarly, in Canada, nearly 50% of patients with hypertension were non-adherent to their medications, despite the healthcare system providing free access to care and the low cost of out-pocket payment of medications (101). Medication persistence is another term which refer to the act of continuing the prescribed medication over time (102). Using administrative and laboratory data between 2012 and 2017 in Alberta, Canada, 52.5% of 103,232 patients were reported non-persistent within 6 months from prescribing antihypertensive medications calculate the numbers of days supplied (103). A retrospective population-based study using the Health Longitudinal Patient Database in Italy showed that only 61% of were adherent to statin/ezetimibe combination after 3 months of treatment and 55.1% were adherent after 6 months of treatment (104). Similarly, findings from various real-world studies, 26 of which were in Europe, showed that the pooled prevalence of good adherence to statin therapy ($\geq 80\%$ medication use) was 62.4% (95% CI 58.3,66.5%) (105). Although self-reported subjective methods are the least reliable and could overestimate true adherence, they have the advantage of being low cost, flexible and practical (91). Self-reported measures for medication-adherence include interview or patients' diaries and self-administered questionnaires and computer-based programs (91). A number of different questionnaires and scales that are validated, among these questionnaires is the Morisky Medication Adherence Scale (MMAS) (91). In 1986, the 4-item MMAS, with four items that each has

a Yes/No response, was developed and was validated in people taking antihypertensive medications in outpatient settings. The four items assessed forgetfulness, carelessness, stopping medications when feeling better or starting medication when feeling worse (106). In 2008, a modified 8-item MMAS was developed. The first seven items were Yes/No response, and the last item was a 5-point Likert response. The additional four items were to identify and address the circumstances or situations related to adherence behavior (91,107,108). The MMAS-8 has been used to assess adherence to statin therapy (109). The concordance between MMAS-8 item and the pill count method in measuring the adherence to statin therapy has been reported, with the majority of those who self-reported low adherence also being non-adherent using pill count, with concordance of 96.5% (109). while medium and high adherence to statin by MMAS-8 method had a concordance of 89.1% with pill count (109).

Other medication adherence scales include the Medication Adherence Rating Scale, Hill-Bone compliance scale (108), the adherence Self-Report Questionnaire (108,110), the 3-Item Extent of Medication Non-adherence Scale (111) and the Screening Tool for Adherence to medicineS (15-STARS) that assess the difficulties with medicine use in practice, reasons for non-adherence, doses missed and need for further help (112). Table

1.2

Table 1.2. Characteristics of different self-reported measures of adherence.

Self-reported measures of adherence	Characteristics of the tool
Morisky medication adherence scale (4-items)	<ul style="list-style-type: none"> • Consists of 4 items, with dichotomous response category (yes/no) • It reverse the wording of question to utilize the “yes-saying” bias, encouraging people to admit non-adherence • Assess forgetfulness, carelessness, stopping medications when feeling better or starting medication when feeling worse and the complexity of the medication regimen.
Morisky medication adherence scale (8-items)	<ul style="list-style-type: none"> • Consists of 8 items, with dichotomous response category (yes/no) and the last item was a 5 point Likert response. • Additional four items help to identify the circumstances or situations related to adherence behavior. • It is commonly used in different clinical settings with different populations, and it has been translated into various languages • Drawbacks: it cannot identify all the factors or reasons with nonadherence and cannot provide a comprehensive assessment of medication adherence, making it difficult to develop intervention to target these factors.
Medication Adherence Rating Scale (MARS)	<ul style="list-style-type: none"> • It consists of 10 items, with dichotomous response (Yes/No) represented in three factors including

	<p>medication adherence behavior, attitude towards medication and general illness control.</p> <ul style="list-style-type: none"> • It has a shorter form MARS-5 for quicker assessment • Assesses forgetfulness, carelessness in taking medicines, stopping medicines, attitude toward medicines and side-effect concern. • The reliability is adequate and the validity is moderate. • First administered to patients with psychosis.
Self-reported measures for extent of medication non-adherence	<ul style="list-style-type: none"> • It consists of 3 items to assess the extent of medication non-adherence. • Participants rated the extent to which they have missed doses of their medication over past seven days via a 5 points Likert scale. • Higher scores indicate higher levels of non-adherence
Adherence Self-Report Questionnaire (ASRQ)	<ul style="list-style-type: none"> • ASRQ used with electronic monitors (medical event monitoring system). • It consists of six levels of adherence ranged from (perfect adherence) to (low adherence) • Due to its low sensitivity, it is not optimal tool to measure medication non-adherence or poor medication adherence.
Hill-Bone compliance scale	<ul style="list-style-type: none"> • It consists of 14 items, with Likert response (all the time) to (none of the time). • It is mainly used for hypertension medication adherence, which limits its generalizability. • Assess reduced sodium intake, appointment timeliness and medication intake.
Screening Tool for Adherence to medicines (15-STARs)	<ul style="list-style-type: none"> • A novel self-report pharmacy-based questionnaire. • It consists of 15 items, with a dichotomous response (yes/no) for 14 items and one 6-point Likert response.

	<ul style="list-style-type: none"> • It assess the practical difficulties (5 items), reasons for non-adherence (6 items), doses missed (3 items) and need for help (1 item).
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1.5. Dyslipidemia and hypertension prevalence and control in Ireland

Ireland is one of the fastest ageing countries in Europe, with the population of people aged 65 years and older expected to double by 2051 (113). The Irish Longitudinal Study on Aging (TILDA) is a national research project, following lives of 10,000 adults aged ≥ 50 years across Ireland. Based on TILDA report across six waves of data (2009-2022), approximately 50% of older adults with hypertension had uncontrolled BP and one third with hypercholesterolemia had it uncontrolled according to the international guideline recommendations (113). Among people aged between 50–64 years, the prevalence of dyslipidemia was 82.4% (95% CI 81.1%, 83.7%), ranging from 94.5% in people being treated for secondary prevention of CVD to 78.8% in people with low CVD risk in TILDA cohort (114). Among the same cohort, the prevalence of hypertension was 63.7% (95% CI 62.3%, 65.1%) (115). Findings from the Dyslipidemia International Study (DYSIS) reported that 30.8% of the Irish cohort did not achieve the recommended LDL-C goals (114).

Despite this, comprehensive studies including the three clinical domains of goal achievements, medication adherence and guideline adherence are very limited in Ireland. This could be due to the absence of a national electronic health record system, which limits access to population level data for large scale research . In addition, few Irish datasets are available to link clinical parameters and medication data. For example, in TILDA, clinical parameters especially lipid profile data were not available in all waves and limited data about medication adherence was available (113). This leads to a gap in existing literature regarding LDL-C and BP goal achievements among patients with various CVD risk score and demographic factors associated with goal achievements. However, in the Mitchelstown

Cohort Study, clinical parameters were linked to patients' medication data and diagnosis data and information about adherence to antihypertensive medications was collected specifically from people with hypertension (116). Another potential source of clinical data in Ireland is clinical trial datasets. For example, the Optimizing Therapy to Prevent Avoidable hospital admissions in Multimorbid Older Adults (OPERAM) trial collected data on participants' prescribed medications and cholesterol levels, enabling assessment of goal achievement and guideline adherence. Medication adherence data was also collected in this trial. The OPERAM trial was conducted in four European centers and therefore further allows for comparison of CVD risk factor control in Ireland to other European centers (117). This is important to determine the generalizability of the data and to guide future measures for prevention of CVD both in Ireland and Europe.

The existing evidence from Ireland emphasises the need to examine the gap in CVD risk factors control, in particular dyslipidemia and hypertension, in relation to the medication adherence to antihypertensive medications and LLT and the adherence to the prescribing guidelines.

1.6. Aims and objectives

The thesis aims to determine control of CVD risk factors control, in particular dyslipidemia and hypertension control, among people treated for primary prevention and people treated for secondary prevention of CVD using patient data from Ireland and Europe. In addition, the thesis aimed to identify the patient and medication factors that could influence the achievement of these goals in clinical practice.

1.6.1. Objectives

- i. Review previous literature in Ireland about LDL-C and BP goal attainments, adherence to medications and adherence to prescribing guidelines. (Chapter 2)
- ii. In an Irish primary care population, assess the (i) level of LDL-C control with respect to guideline recommendations, (ii) prescribing pattern of statin and other LLT and (iii) patients' demographic factors contributing to prescribing of LLT and achievement of LDL-C goals. (Chapter 3)
- iii. In an Irish primary care population, assess the (i) level of BP control with respect to guideline recommendations, (ii) prescribing pattern of antihypertensives, (iii) patients' adherence to medications and (iv) identify the patients' demographic factors contributing to goal achievements and medication adherence. (Chapter 4)
- iv. In a European population, assess the (i) level of LDL-C control with respect to the guideline recommendations, (ii) patients' adherence to medications, and (iii) patients' demographic factors contributing to goal achievements and medication adherence. (Chapter 5)

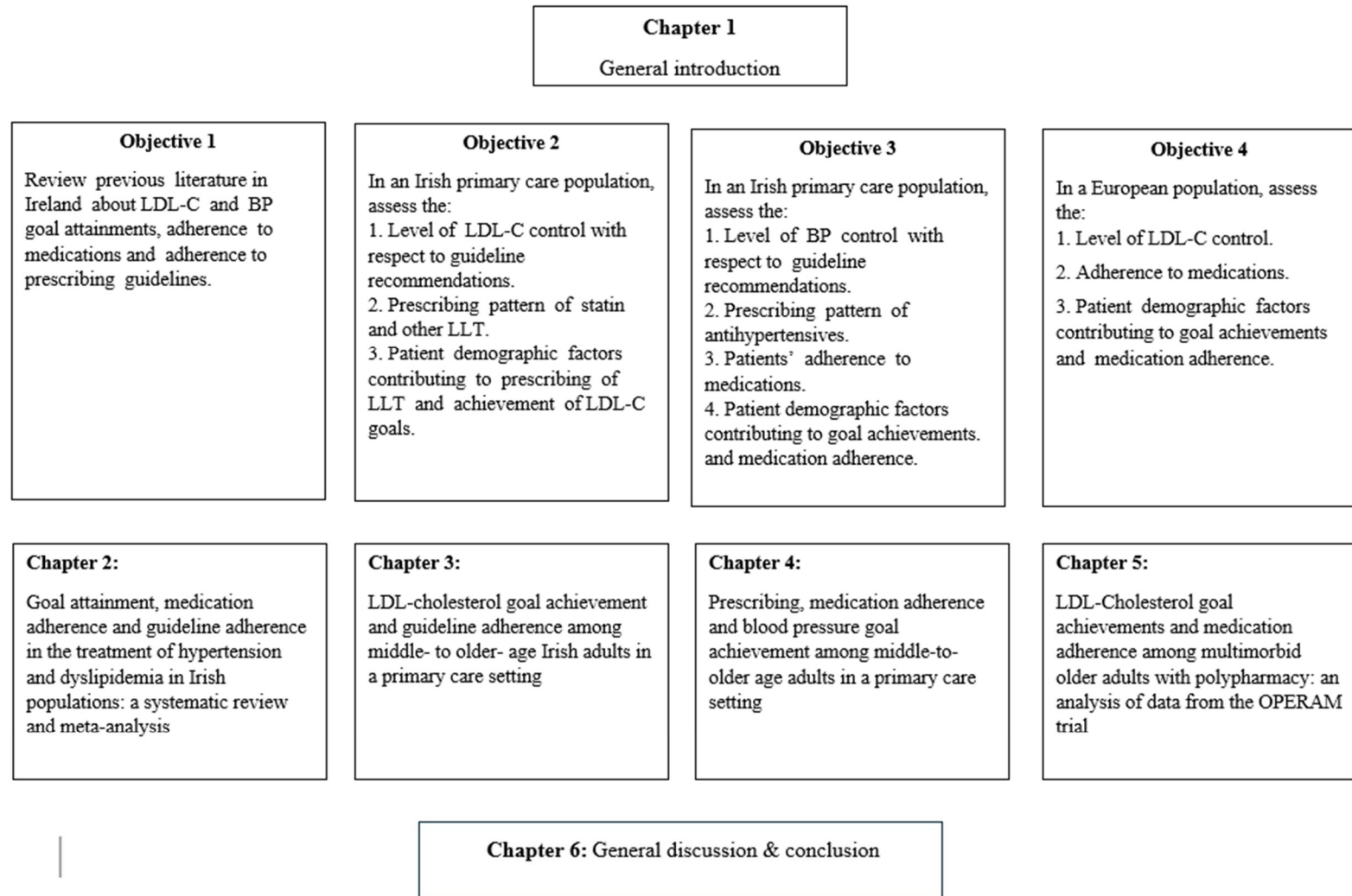


Figure 1.3. Thesis outline

CHAPTER 2. Goal attainment, medication adherence and guideline adherence in the treatment of hypertension and dyslipidemia in Irish populations: a systematic review and meta-analysis

2.1. Key points included in this chapter

- A significant proportion of people did not achieve their cholesterol and/or BP goals in the Irish population.
- Medication adherence among people with prescribed LLT and/or antihypertensive medications varied across different assessment tools.
- Not all people who were with an indication for LLT were prescribed it.
- The choice of antihypertensive medications was not usually aligned with the guideline recommendations.

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2.2. Abstract

2.2.1. Background

The appropriate treatment of high BP and LDL-C, according to clinical guidelines, reduces a patient's risk of a cardiovascular event.

2.2.2. Aim

This systematic review aims to evaluate the attainment of BP and LDL-C goals among the Irish population in both primary and secondary prevention of cardiovascular diseases, the level of adherence to prescribing guidelines by doctors and the level of medication adherence among patients.

2.2.3. Methods

Five databases were searched in March 2024. Quantitative articles reporting levels of goals attainment, medication adherence or guideline adherence for LDL-C and BP among Irish adults aged ≥ 18 years were included. The proportion of patients attaining their LDL-C or BP goals were statistically combined using the random effect model.

2.2.4. Results

Following screening, 23 eligible articles were identified. The achievement of LDL-C < 1.8 mmol/L was 41% (95% CI 31,52), compared to 69% of people (95% CI 62,76) reported to have achieved the less stringent goal of LDL-C < 3 mmol/L. The achievement of BP $< 140/90$ mmHg was 56% (95% CI 46,65). Medication adherence levels ranged between 27% and 92%. Guideline adherence findings demonstrated that not all patients who should be on LLT are, and that choice of antihypertensive is not always in line with the guidelines.

2.2.5. Conclusion

Approximately one-third of deaths in Ireland annually are caused by cardiovascular disease, despite being preventable. There is room for improvement in goal attainments in people at risk of CVDs and optimization of medication adherence and guideline adherence may be beneficial in this population

2.3. Introduction

CVDs are the leading cause of death worldwide (118). Ireland, along with the EU as a whole, continue to have a high prevalence of CVDs, with the prevalence of some CVDs such as hypertension increasing year on year (119). CVD was the second most common cause of death in Ireland in 2021, while it was still the most common cause of death in the EU [2]. In addition, deaths from some CVDs, including hypertension, are increasing in both Ireland and the EU [2]. Poorly controlled risk factors, in particular hypertension and dyslipidemia, are among the primary causes of coronary heart disease and stroke (120,121). However, attaining the guideline goals for blood pressure (BP) and LDL-C in the real world is challenging (52,89,122). The ESC/EAS set goals for LDL-C in the treatment of dyslipidemia, based on the overall cardiovascular risk assessment (22,123). BP goals are generally based on ESC/ESH recommendations; one stringent BP goal for people with high risk or very high risk people including people who have had a previous diagnosis of (MI), stroke, renal dysfunction or proteinuria, and another less stringent goal for hypertensive people generally (58,89,124,125).

According to the EuroAspire IV survey, of 7,653 participants with CVDs across 24 European countries, 42% failed to attain the BP goals outlined in the 2013 ESC/ESH guidelines (89). In EuroAspire V, only 37% of people with CVDs on high-intensity LLT and 26% of those on low to moderate intensity LLT achieved an LDL-C <1.8 mmol/L (126). This demonstrates a low level of goal attainment for BP and LDL-C goals in a European context.

Medication non-adherence is one of the factors that contribute to therapeutic failure and the subsequent clinical consequences, especially among people with CVDs (127).

Suboptimal statin adherence is reported among people with existing CVDs (127). In a cross-sectional study conducted in Sweden, medication adherence was measured among statin users by the MMAS-4 (128). The study reported that among 414 participants on statin therapy; 54.5% were classified as high adherent and 45.5% were classified as low adherent to their statin therapy (128). Anti-hypertensive medication adherence was reported in a systematic review of 25 studies from 19 countries, including 12,628 hypertensive participants in which 45% were non-adherent to antihypertensive medications, and of the 2,606 participants with uncontrolled hypertension, 84% were non adherent (97). Additionally, it has been noted that guideline non-adherence and ineffective dissemination of the guidelines among health care professionals, especially general practitioners, may negatively affect the achievement of the recommended goals (124,129). The suboptimal control of LDL-C and the underutilization of LLT among people at very high risk and high risk has been reported previously in Norway and Germany. In addition, a significant association between using LLT and achieving LDL-C goals was document among the Norwegian population (OR 14; 95% CI 3.6, 57.4) (37,130). A study in the U.S. showed a relationship between adherence to antihypertensive medications and BP goal attainments (131). However, evidence linking BP and LDL-C goal attainment, medication adherence and guideline adherence is still sparse in both an international and Irish context.

Using a systematic review and meta-analysis, the aim of this study is to quantify the levels of goal attainment, patient medication adherence and prescriber guideline adherence for LLT and antihypertensives among people treated for hypertension and/or dyslipidemia (primary prevention) and people with existing cardiovascular diseases (secondary prevention) in adult populations in Ireland.

2.4. Methods

This systematic review and meta-analysis was conducted according to the protocol registered in PROSPERO (CRD42023422050) (132) and in line with The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) 2020 checklist (133). **(Appendix 2)**

2.4.1. Study selection

The search strategy for this systematic review was developed using the population-outcome (PO) framework, as the objective was to identify and describe outcomes of interest within the population rather than determine causal effects associated with interventions. Observational studies including adult participants aged ≥ 18 years with diagnosed hypertension or dyslipidemia and treated for any of these conditions in Ireland only were included in the systematic review. Studies including participants treated for secondary prevention of CVDs including acute coronary syndrome, MI and stroke with antihypertensive and LLT were also included. Systematic reviews, literature reviews, meta-analysis and conference abstracts were excluded. Where studies reported duplicate data, the most recent and complete study was included.

2.4.2. Search methods

A detailed search was conducted in March 2024 using the advanced search function of five databases; PubMed, Scopus, CINAHL, Embase, and Web of Science. No

restrictions were placed on language or date of publications. The search strategy was developed by identifying keywords, synonyms, and MeSH terms for each of the review concepts, namely CVDs, patient adherence, guideline adherence, and goal attainment. Terms were combined using the Boolean operators AND and OR and applied across all databases. The complete search strategy is presented in **Appendix 3**. After removing duplicate results, one author (RE) screened the titles and abstracts of the remaining articles to identify studies for full text review. Studies eligible for full text reviewing were independently reviewed by three authors (MB, LOK, & RE). Reference lists of the eligible studies were screened to identify any further eligible studies not retrieved through the electronic database searches. Relevant data were extracted in Microsoft Excel[®] spreadsheets by two authors (RE & Elizabeth Bodunde). Any disagreements that occurred were resolved by a discussion between the reviewers. The search results were managed using the reference management software Zotero[®]

2.4.3. Data extraction

Data were extracted from each study in a structured Microsoft Excel[®] spreadsheet. Data on the year of the execution of the study, participants demographics, sample size, study design, setting, guideline that was followed, LDL-C, TC, and BP goals, prescribing recommendations, the proportions of participants who achieved LDL-C, TC and BP goals, proportion of people who utilize antihypertensive medications or LLT, assessment tools for medication adherence, and proportions of people who were reported adherent to antihypertensive medications, LLT or secondary prevention medications.

2.4.4. Risk of bias assessment

Risk of bias was assessed using the National Heart, Lung, and Blood Institute Quality Assessment Tool for Observational Cohort and Cross-sectional Studies (134). This tool was chosen for consistency as it facilitated assessment of observational studies including cohort and cross-sectional studies using the same tool and for its focus on evaluating the internal validity of the study. Two authors assessed the articles, and when disagreements arose, they were resolved through discussion and referral to one of the authors for adjudication if necessary. Quality was rated according to the number of questions for which the answer was yes: for poor (0–4 out of 14 questions), for fair (5–10 out of 14 questions), or for good (11–14 out of 14 questions); NA, not applicable, NR, not reported (134,135). Studies were included regardless of the findings of the quality assessment, but scores of the articles selected were reported.

2.4.5. Data analysis

Proportional meta-analysis was conducted using the statistical software STATA (version 17.0). All meta-analysis used the random effects (mixed) model and presented the point estimate with 95% CIs (136,137). Heterogeneity was tested using the I^2 test. A meta-analysis was undertaken on studies identified in the systematic review that included the proportion of participants who attained the lipid targets and BP targets to estimate the overall proportion of participants who attained LDL-C and BP goals. Subgroup analyses was performed in which studies were grouped according to whether the participants were

treated for primary or secondary prevention. Participants in the primary prevention group were those at moderate risk/high risk/very high risk of CVDs without known CVDs, or participants whose target was LDL-C $<3\text{mmol/L}$. The secondary prevention group of participants were those with known CVDs and/or whose target was LDL-C $<2.5\text{ mmol/L}$ or LDL $<1.8\text{ mmol/L}$. Data about medication adherence and levels of guidelines adherence were narratively summarized and grouped; however meta-analysis was not performed due to heterogeneity of methodologies for these outcome measures.

2.5. Results

The initial databases search yielded 4,274 publications. Of these, 1,799 were excluded as duplicates, and 2 were excluded as they had been retracted. After screening the titles and abstracts of the remaining search results, and checking the availability of the entire texts, 105 articles were selected for full text review. A total of 23 articles met the inclusion criteria **Figure 2.1**. All studies included in this review were cohort and cross-sectional studies. The risk of bias assessment found that 15 of the included studies were of fair quality and eight of the included studies met the criteria for being of good quality .

Appendix 4

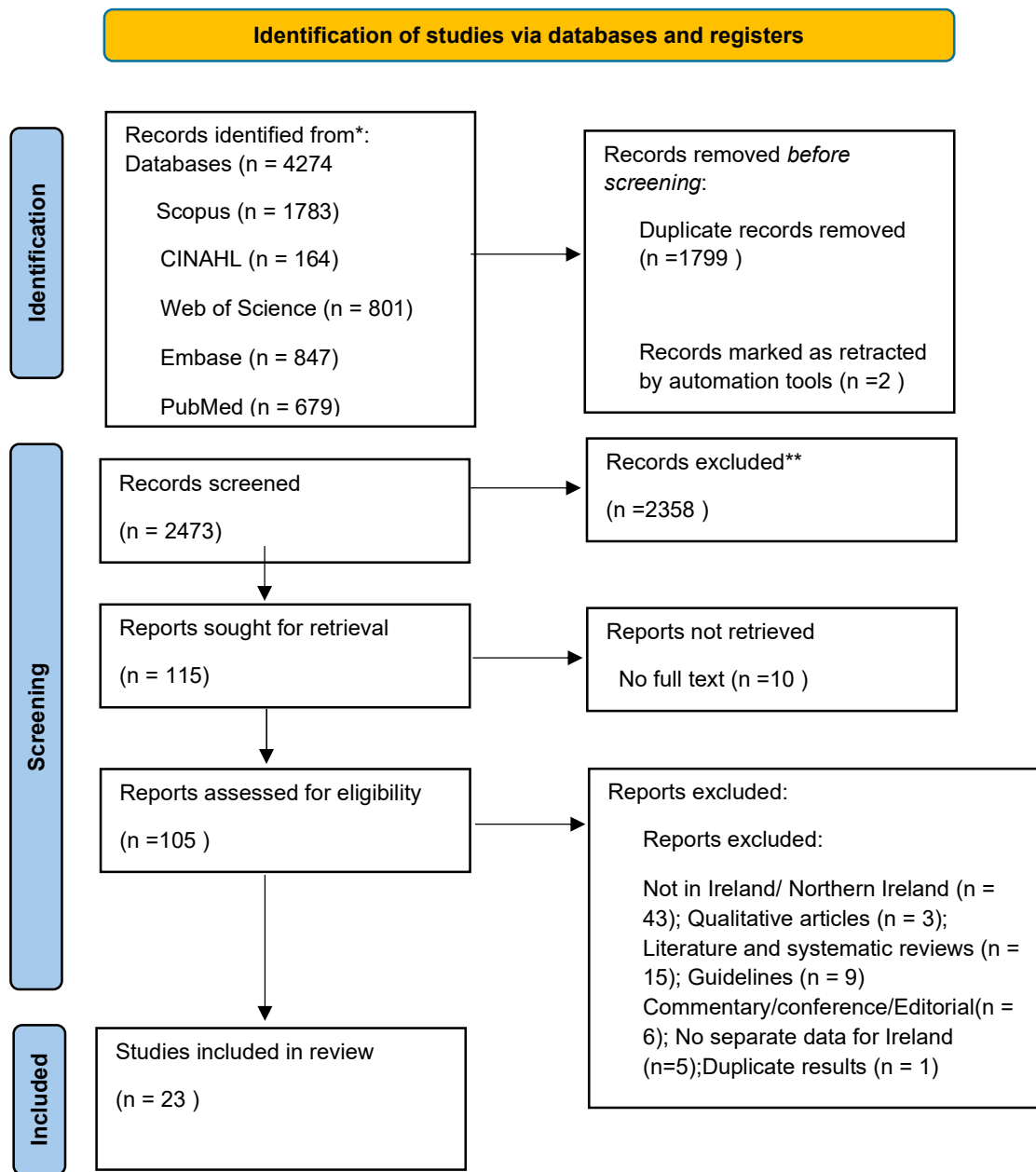


Figure 2.1 PRISMA flow diagram.

2.5.1. Goal Attainment

Twelve studies reported data about BP and lipid target attainments including LDL-C and TC on 8,696 participants (49–52,89,122,124,138–143). Three studies were either retrospective cohort, or retrospective chart review studies (51,122,139), two studies were prospective cohort studies (49,143), and the remaining seven studies were cross-sectional studies (50,52,89,124,138,140,142). Six studies reported outcomes from multiple European countries including Ireland (50–52,89,138,140). Three studies were conducted in community settings (124,142,143), six in hospital settings (122,51,140,50,139,89), and three in combined hospital and community setting (49,52,138). The proportion of people achieving clinical guideline goals was recorded in six studies for BP (50,51,89,122,124,140) and in 11 studies for cholesterol (LDL-C and/or TC) (49–52,122,138–140,142–144). The mean age ($\pm$ standard deviation) of participants ranged from 59 ($\pm$ 9.4) (89) to 71 ($\pm$ 13) years (49). Participants recruited to these studies were treated for both primary prevention and secondary prevention (122,124,138,139,142,143) or secondary prevention of CVDs alone (49–51,89,140). Primary prevention included studies that recruited people with no existing CVDs (122,124,143) and/or people who had been stratified to very high risk, high risk and low -moderate risk based on their CVD risk (52,138,142). **(Table 2.1)**

The BP and lipid targets applied varied across the included studies. For lipid targets; five studies applied LDL-C <3 mmol/L (49,52,122,138,139), seven studies had an LDL-C target of <2.5 or <2.6 mmol/L (49,50,52,122,138,139,142), and five studies applied a target of LDL-C <1.8 mmol/L (50,52,138,139,142). Of the studies using LDL-C goal of

<1.8mmol/L, two studies conducted a comparative analysis between that goal and the stricter target of LDL-C <1.4 mmol/L (52,139). For BP targets; five studies applied <140/90 mmHg (50,51,89,124,141) and four studies applied intensive BP targets $\leq$ 130/80 or $\leq$ 130/85 (50,51,122,124) (**Table 2.1**).

The overall achievements of the LDL-C targets of <3 mmol/L, <2.5mmol/L, <1.8mmol/L, and <1.4 mmol/L in the pooled samples were 69% ([95% CI, 62, 76], $I^2 = 40.6\%$), 53% ([95% CI, 28, 78], $I^2 = 95.87\%$), 41% ([95% CI, 31, 52], $I^2 = 89.2\%$) and 30% ([95% CI, 22, 39], $I^2 = 0\%$) respectively (**Figure 2.2**).

Of the pooled studies in the subgroup analysis, two studies were conducted in hospital settings (50,139), one study was conducted in community settings (142), and two studies were conducted in both community and hospital settings (49,138). The overall proportion of participants treated for primary prevention who achieved their LDL-C target was 58% ([95% CI, 30,86], $I^2 = 98.05\%$), whilst the overall proportion of participants treated for secondary prevention who achieved target was slightly lower at 51% ([95% CI, 42,61], $I^2 = 86.02\%$) (**Figure 2.3**).

In the pooled sample (random effect model), the overall proportions of people attaining the BP goal of <140/90 mmHg was 56%([95% CI 46%,65%]), $I^2 = 93.96\%$). Of these studies, three studies were conducted in hospital settings (51,89,141) and one study was conducted in community settings where a relatively low proportion of people could meet the BP goal (124) (**Figure 2.4**).

Table 2.1. Study Characteristics and Goal Attainment of Lipid and BP targets (12 studies)

Study/ Year	Quality assessment	Participant s demograph ics	CVD (in secondary preventio n cases)	Design	Setting	Guidelines	Recommended guideline goals			Proportion of participants achieving guideline goals		
							BP (mmHg)	LDL-C (mmol/L)	TC (mmo l/L)	BP	LDL-C	TC
(EURO ASPIR E II Study Group), 2001	**	Age ≤ 70, N=345; secondary prevention participants	Acute MI/ Acute myocardi al ischemia	Cross- Section al	Hospita l	Second Joint European Societies Task Force (1998)	<140/9 0		<5	50.4% of 258 participants		55% of 209 partici pants
Buckle y et al,2009	*<***	Age > 50, N=1534; Male (46%); Female (54%) Primary & secondary prevention	History of MI/strok e/PAD/C HF or atrial fibrillatio n	Cross- section al	Commu nity	ESH/ESC 2007	< 140/90 (non- diabetic) <130/8 0 (diabeti c)			48.6% of people without diabetes 16.7% people with diabetes		

							Recommended guideline goals			Proportion of participants achieving guideline goals		
Study/ Year	Quality assess- ment	Participant s demograph ics	CVD (in secondary preventio n cases)	Design	Setting	Guidelines	BP (mmHg)	LDL-C (mmol/L)	TC (mmo l/L)	BP	LDL-C	TC
Kotseva et al, 2009	**	Age ≥18 & <80, N= 386; secondary prevention participants	Acute MI/ Acute myocardial ischemia	Retrospective cohort	Hospital	Joint European Societies' guidelines (2003)	< 140/90 (non-diabetic) 130/80 (diabetic)		<4.5 mmol/L	48% of 354 people with and without diabetes.		75% of 344 patients
Bermingham et al, 2011	***	Age ≥55, N = 183; Male (45%); Female (54.6%) Primary and secondary prevention	Coronary artery disease/hypercholesterolemia/hypertension/ or Arrhythmia	Prospective Cohort	Community	European guidelines on cardiovascular disease prevention in clinical practice 2007		<2.5 <3			Overall, 71.7% of a total 669 participants who are prescribed statins attained their LDL-C goals based 10-year fatal CVD risk	

							Recommended guideline goals			Proportion of participants achieving guideline goals		
Study/ Year	Quality assessment	Participant s demograph ics	CVD (in secondary preventio n cases)	Design	Setting	Guidelines	BP (mmHg)	LDL-C (mmol/L)	TC (mmo l/L)	BP	LDL-C	TC
Dunne et al, 2013	**	Age >30, N = 488; Primary and secondary prevention	Coronary heart disease	Retrospective audit	Hospital; Outpatient clinic in academic teaching hospital	The National Cholesterol Education Program III	Systolic BP <130 mmHg Diastolic BP <85 mmHg	<2.5 mmol/L in people with CHD <3 mmol/L in people without CHD		People with CHD (112 participants) : 64% achieved the systolic goal & 44% achieved the diastolic goal People without CHD (376 participants) : 36% achieved the systolic goal & 56% achieved the diastolic goal	42% participant s with CHD 43% participant s without CHD	
Murph	**	Age >50,	Coronary	Cross-	Commu	Fourth		<2.5	<4.5		LDL-C	53%

							Recommended guideline goals			Proportion of participants achieving guideline goals		
Study/ Year	Quality assessment	Participant s demograph ics	CVD (in secondary preventio n cases)	Design	Setting	Guidelines	BP (mmHg)	LDL-C (mmol/L)	TC (mmo l/L)	BP	LDL-C	TC
y et al, 2015		N = 3372; Male (45%); Female (55%) Primary and secondary prevention	heart disease	section al	nity	(Fifth) Joint Task Force of the ESC and other societies on cardiovascu lar disease prevention in clinical practice ESC 2007 (ESC 2012)		mmol/L accordin g to the ESC 2007 <1.8 mmol/L accordin g to the ESC 2012	mmol/ L accor ding to the ESC 2007		2.5mmol/ L 61% of 166 known CVD 14.6% (142) of people with 10- year fatal CVD risk score $\geq$ 5% could achieve the goal For LDL- C <1.8mmol /L 27.7% of 166 participant s with known CVD	of 166 partici pants with know n CVD.

							Recommended guideline goals			Proportion of participants achieving guideline goals		
Study/ Year	Quality assessment	Participant s demograph ics	CVD (in secondary preventio n cases)	Design	Setting	Guidelines	BP (mmHg)	LDL-C (mmol/L)	TC (mmo l/L)	BP	LDL-C	TC
Gitt et al, 2016	**	Age ≥45, N= 900; Primary and secondary prevention	Coronary heart disease/ PAD	cross-sectional	Communi ty & Hospita l	2016 ESC/EAS Guidelines		<1.8 mmol/L (very high risk) <2.5mm ol/L (high risk) <3 mmol/L (non- high risk)			Overall, 43.5% of total 900 participant s, comprised of: 35.9% of 618 very high risk participant s 58.6% of 87 high risk participant s 64.4% of 160 non- high risk participant s	
Kotseva et al, 2016	**	Age ≥18 & <80, N=201;	Acute MI	Cross-sectional	Hospital; (Academic	Joint European Societies guidelines	<130/80 mmHg	<2.5mm ol/L < 2 mmol/L		52.3% participants attained the goal of BP	74.6% participant s attained the LDL-C	

Study/ Year	Quality assessment	Participant s demograph ics	CVD (in secondary preventio n cases)	Design	Setting	Guidelines	Recommended guideline goals			Proportion of participants achieving guideline goals		
							BP (mmHg)	LDL-C (mmol/L)	TC (mmo l/L)	BP	LDL-C	TC
		Secondary prevention			teachin g hospital)	(JES 2007 & JES 2012)	<140/9 0 mmHg or 140/80 mmHg	<1.8mm ol/L		< 130/80 mmHg 76.2% participants attained the goal of BP <140/90 or 140/80mm Hg	goal of < 2.5 mmol/L 47.5% participant s attained LDL-C goal of < 2 mmol/L 34.8% participant s attained LDL-C goal of < 1.8 mmol/L	
Ní Chróiní n et al,2018	***	Age ≥18, N = 616; Male (50%) Female (50%) Secondary prevention	Ischemic stroke/ transient ischemic attack	Prospec tive Cohort study	Commu nity & Hospita l	National Cholesterol Education Program (NCEP III)		<4.14 mmol/L (patients with 0–1 risk factors) <3.36 mmol/L (≥2 risk factors +			Overall, 54.1% (200/370) achieved their recommen ded goals 80% of 5 participant s with (0-	

							Recommended guideline goals			Proportion of participants achieving guideline goals		
Study/ Year	Quality assessment	Participant s demograph ics	CVD (in secondary preventio n cases)	Design	Setting	Guidelines	BP (mmHg)	LDL-C (mmol/L)	TC (mmo l/L)	BP	LDL-C	TC
								10-year risk ≤20%) <2.59 mmol/L (≥2 risk factors + 10-year risk >20%, or CHD/risk equivale nt)			1) risk factors 66.4% of 370 who have ≥2 risk factors + 10-year risk ≤ 20% 46.2% of 370 participant s who have ≥2 risk factors + 10-year risk >20%, or CHD/risk equivalent	
Cífková, et al, 2019	**	Age >18 & <80, N = 616; Secondary	Coronary artery diseases	Cross- section al		2013 ESC/ESH	Systolic BP <140 mmHg Diastol			Overall, 73.9% of 199 participants attained		

Study/ Year	Quality assessment	Participant s demograph ics	CVD (in secondary preventio n cases)	Design	Setting	Guidelines	Recommended guideline goals			Proportion of participants achieving guideline goals		
							BP (mmHg)	LDL-C (mmol/L)	TC (mmo l/L)	BP	LDL-C	TC
		prevention					ic BP <90 mmHg (non- diabetic) < 85 mmHg (diabeti c)			their BP goals 75.2% of 157 men; 69 % of 42 women attained their BP goals		
Offiah et al, 2022	**	Age >50, N =153; Male (68%); Female (32%) Primary and secondary prevention	Coronary artery disease/ cerebrovas cular disease (Stroke)/ PAD	Cross- section al	Hospita l & Commu nity; Acade mic teachin g hospital	2016 & 2019 2016 ESC/EAS guidelines		2016 Guidelin es Low risk <3 mmol/L Moderat e risk <3 mmol/L High risk <2.6 mmol/L, or 50% reduction from the			Accordin g to 2016 guidelines : Overall, 64.1% of 153 participant s 78.4% of 74 participant s treated for primary prevention	

							Recommended guideline goals			Proportion of participants achieving guideline goals		
Study/ Year	Quality assessment	Participant s demograph ics	CVD (in secondary preventio n cases)	Design	Setting	Guidelines	BP (mmHg)	LDL-C (mmol/L)	TC (mmo l/L)	BP	LDL-C	TC
								baseline Very high risk < 1.8 mmol/L 2019 Guidelines Low risk <3mmol/L Moderate risk <2.6 mmol/L High risk <1.8 mmol/L or ≥50% reduction from the baseline Very high risk <1.4			50.6% of 79 participants treated for secondary prevention According to the 2019 guidelines : Overall, 40.5% of 153 participants 60.8% of 74 participants treated for primary prevention 21.5% of	

							Recommended guideline goals			Proportion of participants achieving guideline goals		
Study/ Year	Quality assessment	Participant s demograph ics	CVD (in secondary preventio n cases)	Design	Setting	Guidelines	BP (mmHg)	LDL-C (mmol/L)	TC (mmo l/L)	BP	LDL-C	TC
								mmol/L or $\geq 50\%$ reduction from the baseline			79 participant s treated for secondary prevention	
McCaughey et al, 2022	**	Age >50, N = 163; Male (77%); Female (23%) Primary and secondary prevention	Atherosclerotic CVD	Retrospective review chart	Hospital	2016 & 2019 ESC/EAS guideline		2016 Guidelines Low risk <3 mmol/L Moderate risk <3 mmol/L High risk <2.6 mmol/L, or 50% reduction from the baseline Very high risk < 1.8			According to 2016 guidelines : 62% of 99 very high risk participants 50% of 2 high risk participants 73% of 11 moderate risk participants Accordin	

							Recommended guideline goals			Proportion of participants achieving guideline goals		
Study/ Year	Quality assessment	Participant s demograph ics	CVD (in secondary preventio n cases)	Design	Setting	Guidelines	BP (mmHg)	LDL-C (mmol/L)	TC (mmo l/L)	BP	LDL-C	TC
								mmol/L 2019 Guidelin es Low risk <3mmol/ L Moderat e risk <2.6 mmol/L High risk <1.8 mmol/L or ≥50% reduction from the baseline Very high risk <1.4 mmol/L or ≥50% reduction from the			g to 2019 Guideline s: 49% of 43 very high risk participant s 50% of 2 high risk participant s 60% of 5 moderate risk participant s.	

							Recommended guideline goals			Proportion of participants achieving guideline goals		
Study/ Year	Quality assessment	Participant s demograph ics	CVD (in secondary preventio n cases)	Design	Setting	Guidelines	BP (mmHg)	LDL-C (mmol/L)	TC (mmo l/L)	BP	LDL-C	TC
								baseline				

Abbreviations: BP blood pressure; CHD Coronary heart disease; CVD Cardiovascular disease; LDL-C Low density lipoprotein cholesterol; LLT Lipid-lowering therapy; MI Myocardial infarction; PAD Peripheral artery disease; TC Total cholesterol; TIA Transient ischemic attack. **As per The National Heart, Lung, and Blood Institute Quality Assessment Tool fo**Observational Cohort and Cross-sectional Studies poor (*); fair (**); good (***)

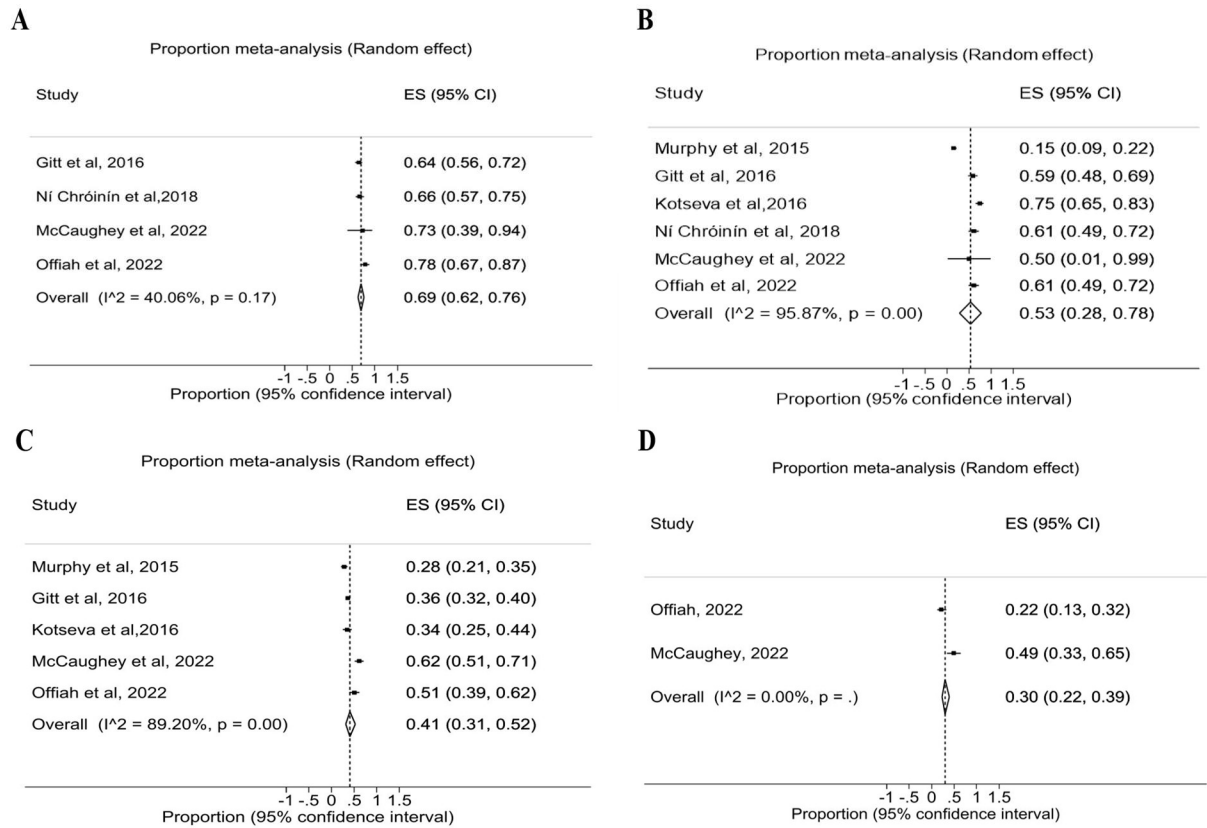


Figure 2.2 Meta-analysis for goal achievements using different LDL-C cutoffs (A) LDL-C <3 mmol/L; (B) LDL-C <2.5 (2.6) mmol/L; (C) LDL-C <1.8 mmol/L; (D) LDL-C <1.4 mmol/L. Each black square represents the proportion of participants who attained LDL-C goals reported in each study, and the extended lines represent the confidence intervals. Abbreviations: ES, effect size; CI, confidence interval.

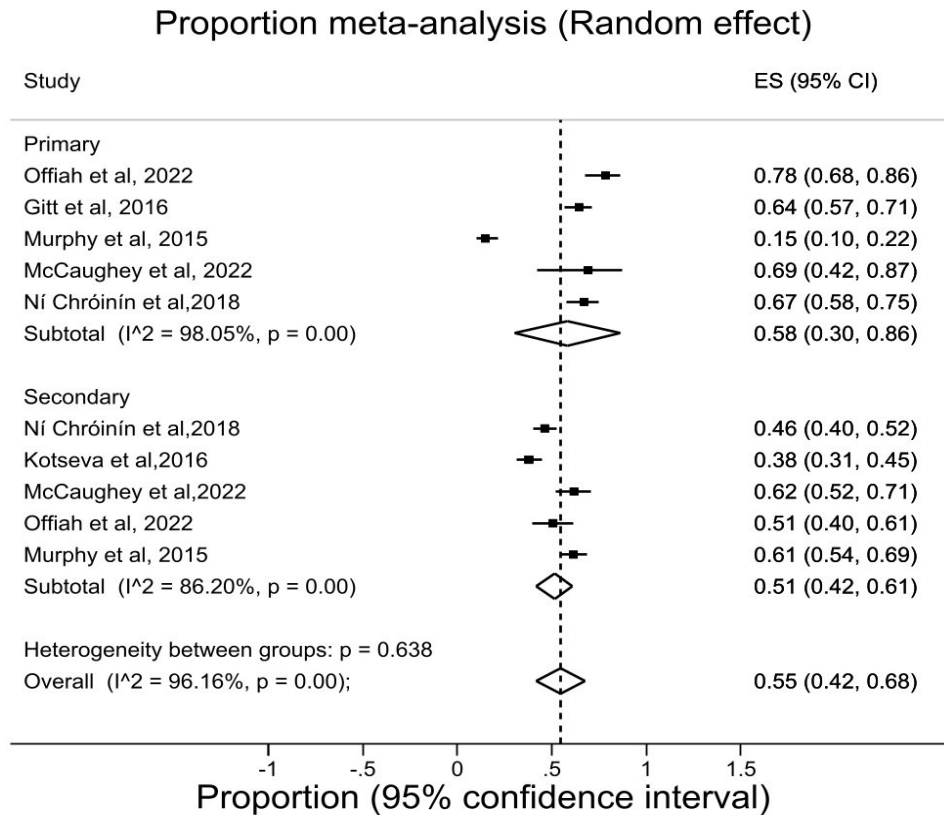


Figure 2.3 Meta-analysis of LDL-C goal attainment among participants treated for primary and secondary prevention. Each black square represents the proportion of participants who attained LDL-C goals reported in each study, and the extended lines represent the confidence intervals. Abbreviations: ES, effect size; CI, confidence interval

Proportion meta-analysis (Random effect)

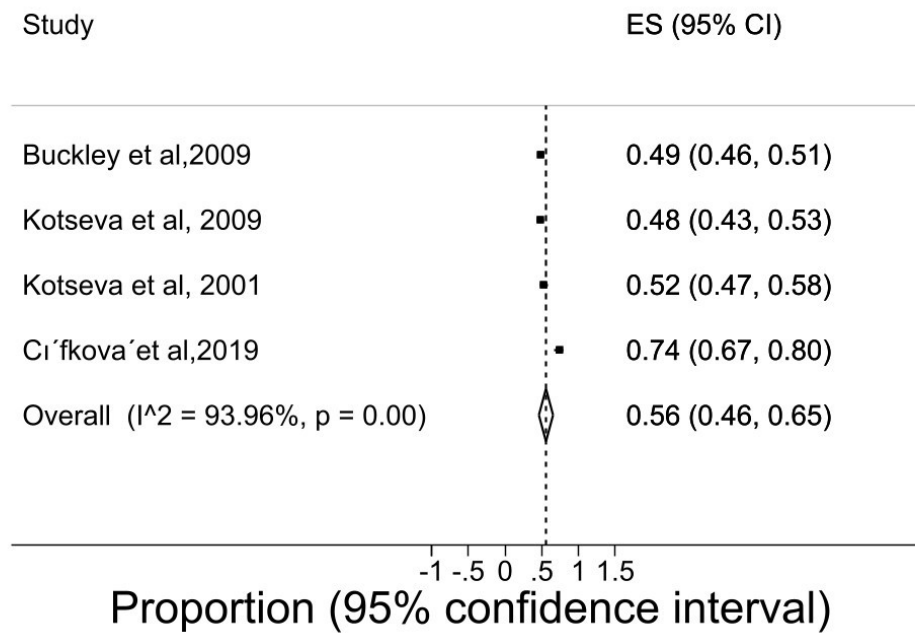


Figure 2.4 Meta-analysis of goal attainment for BP goal of <140/90 mmHg. Each black square represents the proportion of participants who attained BP goals of <140/90 mmHg reported in each study and the extended lines represent the confidence intervals. Abbreviations: ES, Effect size; CI, Confidence interval

2.5.2. Medication adherence

Nine studies reported the level of adherence to antihypertensives and LLT among people treated for primary or secondary CVDs prevention (143,145–152). Six studies were conducted in community settings (143,146,148,150–152) and three studies in hospital settings (145,147,149). The participant mean age ($\pm$ standard deviation) ranged from 64.9 ($\pm$ 9.9) (143) to 77 ($\pm$ 5.4) years (151). Two studies included people treated for secondary CVDs prevention (145,147), one study included people treated for primary CVDs prevention (150), and six studies included people treated for both primary and secondary CVDs prevention (143,146,148,149,151,152). The methods used to assess medication adherence in the included studies were self-report questionnaires, prescription refill data, or direct observation method. Self-report questionnaires used were the MMAS-8 (147,148), MMAS-4 (143), a self-reported assessment of antihypertensive medication adherence using a questionnaire based on the validated Brief Medication Questionnaire which includes patients self-reported adherence and barriers to adherence identified by patients (149), and a self-reported questionnaire in which participants answered questions either over the phone, paper survey, or through study follow-up (145,147). Methods of measuring prescription refill data were proportion of days covered (PDC) (146,148,152), and medication possession ratio (MPR) (151). Urine analysis using mass spectrometry was used as a direct method to assess medication adherence in two studies (149,150). Studies are described in **Table 2.2**.

Seven studies reported the level of adherence to antihypertensive medications (146–152). In Murphy *et al.*, of 103 participants, 41%, 37% and 12% reported high, medium, and low adherence respectively to secondary CVDs prevention medications including antihypertensive medications using MMAS-8 Scale (147). Similarly, in Dillon *et al.* 2018, 52%, 36%, and 12% were high, medium and low adherent to antihypertensive medications using the same assessment tool (148). Using the PDC measure, 73% of people prescribed antihypertensives were classified as adherent ($PDC \geq 80\%$) in a study by Walsh *et al.* (146) and 92% were classified as adherent by the same measure in Dillon *et al.* (152). Dillon *et al.*, further reported that 58%, 36%, and 6% of participants had very high, high and low level of adherence to antihypertensive medication using group-based trajectory modelling. However, Curneen *et al.* 2022, reported that only 36.5% of 55 participants who self-reported adherence to their antihypertensive medications were truly adherent based on their urine analysis results (149). Using the direct assessment tool of urine analysis, Hayes *et al.* found that 74% of a total of 235 participants with resistant hypertension were fully adherent (150). Medication non-adherence was assessed in two studies using PDC threshold of 0.8 and MPR threshold of 0.8 and it was found that 9% and 28.4% were non-adherent to antihypertensive medications respectively (148,151).

Two studies reported the adherence to lipid lowering medications; Murphy *et al.* reported that 87.7% of the included participants self-reported adherence to statin therapy during the study follow-up (147). Bermingham *et al.* reported non-adherence to statins was 48.7% using the self-report 4-item MMAS, where 72% of those reporting non-adherence were unintentionally non-adherent and 25.9% were intentionally non-adherent (143).

Patient factors associated with antihypertensive medications adherence were reported to be using single pill combination, age (≥ 75 years) (146), beliefs that secondary prevention medications including antihypertensive medications and LLT will protect from further stroke events (147) and admission to the hospital (147). However, in Hayes *et al.* it was reported that there was no statistically significant difference in rate of antihypertensive medication adherence by gender (150).

Table 2.2. Characteristics and results of the studies included for medication adherence (9 studies)

Assessment tools		Studies	Quality assessment	Participants demographics	Setting	Medications	Adherence levels
Report Scale/ Questionnaire	8-item Morisky Medication Adherence Scale	Murphy <i>et al</i> , 2015	**	Age ≥ 50 , N = 103	Hospital	Secondary prevention medications	41.2% of 103 participants were high adherent; 36.8% were medium adherent; 12.2% were low adherent.
		Dillon <i>et al</i> , 2018	***	Age ≥ 70 , N = 784	Community	Antihypertensive medications	51.5% of 784 participants were high adherent; 36.2% were medium adherent; 12.2% were low adherent.
	4-Item Morisky Medication Adherence Scale	Birmingham <i>et al</i> , 2011	***	Age > 55 , N = 183	Community	Statin/LLT	51% of 119 participants were adherent.
	Self-reported adherence through phone calls/ paper surveys/	Murphy <i>et al</i> , 2015	**	Age ≥ 50 , N = 114;	Hospital	Secondary prevention medications	11.4% of 114 participants missed their medications at least once in the preceding fortnight; 54% never forget their medications.
						Antihypertensive medications adherence	89% of 114 participants continued using medications until follow-up.

Assessment tools		Studies	Quality assessment	Participants demographics	Setting	Medications	Adherence levels
	study follow-up					Statin/LLT	87.7% of 114 participants continued using medications until follow-up.
		Keating <i>et al</i> ,2022	**	Age 47 - 86, N = 173	Hospital	Secondary prevention medications	93% of 173 participants continued on using medications until follow-up.
		Curneen <i>et al</i> ,2022	***	Age $\geq$ 18, N = 73	Hospital	Antihypertensive medications	27% of 73 participants were adherent.
Pharmacy Refill Records	Proportion of days covered (PDC)	Dillon <i>et al</i> , 2018	***	Age $\geq$ 70, N = 573	Community	Antihypertensive medications	9% of 573 participants were non-adherent.
		Dillon <i>et al</i> ,2019	***	Age $\geq$ 60, N = 905	Community	Antihypertensive medications	92% of 905 participants continued on using medications.
		Walsh <i>et al</i> ,2019	***	Age 67 - 79, N = 1431	Community	Antihypertensive medications	72.9% of 1431 participants continued on using medications.
	Medication possession ratio (MPR)	Kim <i>et al</i> , 2017	***	Age >70, N = 855; n= 518 had hyperlipidemia	Community	Antihypertensive medications	28% of 183 participants were non-adherent.
						Statin/LLT	29.5% of 518 participants were non-adherent.

Assessment tools		Studies	Quality assessment	Participants demographics	Setting	Medications	Adherence levels
				n= 183 had hypertension			
	Group based trajectory modelling (GBTM)	Dillon <i>et al</i> , 2019	***	Age ≥ 60 , N = 905	Community	Antihypertensive medications	58% of 905 participants were very high adherent; 35.8% were high adherent; 6% were low adherent.
Direct	Mass spectrometry (urine-analysis)	Curneen <i>et al</i> , 2022	***	Age ≥ 18 , N = 73	Hospital	Antihypertensive medications	27% of 73 participants were adherent.
		Hayes <i>et al</i> , 2019	**	Age ≥ 60 , N = 235	Community	Antihypertensive medications	74% of 235 participants were high adherent; 23.8% were medium adherent; 2% were non-adherent.

Secondary prevention medications include antihypertensive medications and/or lipid lowering therapy. **As per The National Heart, Lung, and Blood Institute Quality Assessment Tool for Observational Cohort and Cross-sectional Studies** poor (*); fair (**); good (***)

2.5.3. Guideline adherence

Six studies included data regarding adherence to guideline recommendations among people receiving primary and secondary antihypertensives and LLT (49,124,141,142,153,154) (**Table 2.3**). The number of the included participants ranged from 134 to 28,683 (153,154) respectively, and their mean age ($\pm$ standard deviation) ranged from 64.7 ($\pm$ 11.9) (124) to 71.3 ($\pm$ 13) years (49). Three studies documented the prescribed medications among people post-acute events including acute MI (141,154) and stroke (49). According to the EuroAspire II report, 70.4% of the 297 people who should be on LLT actually are; however, among people on LLT, 45% still had TC levels which were above the recommended goal of 5 mmol/L (141). In a national study that included 134 people post-MI, 87% were prescribed statin therapy on hospital discharge (154). Murphy *et al.* examined the statin utilization among participants with high risk CVDs including patients with known CVDs and found that only 67% of 166 patients were using statin treatment, despite the guideline recommending statins for everyone with CVDs. The level of statin utilization varied based on type of CVDs event, with 80.3% of people who reported previous revascularization taking statins compared to only 51.6% of people who self-reported transient ischemic attacks (TIA) (51.6%). In addition, only 57.4% of 141 patients with diabetes were utilizing statin, despite the guideline recommending statin use in all with diabetes (142). Similarly, 24% of people post stroke/TIA were reported not to be taking a statin and 15% of 196 people with LDL-C above the normal levels (LDL-C >2.59 mmol/L) were not on any LLT in another study (49). The trend of antihypertensive

medication prescribing in a primary care setting was examined in relation to the British Hypertension Society guidelines by Okechukwu *et al.* who reported greater adherence to the clinical guideline recommendations among participants aged <55 years than participants aged ≥55 years (OR: 1.31 95% CI 1.26, 1.37). Antihypertensive choice did not always match with the guideline recommendations, for example, ACEIs were commonly prescribed to the participants aged ≥55 years (26.9%) and beta-blockers were often prescribed to participants aged <55 years (36%) (153). Buckley *et al.*, reported guideline adherence by physicians to the British Hypertension Society Guideline was 54%, and to the ESH/ESC guideline was 38% (124). However, 57.5% of the participants did not receive any further action such as increasing the dose, switching to a new medication or combination therapy to control their BP as their physicians considered their BP on target, even though it was not within the clinical guideline goals (124).

Table 2.3. Characteristics and results of studies reporting guideline adherence (6 studies)

Author, Year	Quality assessment	Design	Setting	Demographics	Type of Population	Guideline	Guideline recommendation	Guideline adherence
Kotseva, 2007	**	Cross-sectional	Hospital	Age ≤ 70 N = 339	Secondary prevention (MI)	Second Joint European Societies Task Force 1998	<ul style="list-style-type: none"> TC should stay below 5 mmol/L and LDL-C should be below 3 mmol/L The majority of patients with coronary or atherosclerotic diseases need lipid lowering therapies (LLT) 	<p>For people with TC ≥ 5mmol/L</p> <ul style="list-style-type: none"> 26% not on LLT; 27.7% on LLT <p>Among people with history of hyperlipidemia</p> <ul style="list-style-type: none"> 15.4% of 247 not on LLT; of them 73.7% had TC ≥ 5mmol/L. 84.6% of 247 on LLT; only 55% achieved the goal of TC < 5mmol/L.
Syed <i>et al</i> , 2010	**	Retrospective analysis of cases	Hospital	N = 134	Secondary Prevention (Post MI)	AHA/ACC Guidelines for Secondary Prevention of Patients with Coronary and other Atherosclerotic	<ul style="list-style-type: none"> Patients with LDL-C 100 mg/dL (2.6 mmol/L) or above should be prescribed LLT on hospital discharge, with preference given to statins 	<ul style="list-style-type: none"> Out of 134 participants discharged after MI, 116 (87%) were prescribed statins on discharge.

Author, Year	Quality assessment	Design	Setting	Demographics	Type of Population	Guideline	Guideline recommendation	Guideline adherence
						Vascular Disease 2006.		
Murphy, 2015	**	Cross-sectional	Community	Age >50, N = 3372; Male (44.9%) Female (55%)	Primary & secondary prevention	Fourth Joint Task Force of the ESC and other societies on cardiovascular disease prevention in clinical practice (ESC 2007)	<ul style="list-style-type: none"> Statin therapy is recommended for all CVD and most diabetic patients. If total CVD risk $\geq 5\%$, lipid-lowering drug therapy should be considered. In all patients with an acute coronary syndrome, statin treatment should be initiated while the patients are in the hospital 	Statin utilization was found as below: <ul style="list-style-type: none"> 68.6% of the participants with known CVD. 57.4% of the participants with diabetes. 19.7% of participants with 10-year fatal CVD risk score $\geq 5\%$ 78.6% of the participants who had experienced CV events
Ní Chróinín <i>et al</i> , 2018	***	Prospective cohort study	Community & Hospital	Age >60 N = 616 Male (49.8%)	Secondary Prevention (Ischemi	National Cholesterol Education Program	<ul style="list-style-type: none"> If CHD/ risk equivalent, or 2+ risk factors & 10-year risk (FRS) >20%: 	Statin utilization prior to an event: <ul style="list-style-type: none"> 48.5% of 298 patients with CHD or risk equivalent.

Author, Year	Quality assessment	Design	Setting	Demographics	Type of Population	Guideline	Guideline recommendation	Guideline adherence
				Female (50%)	c stroke/TIA)	(NCEP III)	<p>start LLD if LDL-C >130mg/dl; consider LLT if LDL 100-129mg/dl</p> <ul style="list-style-type: none"> • If 2+ risk factors & 10-year risk, consider LLT if consider LLT if LDL-C 160 mg/dl • If 0-1 risk factor: consider LLT if LDL-C >190mg/dl • LDL measurement following stroke and TIA and pre-discharge initiations of statins 	<ul style="list-style-type: none"> • 21.6% of 245 patients who met the NCEP III criteria for LLT were not on treatment. <p>After stroke/TIA:</p> <ul style="list-style-type: none"> • 24% of patients were not on any pharmacological treatment. <p>Of patients with high LDL-C >100 mg/dl)</p> <ul style="list-style-type: none"> • 15% of 196 were not prescribed statin therapy.
Okechukwu <i>et al</i> , 2007	**	Retrospective Cohort	Community	Under 55 years: 12,745	Primary Prevention	British Hypertension Society	Initiation of antihypertensive medications as the following:	For people aged under 55 years without anti-diabetic medications:

Author, Year	Quality assessment	Design	Setting	Demographics	Type of Population	Guideline	Guideline recommendation	Guideline adherence
				55 years and over: 28,683 Male (39%); Female (60.7%)		guidelines 2004	<ul style="list-style-type: none"> • ACEIs/ARBs or beta-blockers in patients under 55 years old. • CCBs or diuretics for patients 55 years and over. • Beta-blockers should be used with caution for diabetic patients 	<ul style="list-style-type: none"> • 22.5% were prescribed ACEIs. • 36% were prescribed beta-blockers. • 15% were prescribed CCBs. • 26% were prescribed diuretics. <p>For people aged 55 years and over without anti-diabetic medications:</p> <ul style="list-style-type: none"> • 19% were prescribed CCBs. • 32.7% were prescribed diuretics. • 26.9% were prescribed ACEIs. • 21.3% were prescribed beta-blockers. <p>For people with diabetes:</p> <ul style="list-style-type: none"> • 10.5% were prescribed beta-blockers. • 46.7% were prescribed ACEIs • 17% were prescribed CCBs • 25.6% were prescribed diuretics

Author, Year	Quality assessment	Design	Setting	Demographics	Type of Population	Guideline	Guideline recommendation	Guideline adherence
Buckley <i>et al</i> , 2009	***	Cross-sectional	Community	Age >50 N = 1534 Male (46%); Female (53.8%)	Primary & Secondary Prevention	ESH/ESC 2007	<ul style="list-style-type: none"> ESH/ESC 2007 recommended escalation to combination therapy after full dose monotherapy has failed. Combination therapy is recommended for first-line treatment for patients with systolic BP >160 mmHg or diastolic BP >100 mmHg, and/or high and very high risk patients. 	Antihypertensive monotherapy prescribing: <ul style="list-style-type: none"> 40.5% participants were prescribed monotherapy Of them, 32% were prescribed ACEIs, 22% were prescribed ARBs, 39.8% were prescribed beta-blockers, 29.7% were prescribed diuretics, 27.9% were prescribed CCBs. Combination therapy: <ul style="list-style-type: none"> 6.6% & 8% used ACEIs or ARBs with diuretics. 1.2% were using ACEIs with CCBs.

Abbreviations ACEIs angiotensin converting enzyme inhibitors; ARBs angiotensin receptor blockers; CCBs calcium channel blockers; ESH/ESC European Society of Hypertension/ European Society of Cardiology; MI myocardial infarction; TC total cholesterol; LDL-C low density lipoprotein; LLT lipid lowering therapy; TIA transient ischemic attack. As per The National Heart, Lung, and Blood Institute Quality Assessment Tool for Observational Cohort and Cross-sectional Studies: poor (*); fair (**); good (***). To convert LDL-C from mmol/L to mg/dL, multiply by 38.67.

2.6. Discussion

This systematic review is the first to assess the achievement of BP and lipid clinical guideline targets, medication adherence among patients and guidelines adherence among prescribers across studies conducted in Ireland. The results showed that LDL-C goal attainment is low especially when stringent LDL-C cutoff levels are recommended including LDL-C <2.5 mmol/L and LDL-C <1.8 mmol/L as the proportions were 53% (95% CI 28,78) and 41% (95% CI 31,52) respectively. In addition, antihypertensive choice did not always match the guideline recommendations; 15% - 27.9% were prescribed CCBs and 21.3%-39.8% were prescribed beta-blockers, both of which are not first-line antihypertensives in many situations (124,153). LLT was not prescribed to many patients whose risk of CVD warranted LLT, including 27.7% of people with TC >5mmol/L and 48.5% - 68.6% of people with known CVD (49,141,142). Medication adherence varied according to the assessment tool used. In Ireland, CVD kill around 9,000 people every year. These deaths still occur, despite the finding that 80% of premature CVDs are preventable (155). Stamenic *et al*, reported that individuals with CVDs seek healthcare services to a greater extent than individuals without CVDs (156). In 2022, the cost of healthcare services use associated with CVDs among Irish adults aged >50 was €352 million, with hospital admissions accounting for 80% of this cost (156). Therefore, the preventive approach to CVDs is crucial to protect people from developing CVDs and to reduce the risk of repeat cardiovascular events.

It is difficult to estimate the total number of people being treated with LLT or antihypertensives in Ireland. However, data produced by the Primary Care Reimbursement Service (PCRS) in Ireland, shows that high-intensity statins atorvastatin and rosuvastatin

are consistently in the top 10 dispensed medicines across the publicly funded PCRS schemes. Also, antihypertensives such as bisoprolol, ramipril and amlodipine all feature in the top 20 dispensed medicines across PCRS schemes. This demonstrates the prevalence with which community-dwelling adults are taking such medicines, whether for primary or secondary prevention (157).

The review findings showed that there is variation in the achievement of LDL-C and BP targets. The proportion of primary prevention participants who attained LDL-C goals was higher than the proportion of secondary prevention participants achieving this goal. However, primary prevention participants were categorized as low risk or moderate risk patients; therefore, the less stringent LDL-C goal of <3 mmol/L was applied in the majority of included studies. On the contrary, the LDL-C goal of <2.5 mmol/L and <1.8 mmol/L were used for high risk and very high risk participants who constituted the secondary prevention group (22). This aligns with the findings of a review of European settings, which reported that the pooled estimate for goal achievement was higher among high risk patients with LDL-C target of <2.5 mmol/L compared to very high risk patients with LDL-C goal of <1.8 mmol/L, with 46% vs 18% achieving their LDL-C goal, respectively (123). The more aggressive LDL-C target of <1.4 mmol/L recommended in the 2019 ESC guidelines (27) was achieved by an even lower proportion of very high risk population with a pooled estimate of 28%. A retrospective observational cohort study conducted in Wales reported that only 23.4% of 2,353 participants achieved 2019 ESC goals of LDL-C <1.4 mmol/L, one year post percutaneous coronary intervention; however, 47.8% of 4812 participants achieved the LDL-C <1.8 mmol/L (158).

In the present review there is a discrepancy in the proportion of participants who achieved the BP goal of <140/90 mmHg (56%) and participants who achieved the stringent BP goal of <130/80 mmHg (37%). In this systematic review, only Buckley *et al*, 2019 reported the proportion of people who achieved BP goals in community settings (124) and this was lower than the proportion of people who achieved goals in hospital settings (89,122). These findings are broadly similar to studies carried out in other countries. A previous narrative review that included 12 studies evaluating the level of BP goal attainment among participants with hypertension, diabetes or stroke reported that the proportion of participants who attained BP goals ranged from 25% to 76.4% (159). According to Vickie Andros *et al.*, who reported the level of BP control among patients with diabetes in the U.S.; only 31.4% of 1328 participants achieved BP control of <130/80 mmHg (160,161). Similarly, Barrios *et al.*, examined BP goal achievement in a primary care setting in Spain, where the proportion of participants who attained the BP goal of <140/90 mm Hg (or <130/80 mm Hg for diabetics) was 24.8% (162). In a single center, cross-sectional study of hypertensive outpatients in Italy, 36.6% of 1578 participants treated with antihypertensive monotherapy achieved BP goals of <140/90 mmHg (163). Unlike the PORTRAIT-DYS study which found that women were 22% less likely to achieve their LDL-C goal than men, the studies in this review did not identify any patient or prescriber factors to be associated with goal attainment (164). Medication adherence can reduce healthcare utilization and healthcare costs. Dillon *et al.* 2019, reported that each 10% increase in the refill adherence to antihypertensive medications was associated with a 16% lower rate of outpatient hospital visits in Ireland (152). In a large retrospective study conducted in the U.S; healthcare costs were reduced by \$387 - \$813 for patients adherent

to antihypertensive medications, compared to those who are non-adherent (165). This systematic review identified heterogeneous methodologies reporting medication adherence among participants prescribed antihypertensive medications and lipid lowering medications. The proportion of participants who were adherent to antihypertensive medications ranged from 27% to 92% (149,152). Comparable findings were in a retrospective analysis of antihypertensive medications adherence in the U.S which reported that among 625,620 participants, 15.4% were moderately adherent (MPR 60% - 79%), and 74.6% of the participants were reported high adherent to antihypertensive medications using the MPR of >80% as the threshold (165). Similar to the findings from Walsh *et al.*, (146), Beall, *et al.* have reported that age is significantly associated with increasing medication adherence; participants aged 65 years and older were more persistent to their antihypertensive medications (54.6%) compared to those aged 18 - 44 years (39%) (166).

Guideline adherence by clinicians also contributes to improved outcomes in patients with cardiovascular diseases (167). Whilst clinicians are aware that clinical guidelines are helpful educational resources and are intended to improve the quality of care provided to patients, they considered them impractical and too rigid to apply in a person-centered manner (168). In Buckley *et al.*, 54% of physicians in primary care were adherent to the British Hypertension Society Guideline and 38% were adherent to the ESH/ESC guidelines (124). Similarly, a cross-sectional study examining physicians' adherence to hypertension guidelines when prescribing antihypertensive medications for hospitalized patients in an Indian tertiary care hospital reported that out of 198 physicians, only 51% of the physicians were adherent to The Seventh Report of the Joint National Committee on

Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC7), 59% were adherent to JNC8, and 31% were adherent to The 2017 ACC/AHA guidelines (169). The identified studies do not show full compliance with the guideline recommendations. Despite the solid evidence on the benefits of using LLT especially among people who are treated for secondary prevention, a gap exists between guideline recommendations and the clinical practice (21,29,170). Syed *et al.*, and Murphy *et al.*, reported that not all people who were discharged post-MI or with known CVDs were prescribed LLT (142,154). On the other hand, Kotseva *et al.* reported that more than half of the people who were on LLT still have TC level above 5 mmol/L (141). Although the pattern of choosing the initial antihypertensive medications was relatively similar to studies in Europe and U.K. as reported in Okechukwu's study (153,171,172), Buckley *et al.* reported that prescribers miss necessary escalation of antihypertensive monotherapy into combination therapy.

There are limited data about guideline adherence, and in particular its relationship with goal achievements, in Ireland. Another study described the LLT pattern among German people in general practices where 2.8% were using high-intensity statin, 32% were using low-moderate intensity statin, and 1.3% were on non-statin LLT. Among patients with ASCVD (recent acute coronary syndrome, ischemic stroke, or peripheral artery disease (PAD)), 44.9% received any LLT and 43.6% of patients received prescriptions for statins on the index date. However, 8.5% of patients achieved LDL-C <1.8 mmol/L and 25.6% of the participants achieved LDL-C 1.8 mmol/L to <2.6 mmol/L (37). These European studies have shown that secondary prevention of CVDs is often undertreated, and often the target goals set out by the guidelines are not achieved.

Although none of the included studies assessed the relationship between achieving LDL-C goals and prescriber adherence to guideline recommendations and/or patient adherence to medications within Irish context, Parris *et al.*, reported a significant correlation between the MPR for statin therapy and LDL-C goal achievements among people with dyslipidemia and diabetes (173). Similarly, a Norwegian study reported a strong association between the use of LLTs for secondary prevention and the achievement of LDL-C goals, but the same study did not find an association between using antihypertensives and achieving target BP. However, the study did not assess the level of medication adherence among participants, and the sample size may have been underpowered for hypertensive patients (130). However, Bramley *et al.*, reported that people with high adherence to antihypertensive medications were 45% more likely to achieve the BP goals compared to medium and low adherence with monotherapy after reviewing the medical and pharmacy claims from 13 U.S. health plans (131). On the other hand, Vashitz *et al.*, assessed the rates of physician adherence to prescribing guidelines and found low rates of adherence to guidelines for both LLT initiation and up-titration, but found relatively high rates of medication adherence by patients (174). This review has found studies which independently examine goal attainment in CVD, prescriber adherence to guidelines and medication adherence by patients. However, there are a lack of studies examining the relationship between guideline adherence, medication adherence and goal attainment in CVDs.

As with all systematic reviews, many of the limitations of the review reflect those of the included studies. The quality of the included studies was assessed using an established tool. The quality of some included studies was scored fair; this was primarily

due to the nature of the cross-sectional studies, namely having no time lag between the exposure and the outcome, and low sample size in some studies. However, funnel plot asymmetry was not conducted as few studies (<10 unique studies) were included in each meta-analysis (175).

None of the included studies assessed the relationship between medication adherence or guideline adherence and the achievement of BP or LDL-C goals. A large number of studies were conducted in hospital settings rather than community settings; that might lead to higher values of pooled estimates, as the patients were being monitored. As with the purpose of the meta-analysis to determine the overall achievement of LDL-C goals and BP goals across different studies, a random-effects model was used to account for the heterogeneity within and between the study variations across the included studies. All meta-analyses in this review showed high levels of heterogeneity, with I^2 values greater than 75% in many pooled and subgroup analyses, suggesting substantial variation in effect estimates across studies. As this was a proportional meta-analysis it is expected that the I^2 test for prevalence pooled estimates is high due to the difference in the time and place where the included studies were conducted (137). The heterogeneity in our review resulted from the variation in BP and LDL-C targets across the included studies and the variation in whether the participants were treated for primary or secondary CVDs prevention. Although some studies recruited participants from hospital and community settings, there were not enough findings to examine the differences in goal achievements in both settings. In addition, there are few studies that examine the differences in goal achievements and medication adherence among people treated for primary and secondary prevention.

2.7. Conclusion

This review has found evidence that prescriber adherence to guidelines in CVDs is low, that patients' adherence to medications for CVDs is variable, and that the achievement of LDL-C and BP goals is often concerningly low. Nationally representative studies examining objective measures of medication adherence, guideline adherence and goal attainment are needed to examine the relationship between these three variables in CVDs, as CVDs remain a leading cause of morbidity and mortality across the globe.

2.8. Systematic review search update (2024-2026)

A detailed search was conducted in March 2026 for any relevant papers published between March 2024 and March 2026. Five databases were searched: PubMed, Scopus, CINAHL, Embase, and Web of Science using the same search strategy as the original systematic review. Title and abstract screening was performed by one author. Full text screening was conducted independently by two authors (RE and MB). Data was extracted to an Excel spreadsheet as described earlier in this chapter (section 2.4.3).

2.8.1. Systematic Review Results - Updated Search

The search yielded 312 studies. After removing duplicates, 225 studies were remaining for title and abstract screening. After screening, the full texts of twenty studies were reviewed. A total of four studies were included in the updated review (**Figure 2.5**).

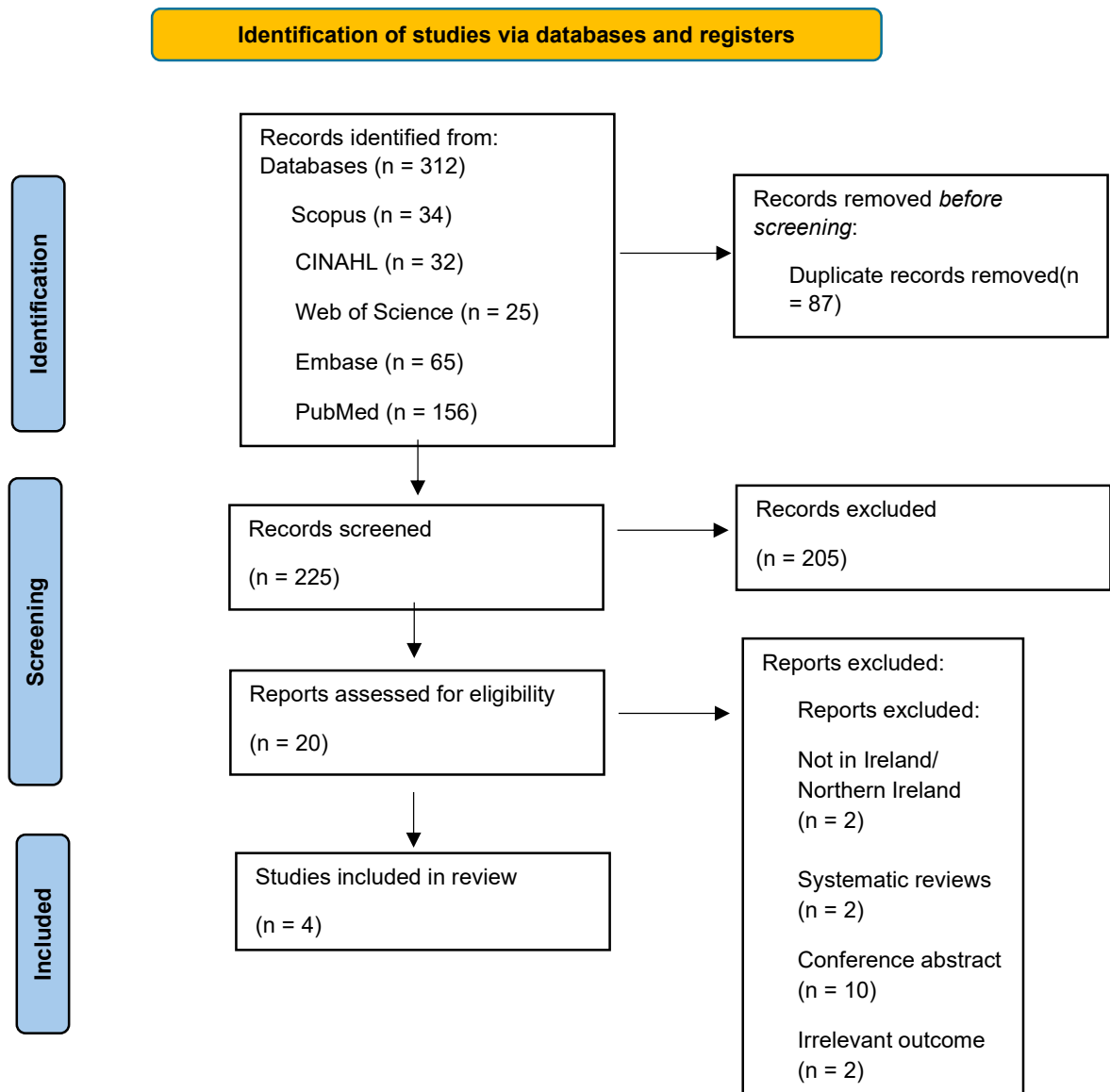


Figure 2.5. PRISMA flow-chart for the search updates (March 2026)

2.8.2. Goal achievement

Two studies included data about LDL-C goal achievements (176,177) and one study included data about BP goal achievement (178). The Irish cohort in the Santorini study included 98 patients recruited from primary care and secondary care settings, with 79 very high risk and 19 high risk patients (177). In accordance to the 2019 ESC/EAS guideline recommendations, the overall LDL-C goal achievement for the Irish cohort was 25.7%. A secondary analysis of the rescreen data from the Mitchelstown Cohort Study, showed that among 547 patients prescribed LLT, 42.1% achieved the LDL-C recommended goals, based on the 2011 ESC/EAS and 6% of the very high risk and high risk group achieved the 2019 ESC/EAS guideline LDL-C recommended goals (176). A longitudinal analysis of waves 1, 3 and 6 of the TILDA cohort showed that among people on antihypertensive treatment, 48.8%, 53.2% and 53.8% respectively achieved the BP goals recommended in the 2018 ESC guidelines and 27.9%, 32.2% and 32.8% achieved the 2024 ESC goals (178). **(Table 2.4)**

2.8.3. Guideline adherence

Three studies included data about prescriber adherence to guidelines, one examined adherence to the 2011 NICE Guidelines for Hypertension Management in Primary Care (179,180), one assessed adherence to the 2024 ESC Guidelines for Management of Elevated Blood Pressure and Hypertension and one examined adherence to the 2019 ESC/EAS guidelines for the management of dyslipidemia (27,177). Akhtar *et al.*, 2024,

using data from the third wave of the TILDA study, showed that 46.2% of people aged <55 years were prescribed ACEIs or ARBs and 24.1% of people aged ≥ 55 years were prescribed CCBs as recommended in step 1 in the 2011 NICE guideline (180). According to McGarvey *et al.*, among people in the TILDA study on antihypertensive treatment, 49.5% of wave 1, 55.2% of wave 3 and 56.9% of wave 6 participants were on at least one of the hypertension medications recommended in the 2024 ESC guidelines (178). Despite the 2019 ESC/EAS recommendations about the necessity of prescribing LLT for people at very high risk and high risk of CVD, Rai *et al.*, showed that 20.4% of people in these risk categories were not on LLT at enrollment to the Irish arm of the SANTORINI study from hospital/specialist settings. In SANTORINI, of those who were prescribed LLT, the majority (70%) were on statin monotherapy, however, only 45.8% and 50% of very high risk and high risk participants were prescribed high intensity statin as per 2019 ESC/EAS guidelines (177) (**Table 2.5**).

Table 2.4. Study characteristics and goal attainment of lipid targets (3 studies)

Study/ Year	Participants Demographics	CVD (in secondary prevention)	Design	Setting	Guidelines	Proportion achieving goals		LDL-C	BP
						LDL-C goal mmol/L	BP goal mmHg		
Rai <i>et al</i> , 2024	Patients aged ≥ 18 years. N = 98; Very high risk n = 79 with ASCVD; High risk (n = 19)	Atherosclerotic CVD	Prospective observational study	Primary care and secondary care	2019 ESC/EAS guidelines	<1.8 high risk <1.4 very high risk		25.7% of 98 participants; 26.1% of the very high risk group 25% of high risk group	
Elhiny <i>et al</i> , 2025	Patients median (IQR) aged 65 (60 - 69); N = 1,183 very high risk (n = 645), high risk (n = 347).	Ischemic heart disease; acute MI; atherosclerosis; PAD; cerebrovascular disease (stroke, transient ischemic attack)	Cross-sectional analysis	Primary care	2011 ESC/EAS guidelines	<3 low risk <2.5 Moderate risk <1.8 high risk		42.1% of 574 participants with prescribed LLT.	
					2019 ESC/EAS guidelines	<1.8 high risk <1.4		4.0% of 347 high risk	

						very high risk		2.6% of 191 very high risk	
McGarvey <i>et al</i> , 2025	Participants aged ≥ 50 years n = 5879 wave 1; n = 1,5329 wave 3; n = 3,202 wave 6		Longitudinal analysis of 1 st , 3 rd and 6 th waves of TILDA	Primary care	2018 ESC guidelines		<140/90		48.8% of 5,195 53.2% of 4,698 53.8% of 3,092
					2024 ESC guidelines		<130/80		27.9% of 5,195 wave 1; 32.2% of 4,698 wave 3; 32.8% of 3,092 wave 6.

Abbreviation IQR, Interquartile range

Table 2.5. Characteristics and results of studies reporting guideline adherence (3 studies)

Study/ Year	Participants Demographics	CVD (in secondary prevention)	Design	Setting	Guidelines	Guideline recommendation	Guideline adherence
Rai <i>et al</i> , 2024	Patients aged ≥18 years. N = 98; Very high risk n = 79 with ASCVD; High risk (n = 19)	Atherosclerotic CVD	Prospective observational study	Primary care and secondary care	2019 ESC/EAS guidelines		At baseline: 20.4% were not prescribed LLT; 71.4% of whom were on statin monotherapy; Among high risk, 45.8% were on high intensity statin; 50.0% of very high risk were on high intensity statin.
McGarvey <i>et al</i> , 2025	Participants aged ≥50 years		Longitudinal analysis of 1 st , 3 rd and 6 th waves of Irish Longitudinal Study on Aging (TILDA)	Primary care	2024 ESC guidelines	First line treatment: ACEIs, ARBs, dihydropyridine CCBs, diuretics (Thiazides, and thiazides like drugs); combined therapy is recommended if BP >140/90 as initial therapy; recommended combination (ACEIs or ARBs + CCBs or diuretics)	Among people on hypertension medicines, 18.6% (wave 1), 21% (wave 3), 14.4% (wave 6) were prescribed dual therapy. 49.5%, 55.2% and 56.9% of those on treatment in wave 1,3 and 6 respectively were taking at least one of the guideline recommended

							antihypertensive medication.
Akhtar <i>et al</i> , 2024	Participants aged 65.69 ($\pm$ 9.23) N = 2992	Previous heart attack (7.02%); HF (1.84%); stroke (2.57%); TIA (3.58%)	Secondary analysis of the 1 st wave of TILDA (2009-2011)	Primary care	2011 NICE Guidelines for Hypertension Management in Primary Care	Step 1: CCBs age $\geq$ 55 years; ACEIs or ARBs age <55 years; Step 2: ACEIs or ARBs + CCBs; Step 3: ACEIs or ARBs + CCBs + thiazides diuretics; Step 4 ACEIs or ARBs + CCBs + thiazide diuretics + further diuretics or Alpha blockers or beta-blockers.	46.2% of people aged <55 years were adherent to step 1; 24.01% of people aged $\geq$ 55 years were adherent to step1. 57.4% were prescribed ACEIs; 22.8% were prescribed CCB; 17.9% were prescribed diuretics; 27.7% were prescribed beta blockers.

CHAPTER 3. LDL-cholesterol goal achievement and guideline adherence among middle- to older- age Irish adults in a primary care setting

3.1. Key points included in this chapter

- LDL-C control is sub-optimal among adults in a primary care setting, independent of their CV risk stratification.
- Participant age, sex, and body weight were associated with achieving LDL-C treatment goals in this population.
- The prescription of lipid-lowering therapy was not as intensive as recommended for people at high/very high risk of CVD

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3.2. Abstract

3.2.1. Background

A significant gap exists between recommended LDL-C treatment goals and the achievement of these goals in clinical practice. In addition, there remains suboptimal utilization of LLT. This study examines the prescribing pattern of LLT and the level of LDL-C goal achievement among Irish adults in a primary care setting. In addition, it identifies patient factors associated with the prescribing of LLT and LDL-C goal achievement.

3.2.2. Methods

This was a cross-sectional analysis of rescreen data from the Mitchelstown Cohort Study. Demographic, medication and diagnosis data were obtained from participant electronic health records. Cardiovascular risk was assessed using the SCORE tool. LDL-C goal achievement was determined using the LDL-C goals set out in the 2011 ESC/EAS guidelines for the management of dyslipidemia.

3.2.3. Results

Among 1,183 participants (median age = 65 years), 48.5% were prescribed LLT, 42% of whom attained their LDL-C goal. Only 17.5% were prescribed high-intensity statin therapy and 13% were prescribed combination therapy. In multivariable analysis, diabetes history, polypharmacy, and hyper-polypharmacy were associated with prescribing LLT. Being male or ≤ 59 years of age was associated with lower likelihood of LLT prescription. Target LDL-C goal achievement was associated with male sex and age ≤ 64 or ≥ 70 years, while BMI 25 – 29 kg/m² was associated with lower LDL-C goal achievement.

3.2.4. Conclusion

Dyslipidemia is undertreated in this Irish primary care population with limited use of high-intensity statins. This study highlights the gap between guideline recommendations for LLT prescription and LDL-C target goals and real-world implementation of guidelines.

3.3. Introduction

Cardiovascular disease (CVD) is a major public health challenge and accounts for 45% of all mortalities in Europe and 26.5% of all mortalities in Ireland (2,181,182). The total cost of CVD in the EU is estimated to be €210 billion per year and €1.7 billion in Ireland, with healthcare services making up about half of this expenditure (2,182).

LDL-C is a significant risk factor for the development of atherosclerotic cardiovascular diseases (182,183). Elevated LDL-C levels were implicated in 19.2% of CVD deaths in the EU in 2021 (119). Robust evidence from randomized control trials has shown that reducing LDL-C levels by 1 mmol/L (40mg/dL) using LLT reduces major adverse cardiovascular events by one-fifth both among people who previously experienced a CV event (secondary prevention) and those who were treated for primary prevention (184,185).

LLT is therefore a first line treatment in primary and secondary prevention of CVD (186,187), with targets set for LDL-C levels by the Task Force for the management of dyslipidemias of the ESC/EAS(21). However, despite robust evidence for the use of LLT in primary and secondary prevention of CVD (188,189), there is a significant gap between the target LDL-C goals and the achievement of LDL-C goals in practice (34,52,123,139,190,191). For example, in a systematic review of 81 studies conducted in Europe of people at very high risk of CVD, only 18% achieved the stringent target of LDL-C <1.8 mmol/L (123). It has been suggested that this gap could be attributed to medication non-adherence among participants and/or guideline non-adherence among prescribers (47).

In chapter 2 of the thesis, the pooled proportion of seven studies has shown that LDL-C goal attainments among Irish people is generally low, especially among people

aiming for stringent LDL-C targets, including those in the very high-risk and high-risk groups. Furthermore, there was no study identifying patient characteristics which are associated with unmet LDL-C goals. In addition, there are limited data on what role prescriber adherence plays in bridging the gap to achieve the recommended LDL-C goals in Ireland.

To address these gaps, the aims of this study were to examine the prescribing pattern of LLT and the level of LDL-C goal achievement in a primary care setting in Ireland. In addition, the study aims to identify the factors associated with prescribing LLT, as well as the characteristics associated with achievement of LDL-C goals.

3.4. Methods

3.4.1. Study population

The Mitchelstown Cohort Study recruited 2,047 participants at baseline in 2010 from a large general practice in the Cork region of Ireland (116). Participants were aged 51 – 77 years, and the sample was broadly similar to the local background population in terms of proportional age representation, marital status and education, representing a low risk of selection bias. A follow-up study was conducted in 2015, with 1,378 of the baseline participants being re-screened (192). The present study uses data from the 2015 re-screen. The follow-up involved two visits. The first visit involved urinalysis and fasting blood samples for assessment of biochemistry and hematological parameters including fasting plasma glucose, glycated hemoglobin A1c and lipoprotein profile. During the second visit, a computer assisted personal interview was used to collect various health information including medication use. In addition, physical examination was undertaken with measurements including weight, height, and resting BP. Detailed information on medical diagnosis and medication data was obtained during the annual screening of electronic health records which were recorded as part of the routine general practice care. Full details regarding study design, sampling methods, and data collection were described previously in the Cohort profile update (192).

Variables selection in this chapter was based on the availability of data collected within the Mitchelstown dataset and previous evidence regarding dyslipidemia control and prescribing medications (48, 212).

Ethics committee approval conforming to the Declaration of Helsinki was obtained from the Clinical Research Ethics Committee of University College Cork (The Cork and Kerry Diabetes and Heart Disease Study (Phase II) Mitchelstown Cohort, clinical trials.gov identifier NCT03191227). All participants gave signed informed consent, including permission to use their data for research purposes.

3.4.2. Demographic data

Age and sex were obtained from electronic health records. In this analysis, age was categorized into four age ranges ≤ 59 years, 60 – 64 years, 65 – 69 years, and 70+ years, while sex was categorized into two groups: male and female. The weight and height of each participant were measured to the nearest 0.1 kg and 0.1 cm respectively. Portable electronic Tanita WB-100MA weighing scales (Tanita Corporation, IL, USA) were placed on a firm, flat surface and were calibrated weekly to ensure accuracy. Height was measured using a portable Seca Leicester height/length stadiometer (Seca, Birmingham, United Kingdom). BMI was calculated as weight in kilograms divided by the square of height in meters (194) and categorized into four categories: underweight ($<18.5\text{kg/m}^2$), normal weight ($18.5 - 24.9\text{ kg/m}^2$), overweight ($25 - 29.9\text{ kg/m}^2$) and obese ($\geq 30\text{ kg/m}^2$).

Education level and smoking status were self-reported as part of the computer assisted personal interview. Education level was included here as a measure of socioeconomic status and was categorized into one of three categories: (i) primary level only (some primary/primary equivalent), (ii) secondary level (some secondary/secondary

equivalent) or (iii) third level (diploma/ primary university degree/ postgraduate degree). Smoking status was categorized into either current smoker, former smoker, and non-smoker. For the calculation of CVD risk using the SCORE tool, smoking status needed to be categorized as current smokers or other (to include all other categories such as former smokers, non-smokers). Thus, for the purposes of the SCORE risk calculation, former smokers and non-smokers were merged into a single category labelled “Other”.

3.4.3. Medication data

Electronic health records were used to identify participants with prescribed LLT, with medications classified by their generic names and Anatomical Therapeutic Chemical (ATC) Codes. LLT was categorized into (i) statin monotherapy, (ii) combination therapy involving statin and non-statin LLT, or (iii) non-statin therapy. Statin monotherapy was subdivided into three sub-categories according to the intensity of the statin: high-intensity (atorvastatin 40 – 80 mg and rosuvastatin 20 – 40 mg), moderate intensity (atorvastatin 10 – 20 mg, rosuvastatin 5 – 10 mg, simvastatin 20 – 40 mg, pravastatin 40 – 80 mg, lovastatin 40 mg, fluvastatin XL 80 mg, fluvastatin 40 mg twice daily, pitavastatin 2 – 4 mg) or low-intensity (simvastatin 10 mg, pravastatin 10 – 20 mg, lovastatin 20 mg, fluvastatin 20 – 40 mg and pitavastatin 1 mg) (23) **Appendix 5**

Polypharmacy was defined as the use of five to nine medications. Hyper-polypharmacy was defined as the use of 10 or more different medications. No polypharmacy was defined as taking four or less medications (including those taking no medications) (195). Patients receiving statin monotherapy for both primary prevention

(very high-/high-risk groups) and secondary prevention were categorized according to whether they were prescribed a target high-intensity statin dose as per 2011 ESC/EAS recommendations (21).

3.4.4. Cardiovascular disease data

Fasting blood samples were drawn at the follow-up visit. Serum total cholesterol was measured enzymatically by an Olympus automatic analyzer (model AU5400; Olympus Optical, Tokyo, Japan). Triglyceride, HDL-C, LDL-C and creatinine levels were measured on Olympus 5400 biochemistry analyzers with Olympus reagents using standardized procedures and fresh samples (Olympus Diagnostica GmbH, Hamburg, Germany). Three independent measurements of systolic BP and diastolic BP were obtained with the subject in a seated position using an Omron M7 digital sphygmomanometer (Omron Healthcare Co. Ltd., Japan) (194,196). CVD and diabetes diagnoses were obtained through electronic health records. The estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation:

$$eGFR = 141 \times \min(\kappa Creatinine, 1)^\alpha \times \max(\kappa Creatinine, 1) - 1.209 \times 0.993^{Age} \times (1.018 \text{ if female})$$

(197).

Participants were categorized as being treated for either primary prevention or secondary prevention of CVD. Primary prevention was defined as undergoing treatment with LLT without the presence of ischemic heart diseases, acute MI, atherosclerosis, PAD, cerebrovascular diseases stroke and transient ischemic attack (20). For primary prevention, patients were further categorized by level of risk into (i) very high-risk (ii) high-risk and

(iii) low-moderate risk based on 2012 European Guidelines on CVD prevention in clinical practice (20). The 10-year risk of fatal and non-fatal cardiovascular disease events was calculated using the SCORE algorithm for participants aged <65 years. The SCORE algorithm for low-risk population was applied (20,21). The updated 10-year risk estimate for fatal and non-fatal CVDs (SCORE2 and SCORE2-OP) was calculated for people aged 65–69 years and 70+ years (198). The SCORE used to categorize individuals is outlined in **Appendix 5**. Following calculation and categorization with SCORE and in line with the guidelines (20,21), people with diabetes who had one or more additional CVD risk factors (smoking, total cholesterol >8 mmol/L, or systolic BP >180 mmHg) were then re-categorized as being very high risk, while individuals with diabetes who had no additional risk factors were re-categorized as being high-risk. Similarly, people with moderate renal function impairment ($\text{eGFR} \geq 30 - < 60 \text{ ml/min/1.73m}^2$) and severe renal function impairment ($< 30 \text{ ml/min/1.73m}^2$) were re-categorized as high-risk and very high-risk, respectively.

Secondary prevention was defined as undergoing treatment with LLT with a documented diagnosis of CVD (ischemic heart diseases, acute MI, atherosclerosis, PAD, cerebrovascular diseases (stroke and transient ischemic attack) (20).

3.4.5. Goal achievement data

LDL-C goal achievement was determined using LDL-C goals set out in the 2011 ESC/EAS Guidelines for the management of dyslipidemias according to individual CVD risk (21). LDL-C goals varied according to the CVD risk categorization: <3 mmol/L in

patients at low-moderate risk of CVD, <2.5 mmol/L in patients at high-risk of CVD, and <1.8 mmol/L in patients at very high-risk of CVD including the secondary prevention group (21). Details on participant categorization are shown in **Appendix 5**.

3.4.6. Data analysis

The demographics of the study population were stratified by (i) prescription of LLT and (ii) achievement of LDL-C goals. Categorical features are presented as numbers (n) and percentages (%), and continuous variables are shown as a mean, plus or minus one standard deviation (SD), or a median and interquartile range (IQR) for skewed data.

The association between patients' characteristics and prescribing of LLT was examined using a multivariable logistic regression model. This model included participants' age categories, BMI, sex, smoking status, diabetes status, education level, CVD risk, and extent of polypharmacy. A second multivariable model examined associations between patient characteristics and achieving LDL-C goals. This model included participants' age categories, BMI, sex, smoking status, diabetes status, and education level. For age categories, the age group 65 – 69 years was used as the reference category, as it had the largest sample size among the age groups. Odds ratios (ORs) and 95%CI are shown. Multicollinearity among independent variables was assessed using variance inflation factors (VIF). A threshold of VIF above 2.5 was considered indicative of potential multicollinearity. Statistical analysis was performed using Stata/SE 17.0 (Stata Corporation, College Station, TX, USA). For all analyses, a p-value (two-tailed) of less than 0.05 was considered to indicate statistical significance.

A sensitivity analysis was conducted to check whether the results were consistent when applying stricter LDL-C goals as recommended by the 2019 ESC/EAS guidelines for the management of dyslipidemias. The proportion of very high-risk and high-risk people who achieved their LDL-C goals was calculated, with an LDL-C goal of <1.4 mmol/L for those deemed very high-risk and a goal of <1.8 mmol/L for those deemed high-risk. The LDL-C goal for those deemed low-moderate risk remained 3.0 mmol/L (27). The focused update guidelines released by the ESC/EAS in 2025 have the same LDL-C goals for the very high-risk and high-risk population as the 2019 guidelines and therefore this sensitivity analysis also aligns with the 2025 ESC/EAS guidelines (26).

3.5. Results

A total of 1,183 participants with complete data on age, sex, smoking status, systolic BP, total cholesterol, triglycerides, HDL-C, LDL-C and eGFR were included in this analysis. Their median age was 65 (60.5 – 69.3) years and 51.6% were female (**Table 3.1**). Among the participants included, 1,085 (91.7%) were categorized as primary prevention, 27 (2.2%) were categorized as secondary prevention, and 71 (6%) had diabetes.

LLT was prescribed to 48.5% of the participants. Participants prescribed LLT were older (67, 62.6 – 70.8 vs. 63, 59.4 – 67.6 years), had a higher percentage of females (51.7% vs. 48.3%), and a greater proportion of high-risk (36.9% vs. 22%) and very high-risk participants (16.7% vs. 10.5%) and when compared with those who were not prescribed LLT (**Table 3.1**).

Table 3.1. Characteristics of the study population according to lipid-lowering therapy prescribing (N = 1,183)

	On lipid-lowering therapy N = 574 (48.5%)	Not on lipid-lowering therapy N = 609 (51.4%)	All participants N = 1,183
Age, years (median, IQR)	67.1 (62.6–70.8)	63.2 (59.4–67.6)	65 (60.5–69.3)
Total cholesterol, mmol/L (mean, SD)	4.9 (1.1)	5.5 (0.8)	5.2 (1.0)
LDL-C, mmol/L (mean, SD)	2.8 (0.9)	3.5 (0.7)	3.20 (0.9)
Triglycerides, mmol/L (median, IQR)	1.2 (0.9–1.5)	1.1 (0.7–1.4)	1.1 (0.8–1.5)
HDL-C, mmol/L (median, IQR)	1.3 (1.1–1.6)	1.4 (1.2–1.6)	1.4 (1.2–1.6)
Systolic BP, mmHg (mean, SD)	128.9 (18.5)	128.7 (18.3)	129 (18.4)
Diastolic BP, mmHg (mean, SD)	75.2 (9.9)	77.2 (10)	76.1 (10.1)
BMI, kg/m ² (mean, SD)	28.8 (4.8)	28 (7.2)	28 (6.2)
Male (n, %)	277 (48.2)	333 (54.6)	610 (51.6)
Non-smoker ^a (n, %)	296 (51.6)	329 (54.0)	625 (0.5)
Former smoker (n, %)	236 (41.1)	226 (37.1)	462 (39.1)
Current smoker (n, %)	42 (7.3)	54 (8.8)	96 (8.1)
Morbidities			
Diabetes	60 (10.4)	11 (1.8)	71 (6.0)
Moderate or severe renal impairment ^b (n, %)	56 (9.7)	23 (3.7)	79 (6.6)
Education Level			

	On lipid-lowering therapy N = 574 (48.5%)	Not on lipid-lowering therapy N = 609 (51.4%)	All participants N = 1,183
Primary level (n, %)	167 (29.0)	126 (20.6)	293 (24.8)
Second level (n, %)	279 (48.6)	318 (52.2)	597 (50.5)
Third level (n, %)	128 (22.3)	165 (27.1)	293 (24.8)
Cardiovascular disease risk:			
Primary Prevention			
Low-moderate risk (n, %)	239 (41.6)	406 (66.6)	645 (54.5)
High-risk (n, %)	212 (36.9)	135 (22.2)	347 (29.3)
Very high-risk (n, %)	96 (16.7)	64 (10.5)	160 (13.5)
Secondary prevention	27 (4.7)	4 (0.6)	31 (2.6)
Polypharmacy			
No polypharmacy (≤ 4 medicines) (n, %)	267 (46.5)	521 (85.5)	616 (60.9)
Polypharmacy (5 – 9 medicines) (n, %)	247 (43.0)	79 (12.9)	326 (32.2)
Hyper-polypharmacy (≥ 10 medicines) (n, %)	60 (10.4)	9 (1.5)	69 (6.8)

Abbreviations: BMI, body mass index; BP, blood pressure; HDL-C, high density lipoprotein cholesterol, LDL-C, low-density lipoprotein cholesterol. ^a Non-smoker is defined as people who were labelled ‘not applicable’ on answering “Are you current or former smoker?” ^b Moderate renal impairment was defined as having eGFR ≥ 30 – < 60 ml/min/1.73m² and severe renal impairment was defined as having eGFR < 30 ml/min/1.73m²

Among those prescribed LLT, statin monotherapy was prescribed to 83.6%, with 9.3% low-intensity, 73% moderate intensity, and 17.5% prescribed high-intensity statin monotherapy. In addition, 13.8% were on combination therapy including 11.8% on statin and ezetimibe and 1.9% on statin and omega-3 fatty acids. Nine participants (0.65%) were on ezetimibe monotherapy.

Among participants who were prescribed LLT, 42.1% achieved the 2011 ESC/EAS guideline defined LDL-C goals recommended for their CVD risk. Those who achieved LDL-C goals were younger (66.3, 61.9 – 71.1 vs. 67.6, 63.1 – 70.5 years), more likely to be male (55.4% vs. 43.0%) and less likely to be a current smoker (6.6% vs. 7.8%) when compared to participants who did not achieve their LDL-C goals. Those who achieved LDL-C goals were more likely to have low-moderate risk of CVD (52.8% vs. 33.4%) and more likely to be prescribed a high-intensity statin therapy (22.8% vs. 13.6%) or combination therapy (16.5% vs. 11.7%) when compared to participants who did not achieve their LDL-C goal. **(Table 3.2)**

Among those who were not prescribed LLT, 23% were among the high-risk group and 12% were among the very high-risk group who did not achieve their LDL-C goals **(Table 3.3)**. Among the very high-risk group including people with secondary prevention (n = 191), 26 (13.6%) were prescribed their target statin dose (high intensity), and 10 (5.2%) achieved their LDL-C goals (

Table 3.4).

Table 3.2. Characteristics of participants who were prescribed lipid-lowering therapy according to low-density lipoprotein cholesterol goal achievements (21) (N = 574)

	Achieved LDL- cholesterol goals N = 242 (42.1%)	Did not achieve LDL- cholesterol goal N = 332 (57.8%)
Age (years) (median, IQR)	66.3 (61.9 – 71.1)	67.6 (63.2 – 70.5)
Total cholesterol (mmol/L) (mean, SD)	4.1 (0.6)	5.4 (1.1)
LDL-C (mmol/L) (mean, SD)	2.1 (0.4)	3.3 (0.9)
Triglyceride (mmol/L) (median, IQR)	1.1 (0.8 – 1.5)	1.2 (0.9 – 1.6)
HDL-C (mmol/L) (median, IQR)	1.4 (1.1 – 1.6)	1.4 (1.2 – 1.6)
Systolic BP (mmHg) (mean, SD)	127.4 (18.4)	130.1 (18.6)
Diastolic BP (mmHg) (mean, SD)	74.8 (9.5)	75.5 (10.2)
BMI (kg/m ²) (mean, SD)	28.9 (5.2)	28.8 (4.5)
Male (n, %)	134 (55.4)	143 (43.1)
Nonsmoker ^a (n, %)	111 (45.8)	185 (55.7)
Former smoker (n, %)	115 (47.5)	121 (36.4)
Current smoker (n, %)	16 (6.6)	26 (7.8)
Education level		
Primary level (n, %)	69 (28.5)	98 (29.5)
Secondary level (n, %)	117 (48.3)	162 (48.8)
Third level (n, %)	56 (23.1)	72 (21.7)
Cardiovascular disease risk		
Primary prevention		
Low-moderate risk (n, %)	128 (52.8)	111 (33.4)

High risk (n, %)	91 (37.6)	121 (36.4)
Very high risk (n, %)	19 (7.8)	77 (23.2)
Secondary prevention	4 (1.7)	23 (6.9)
Treatment		
Non statin therapy (n, %)	1 (0.4)	14 (4.2)
Statin monotherapy (n, %)	201 (83.0)	279 (84.0)
Combination therapy (n, %)	40 (16.5)	39 (11.7)
Statin intensity		
Low intensity (n, %)	10 (4.9)	35 (12.5)
Moderate intensity (n, %)	145 (72.1)	206 (73.8)
High intensity (n, %)	46 (22.9)	38 (13.6)
Statin target dose		
Yes (n, %)	30 (32.6)	28 (15.1)
No (n, %)	62 (67.3)	158 (84.9)

Abbreviations: BMI, body mass index; BP, blood pressure; HDL-C, high density lipoprotein cholesterol, LDL-C, low-density lipoprotein cholesterol.

^a Non-smoker is defined as people who were labelled 'not applicable' on answering "Are you current or former smoker?"

Table 3.3. Characteristics of people who were not prescribed lipid-lowering therapy

	Achieved LDL- cholesterol goal N = 89 (14.6%)	Did not achieve LDL- cholesterol goal N = 520 (85.3%)
Age (years) (median, IQR)	62.9 (59.8 – 65.4)	63.2 (59.3 – 68.1)
Total cholesterol (mean, SD)	4.5 (0.6)	5.7 (0.8)
Triglyceride (median, IQR)	0.9 (0.6 – 1.4)	1.1 (0.8 – 1.4)
HDL (median, IQR)	1.4 (1.1 – 1.6)	1.4 (1.2 – 1.7)
LDL-cholesterol (mmol/L) (mean, SD)	2.4 (0.3)	3.7 (0.7)
Systolic blood pressure (mmHg) (mean, SD)	125.3 (18.2)	129.3 (18.2)
Diastolic blood pressure (mmHg) (mean, SD)	74.7 (10.6)	77.6 (10.1)
Body mass index (kg/m ²) (mean, SD)	28.5 (5.3)	28.1 (7.4)
Male (n, %)	50 (56.2)	283 (54.4)
Current smoker (n, %)	39 (43.8)	237 (45.5)
Education level		
Primary level (n, %)	19 (21.3)	107 (20.5)
Secondary level (n, %)	40 (44.9)	278 (53.4)
Third level (n, %)	30 (33.7)	135 (25.9)
Cardiovascular disease risk		
Primary prevention		
Very high-risk (n, %)	0	64 (12)
High-risk (n, %)	13 (14.6)	122 (23.4)
Low-moderate risk (n, %)	76 (85.3)	330 (63.4)
Secondary prevention	0	4 (0.8)

Polypharmacy		
No polypharmacy (≤ 4 medicines) (n, %)	75 (84.2)	446 (85.7)
Polypharmacy (5 – 9 medicines) (n, %)	12 (13.4)	67 (12.8)
Hyper-polypharmacy (≥ 10 medicines) (n, %)	2 (2.2)	7 (1.3)

Abbreviations: LDL-cholesterol, low-density lipoprotein cholesterol; HDL-cholesterol, high-density lipoprotein cholesterol

^a Non-smoker category were participants who were labelled ‘not applicable’ on answering *Are you a current or former smoker*

Table 3.4. The prescribing pattern of statin therapy among the secondary prevention group and high-risk/very high-risk participants in the primary prevention group.

	LDL-C Goal Achieved		LDL-C Goal Not Achieved	
	Very high risk (n=23) n (%)	High risk (n=104) n (%)	Very high risk (n=168) n (%)	High risk (n=243) n (%)
Statin monotherapy	19 (82.6)	73 (70.2)	84 (50)	102 (42)
At target dose	10 (52.6)	20 (27.4)	16 (19.1)	12 (11.7)
Combination therapy	4 (17.4)	18 (17.3)	12 (7.1)	16 (6.6)
Non-statin therapy	0 (0)	0 (0)	4 (2.4)	3 (1.2)
No lipid-lowering therapy	0 (0)	13 (12.5)	68 (40.5)	122 (50.2)

Statin target dose: The group of very high-risk and high-risk people who were receiving statin monotherapy at the target high-intensity statin dose as per 2011 ESC/EAS recommendations.

In multivariable logistic regression analysis, diabetes (OR 2.27; 95% CI 1.06, 4.82), polypharmacy (OR 4.74; 95% CI 3.47, 6.47) and hyper-polypharmacy (OR 8.37; 95% CI 3.92, 17.79) were associated with greater likelihood of prescription of LLT. Being male (OR 0.69; 95% CI 0.52, 0.91) and age (≤ 59 years) (OR 0.53; 95% CI 0.32, 0.86) were both associated with a lower likelihood of LLT prescription (**Table 3.5**)

Table 3.5. Odds ratios of prescription of lipid-lowering therapy from multivariable logistic regression.

Predictors for prescribing lipid-lowering therapy	Odds ratio	95% confidence interval	p-value
Age (Years)			
65 – 69	Reference		
≤59	0.53	[0.32, 0.86]	0.012
60 – 64	0.88	[0.56, 1.38]	0.595
70+	1.19	[0.82, 1.73]	0.349
Body mass index			
Normal weight	Reference		
Underweight	0.54	[0.14, 2.07]	0.372
Overweight	1.32	[0.93, 1.86]	0.109
Obese	1.15	[0.79, 1.69]	0.451
Sex			
Female	Reference		
Male	0.69	[0.52, 0.92]	0.011
Smoking status			
Non-smoker	Reference		
Former smoker	1.07	[0.81,1.42]	0.596
Current smoker	0.77	[0.46, 1.29]	0.332
Diabetes status			
No Diabetes	Reference		
Diabetes	2.27	[1.07, 4.82]	0.033
Education level			
Third level	Reference		
Primary level	1.05	[0.71,1.53]	0.804
Secondary level	0.91	[0.66, 1.24]	0.568
Cardiovascular disease risk			

Predictors for prescribing lipid-lowering therapy	Odds ratio	95% confidence interval	p-value
Low-moderate risk	Reference		
High-risk	1.34	[0.86, 2.06]	0.191
Very high-risk	1.32	[0.78, 2.24]	0.290
Polypharmacy			
No polypharmacy (≤ 4 medicines)	Reference		
Polypharmacy (5 - 9 medicines)	4.74	[3.47, 6.47]	<0.001
Hyper-polypharmacy (≥ 10 medicines)	8.36	[3.92, 17.79]	<0.001
Mean VIF	1.83		

With regard to achieving LDL-C goals (**Table 3.6**), multivariable analysis showed that people aged ≤ 59 years (OR 2.08; 95% CI 1.18, 3.67), those aged 60 – 64 years (OR 1.78; 95% CI 1.13, 2.82) and study participants aged 70+ years (OR 1.58; 95% CI 1.02, 2.45) were more likely to achieve their LDL-C goals than those aged 65 – 69 years. In addition, males were more likely to achieve LDL-C goals than females (OR 1.63; 95% CI 1.13, 2.35). Patients categorized as overweight were less likely to achieve LDL-C treatment goals compared to people categorized as normal weight (OR 0.58; 95% CI 0.36, 0.95). When the 2019 ESC/EAS guideline is applied, 14 (4.0%) of the 347 people in the high-risk group and 5 (2.6%) of the 191 people in the very high-risk group achieved the stricter 2019 LDL-C goals of <1.8 mmol/L and <1.4 mmol/L respectively (**Table 3.7**).

Table 3.6 Odds ratios of achieving low-density lipoprotein cholesterol goals from multivariable logistic regression

Predictors for goal achievements	Odds ratio	95% Confidence interval	p-value
Age			
65 – 69	Reference		
≤59	2.08	[1.18, 3.67]	0.011
60 – 64	1.78	[1.13, 2.82]	0.012
70 +	1.58	[1.02, 2.45]	0.039
Body mass index			
Normal weight	Reference		
Underweight	0.33	[0.03, 3.62]	0.368
Overweight	0.58	[0.36, 0.95]	0.030
Obese	0.62	[0.37, 1.05]	0.077
Sex			
Female	Reference		
Male	1.63	[1.13, 2.35]	0.009
Smoking status			
Non-smoker	Reference		
Former smoker	1.44	[0.99, 2.08]	0.051
Current smoker	0.93	[0.46, 1.87]	0.843
Diabetes status			
No diabetes	Reference		
Diabetes	0.93	[0.52,1.67]	0.829
Education level			
Third level	Reference		
Secondary level	0.94	[0.60, 1.46]	0.786
Primary level	0.95	[0.58, 1.57]	0.866
Mean VIF	1.19		

Table 3.7. Proportion of those deemed very high-risk (including people treated for secondary prevention) and high-risk groups who achieved the LDL-C levels recommended in the 2019 ESC/EAS guidelines.

Guidelines	LDL-C goals	High risk (n, %) N = 347	Very high risk (n, %) N = 191
2011 ESC/EAS guidelines	LDL-C <2.5 mmol/L	86 (24.7)	42 (21.9)
2019 ESC/EAS guidelines	LDL-C <1.8 mmol/L	14 (4.0)	18 (9.4)
2019 ESC/EAS guidelines	LDL-C <1.4 mmol/L	4 (1.2)	5 (2.6)

3.6. Discussion

Among this population of Irish adults attending primary care, just under one-half of participants was prescribed a LLT, primarily statin therapy. Even though 45.5% were eligible for high-intensity statin therapy, a moderate intensity statin was the most prescribed form of LLT, and just one-fifth of those within the high-risk/very high-risk or secondary prevention group were prescribed a target high-intensity statin dose. Less than 40% of those prescribed LLT achieved their LDL-C goals according to their risk category. While diabetes diagnosis was associated with prescription of LLT, males and those aged ≤ 59 years were less likely to be prescribed LLT. Furthermore, females, people aged 65 – 69 years of age and those who were categorized as overweight were less likely to achieve their LDL-C goals. Dyslipidemia is a significant modifiable risk factor for CVD (199). However, studies have shown that outpatients, whether treated for primary or secondary prevention, may not achieve recommended LDL-C goals (34,200,201). According to the Irish data analysis of the DYSIS study, 34% of Irish participants did not achieve the LDL-C goals of $<3\text{mmol/L}$ and $<2.5\text{mmol/L}$. Similarly, the German and Belgian results from DYSIS reported that 58% and 56% respectively did not achieve recommended LDL-C goals of $<3\text{mmol/L}$, $<2.5\text{mmol/L}$ and $<1.8\text{mmol/L}$ (202–204). According to the German CoRiMa study, the achievement of LDL-C goals is low overall, with 24% of 79,689 people with hyperlipidemia achieving target LDL-C levels, and only 14% of 38,484 high-risk people with coronary artery disease and/or diabetes achieving their target LDL-C level (205).

The Irish Health Service Executive has rolled out a Chronic Disease Management Programme (CDM) in general practice since 2020. The programme is targeted at specific chronic conditions including ischemic heart disease and type 2 diabetes mellitus. Data from the first four years of the programme showed that among 15,081 participants with type 2 diabetes and ischemic heart diseases, 49% had an LDL-C of < 1.8 mmol/L and 31.7% had an LDL-C of < 1.4 mmol/L. In addition, the report showed that among 31,686 participants with ischemic heart diseases, the majority of participants had an LDL-C between 1.8 – 2.5 mmol/L and 15.2% achieved an LDL-C ≤ 1.4 mmol/L (206). These findings demonstrate that achieving LDL-C goals remains a challenge, in particular among those in the very high-risk category, even among people enrolled in a targeted clinical programme.

Despite the evidence of statin efficacy among eligible individuals for primary and secondary prevention of CVD (21,207), the underutilization of statin therapy in both groups has been documented in international and national studies (52,139). Of concern in the current study are the 33% of those who were not prescribed a statin but who were classified as secondary prevention or as high-risk/very high-risk primary prevention. These results align with findings elsewhere in Europe. In the Netherlands, while 67% of high-risk people were on LLT, 7% were prescribed high-intensity statin therapy and 2% statin plus ezetimibe therapy (36). Similarly, the DA VINCI study highlighted the underutilization of LLT and non-optimal statin dose prescribing among high-risk and very high-risk people in Central-Eastern Europe (208).

In Ireland, as of 2020, there are just six designated lipid clinics, all in secondary care settings, and one specialist lipid nurse (209). This highlights the limited resources allocated to tackle dyslipidemia in Ireland and that the responsibility for managing

dyslipidemia falls mostly on general practitioners. Agar *et al.* have reported that there is no defined strategy to address lipid disorders, especially in primary care settings in Ireland (209). According to the ACS Euro Path III study, general practitioners (GPs) are limited in their care of people prescribed LLT for secondary prevention due to lack of knowledge of optimal therapies, discomfort at prescribing non-statin LLT, and hesitation in making referral to specialists for this condition (210). This emphasizes the importance of embedding a guideline-directed approach to lipid management in primary care. Such an approach could enable GPs to assess goal attainment and individualize treatment based on each patient's risk SCORE (52,210).

The findings from the present study align with those found in a retrospective cohort study conducted in the U.K., which reported that diagnosis of diabetes and being ≥ 65 years of age were strong predictors for prescribing LLT (45). However, our findings contradict those shown in a recent Dutch study, which found that females were less likely to be prescribed statin treatment than males (211). However, Kiss *et al.* included only primary prevention patients in their study (211). A 2019 survey reported that 82% of Irish females had visited their general practitioner in the previous 12 months compared to just 62% of Irish males (212). This may lead to general practitioners having greater opportunities to identify and treat dyslipidemia and CVD risk factors in female patients (45). Polypharmacy and hyper-polypharmacy may serve as markers of greater multimorbidity and clinical complexity. The observed association between these variables and LLT prescribing may reflect increased healthcare utilisation among individuals with multiple chronic conditions, providing more opportunities for cardiovascular risk assessment and treatment initiation, particularly for primary prevention (213).

Few studies have assessed variables associated with LDL-C treatment goals. Breuker *et al.* reported that very high-risk females with diabetes were less likely to achieve their LDL-C goals than similar males (46). Berteotti *et al.* reported female sex as the only independent variable associated with low probability of achieving LDL-C goals for treated and untreated high-risk participants (48). A possible explanation for this is medication non-adherence. According to a study by Nanna *et al.*, females were more likely to decline or discontinue statin therapy and were less likely to believe in the safety and effectiveness of statins than men (193).

It should be noted that the data for the present study was collected prior to the advent of biological lipid-lowering therapies such as PCSK9 inhibitors. However, at present the use of these agents is limited in Ireland and their prescription is restricted to a small number of approved prescribers (214). Given the cost of these biological agents (215) and their parenteral use, it is preferred that they are restricted to use in those at exceptionally high CV risk and those with ongoing failure to achieve goals, despite optimal treatment with oral agents (215). With just 40% of those prescribed LLT in the present study achieving their LDL-C goal, and the majority of those prescribed a statin being prescribed a moderate intensity agent, there is clear scope to expand the use of high intensity oral agents before considering the prescription of biologicals in the general practice population. Future studies should be conducted to identify facilitators and barriers that influence prescribers' implementation of guideline recommendations, and in particular, prescribing of high-intensity statins.

This study provides a valuable insight into prescribing patterns of LLT and LDL-C goal achievement in an Irish primary care setting. However, it has some limitations. It is a

cross-sectional observational study. Therefore, LDL-C levels were measured at a single timepoint only and pre-treatment LDL-C levels are not available. The sample size of the study population was large compared to the Irish arm of comparable studies such as The DA VINCI study (52), McCaughey *et al.*, 2022 (139) and Ci'fkova *et al.*, 2019 (89); however, the data were collected in a single primary care center in the greater Cork region and this may limit the generalizability of the study. In addition, data were not available on some patients and prescriber factors that may influence prescription of LLT and achievement of LDL-cholesterol goals. Such factors include medication adherence, private medical insurance, and number of prescribers in the primary care center.

Choice of statin may have been influenced at the time of data collection by guidance from the Irish Health Service Executive, which at the time recommended moderate intensity simvastatin as the first-choice statin (216). At present, there is no national electronic health record in Ireland and there exist few datasets that record both clinical parameters and medications data. Therefore, although the study data were collected in 2015, this remains is a comprehensive and relevant dataset, providing data on relevant variables including demographic factors, all variables needed to calculate SCORE and LDL-C measurements, enabling analysis of dyslipidemia management in an Irish primary care setting. The issues and patterns highlighted by this research are likely still relevant today, making this study a useful starting point for understanding ongoing trends and as dyslipidaemia management evolves in Ireland, the data presented here offer an opportunity to identify target populations and initiatives to improve care.

3.7. Conclusion

This research highlights the gap between guideline recommendations and implementation of these recommendations in real world practice. This is apparent in the inadequate achievement of LDL-C goals among people at high risk of cardiovascular events. In addition, the prescribing pattern of LLT indicates that many people remain sub-optimally treated. Further studies should be conducted to identify the barriers toward the prescribing of high intensity statins and the implementation of contemporary, more aggressive LDL-C targets in Irish primary care settings. In addition, longitudinal multicenter studies are needed to provide a robust data on dyslipidemia care in Ireland.



Elhiny, R. H. A. 2026. Patient factors affecting prescribing and outcomes in cardiovascular disease. PhD Thesis, University College Cork.

Please note that Chapters 4 & 5 (pp. 122-180) are unavailable due to a request by the author.

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CHAPTER 6. General discussion

The overall aim of the thesis was to determine dyslipidemia and hypertension control among people treated for primary prevention and people treated for secondary prevention of CVD. In addition, the thesis aimed to identify the patient and medication factors that could influence the achievement of LDL-C and BP targets in clinical practice. This chapter will discuss how the thesis has addressed these aims. (Figure 6.1)

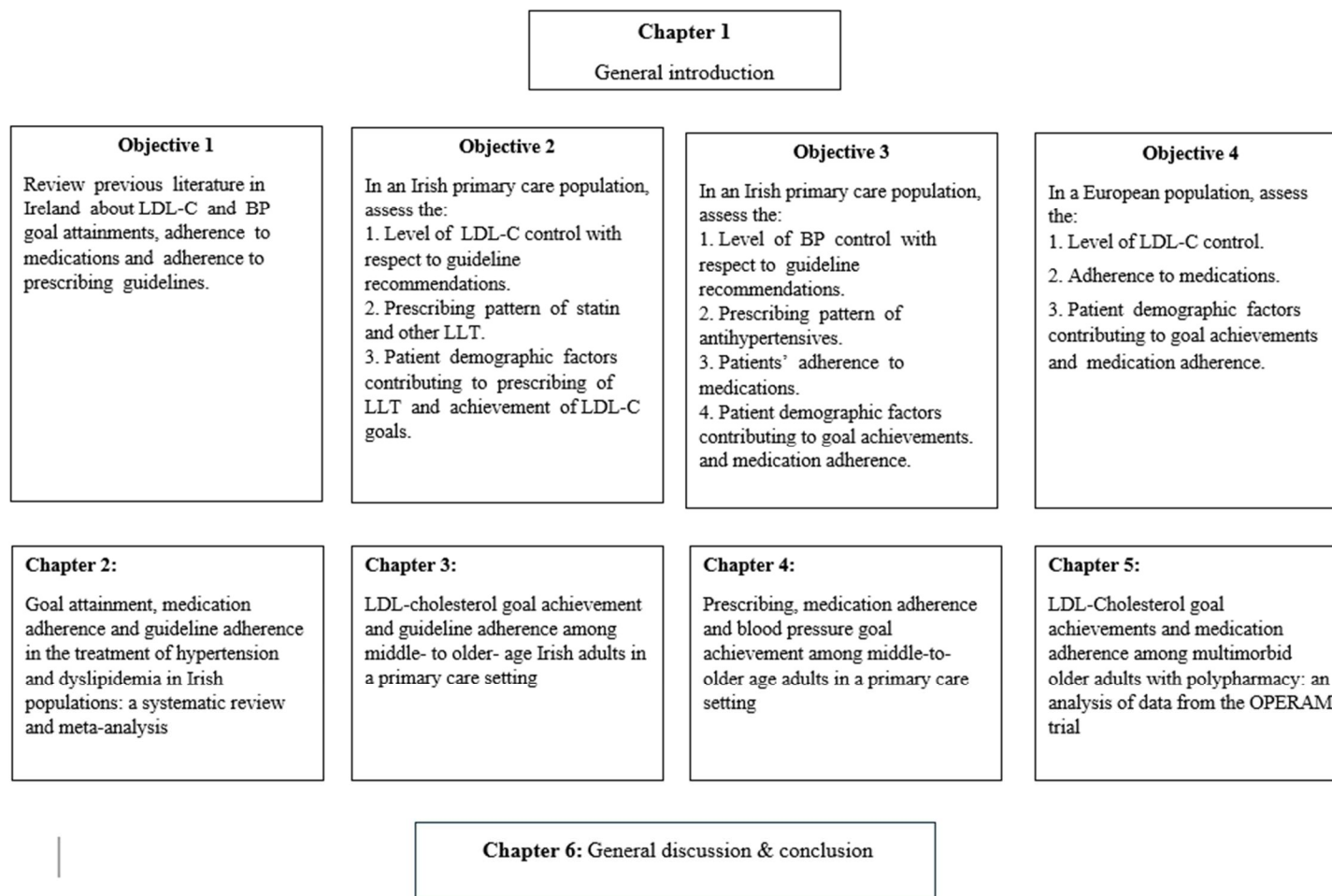


Figure 6.1

6.1. Overview of key findings and contribution to existing knowledge

This thesis demonstrates suboptimal control of LDL-C and BP among adults in primary care settings at different levels of CVD risk. It highlights the insufficient prescription of LLT among people at different levels of CVD risk and older people with multimorbidity despite guideline recommendations. It demonstrates that specific demographic factors, such as female sex and being overweight, were associated with lower odds of achieving LDL-C goals. In addition, a higher BMI (obese or overweight) was associated with lower odds of achieving BP goals as well as having a complex antihypertensive medications regimen. The prescription of medications such as LLT was higher among people with diabetes as well as people who are prescribed polypharmacy or hyper polypharmacy.

Findings from Chapter 2 show that in Ireland over the past 20 years, the prescribing of LLT was suboptimal even among people at higher risk of CVDs and the prescribing of antihypertensive medications did not align with the guideline recommendations. The level of LDL-C goal achievement was low and varied across the studies according to the risk of CVD of the patients and/or the stringency of the LDL-C goal applied. Across eleven studies reporting data for TC and LDL-C goal achievements in Ireland, six studies were included in the proportional meta-analysis. The proportion of those who achieved LDL-C goal was 69% for LDL-C <3 mmol/L, 53% for LDL-C <2.5 mmol/L, 41% for LDL-C <1.8 mmol/L and 30% for LDL-C <1.4 mmol/L. This variation was consistently observed, as LDL-C goal achievements were 58% among people treated for primary prevention and 51% among

people treated for secondary prevention. Similarly, only 56% achieved BP goal, despite applying the less strict BP cut off level of <140/90 mmHg. Medication adherence varied, depending on the assessment tool used. While adherence to antihypertensive medications was found to be satisfactory, limited adherence data was reported among people prescribed LLT. The review identified some gaps in the literature including the patient and medication factors that could influence the prescribing of LLT and achieving the optimal control of LDL-C and BP. In the updated search, conducted in March 2026, four further studies were identified. Findings from these studies were consistent with the previously included studies in the review.

In chapter 3, the study findings showed that almost half of a cohort of middle-to-older aged Irish adults in a primary care setting were prescribed LLT. People with diabetes diagnosis and people with polypharmacy or hyper-polypharmacy were more likely to be prescribed LLT, while males and people aged <59 years were less likely to be prescribed LLT. The prescribed statin intensities were not aligned with the participants' CVD risk, LDL-C goal achievement was suboptimal on applying the 2011 ESC/EAS goals and poor control was also found when applying the strict goals recommended in the 2019 ESC/EAS guidelines. Females and those who were overweight were less likely to achieve goals.

In chapter 4, findings from the same middle-to-older age Irish cohort showed a suboptimal control of BP among people with prescribed antihypertensive medications according to the 2013 ESH/ESC guidelines, with a lower proportion of people achieving the stricter BP goals in the 2024 guidelines. Females in this cohort were more likely to be adherent to their antihypertensive medications than males. People on multiple antihypertensive tablets (whether FEC or SPC) had poorer control of their BP compared to

those on a single antihypertensive. Medication non-adherence, and being overweight or obese, were associated with a lower likelihood of achieving the 2024 goals. Polypharmacy and hyper-polypharmacy were determinants of achieving the 2024 goals.

In chapter 5, findings from a cohort of older aged adults with polypharmacy and multi-morbidities across four European centers showed suboptimal LDL-C control across all four centers. This emphasises that the challenge of effectively controlling LDL-C in people at risk of CVD extends beyond Ireland and across a wide range of age groups. Consistent with the findings in chapter 3, females were less likely to achieve LDL-C goals than males. Results showed that people treated for primary prevention of CVD had a higher likelihood of achieving goals compared to people treated for secondary prevention.

The thesis findings align with international findings regarding dyslipidemia and hypertension control, reported in the literature. CVDs are the second main cause of mortality in Ireland, with around 9,500 people dying from CVD each year. Statistics showed that 600,000 people in Ireland live with CVD, with almost 7,500 people experiencing stroke and 6,000 people experiencing heart attack each year. Although 80% of these conditions are preventable, the second report of the Structured CDM Programme conducted for years 2020–2024 demonstrated the suboptimal control of modifiable risk factors such as LDL-C and BP among participants at baseline, with a proportion continuing to have poor risk factor control by their third annual visit (206).

Despite the strong evidence of the relationship between cholesterol and developing ASCVD, dyslipidemia control remains suboptimal (36,47,48,50–52,272). Despite the strong evidence supporting the use of LLT, particularly among people treated for primary prevention who at high risk and very high risk of developing CVD and among people

treated for secondary prevention, underutilization of LLT is well documented in real-world studies, including the studies in this thesis, with a large proportion of people having no documented LLT despite failing to attain LDL-C goals (54,55,114,177). In addition, epidemiological studies show that the choice of LLT regimen favors statin monotherapy over combination therapy, alongside an under-prescription of high intensity statin, even among people at high and very high risk of CVD, which aligns very well with the findings of this thesis (54,142,279). Findings from administrative claims and patients' charts showed that 48% of people were not treated according to guideline recommendations, with many patients with ASCVDs not being prescribed a high intensity statin (280). Similarly, baseline findings from a data registry in the U.S. showed that only 44% and 9% of people with ASCVD were prescribed high intensity statin and ezetimibe respectively (281). In fact, Silverman *et al.* showed that the reduction in ASCVD risk with LLT is directly associated with the absolute LDL-C reduction, suggesting that other treatments that mainly work by up-regulation of LDL-C receptors could be additional therapeutic options (26,252). In addition, doubling the dose of statin can only result in a further reduction in LDL-C by 6%, while combination therapies such as high intensity statin plus ezetimibe can reduce LDL-C by 60% from baseline (282,283). This indicates the appropriateness of combination therapy as initial treatment for very high risk and high risk people to achieve the latest strict goals in 2019 ESC/EAS guidelines (282,283). A simulation based on the DA VINCI study showed that escalating the statin dose to high intensity statin among people treated for primary prevention could lead to 27% of patients achieving their 2019 ESC/EAS goals. However, stepwise addition of ezetimibe to high intensity statin could result in 57% of patients achieving LDL-C goals. In the same study, the addition of PCSK9i

could result in 88.1% of very high risk patients without ASCVD achieving their recommended 2019 ESC/EAS goals. On the other hand, among people with ASCVD, intensifying the statin dose would result in 12% achieving their goals, with 42.1% and 93.2% achieving the goal with a further addition of ezetimibe or PCSK9i, respectively (284).

Taken together, this evidence suggests that there is a lag time in implementing guidelines in clinical practice. One potential reason for this consistent observation is that prescribers underestimate patients' CVD risk especially when treating people without any documented CVD (285). Clinical inertia is another factor underlying the failure to initiate and intensify LLT (47). This could be attributed to time constraints in clinical practice, in addition to the evidence demonstrating the reluctance in monitoring LDL-C levels after initiating LLT despite people not achieving their recommended LDL-C goals (47,286). It is important to note that the data collection in chapters 3 and 5 happened before the advent of new biological LLT such as PCSK9i, siRNA-based treatment like inclisiran and novel oral agents such as bempedoic acid, which have efficacy in reducing LDL-C, with minimal intolerance among patients. In addition, these medications have been proven to reduce adverse CVD events. However, prescribing these medications is limited in Ireland and internationally due to the reimbursement constraints (272,282,287–289). PCSK9i eligibility criteria in Ireland includes a diagnosis of MI or CABG, an LDL-C >4.0 mmol/L and treated with high dose statin and ezetimibe (290). A retrospective analysis in Ireland showed that among 299 patients who were at very high risk of CVD, and eligible for PCSK9i treatment according to the ESC/EAS guidelines, only 1 patient was eligible for PCSK9i based on the Irish criteria (290).

An important finding from this thesis is the gender difference in prescribing LLT and in attaining LDL-C goals. Findings in chapter 3 showed that females were more likely to be prescribed LLT than males; however, results in chapter 3 and chapter 5 highlight that females are less likely to achieve the recommended LDL-C goals. Although previous studies reported higher rates of statin prescribing among males than females (211,279), females were less likely to be prescribed high intensity statin therapy compared to males even when having a similar risk profile (291–293). In addition, it is reported that females are more likely to discontinue their medications and more likely to experience statin intolerance, which could be reasons for not attaining LDL-C goals compared to males (291–293). Medication adherence is another contributing factor to achieving LDL-C goals, in particular the stricter goals (105,258,275). Our findings in chapter 5 showed that more than half of older aged multimorbid people who were prescribed LLT were considered low/medium adherent to their medications. Among people with prescribed LLT, adherence to these medications is generally satisfactory among those newly prescribed (279). However, non-persistence and discontinuation of medication are commonly documented, in particular in those treated for primary prevention of CVD. Consequently, non-persistence and discontinuation of medication could be a reason for failure to achieve LDL-C goals (105,279,294). Generally, females are less likely to adhere to LLT and more likely to discontinue treatment compared to males, which in some cases could be attributed to the statin-associated muscle symptoms (292,295).

Consistent with previous literature, our findings showed that BP control is suboptimal in the populations studied, with many patients not meeting the <140/90 mmHg guideline goal and a higher proportion not achieving the stricter <130/80 mmHg goal

(84,87,115,220,221). Our findings are limited to people with prescribed antihypertensive medications; however TILDA findings over 12 years showed that the prevalence of hypertension among older Irish adults increased from 63% to 71%, with a wide range of people not being aware of having hypertension (178). In addition, findings from the CDM in Ireland showed that almost 43% of 43,600 people had a systolic BP above >140 mmHg despite participating in the structured programme (206). This reflects a gap between clinical guidelines and applying the guidelines in clinical practice, where detecting hypertension among individuals is challenging in primary care due to some healthcare factors such as time constraints, uncertainty about the BP levels and distrust of the evidence regarding BP management among GPs (178,296). In chapter 4, in alignment with international literature, single antihypertensive therapy is often favored over combination therapy, despite guidelines recommending intensification of therapy. Similar to issues identified with intensification of LLT, this may be due to clinical inertia (84,153,178,223). In contrast, guideline recommendations advocate for initiating treatment with antihypertensive combination therapy, due to evidence of greater efficacy when two antihypertensives targeting different mechanisms are used (58,60,297). In addition, this approach showed less adverse effects such as hypotension, even among people with grade 1 hypertension, leading to better persistence (297,298). Findings in chapter 4 showed a negative association between having more than one antihypertensive and achieving the optimal control of BP. This finding may support the guideline recommendations that favor the use of single pill combinations.(299).

Our findings and those of two previous studies showed that gender differences were observed in medication adherence, with females self-reporting higher medication

adherence compared to males (243,300). However, another study has shown that gender difference does not significantly affect medication adherence overall. However, predictors of low medication adherence are different between males and females (300). For example, reduced sexual functioning and elevated BMI were associated with low adherence in men compared to women, while dissatisfaction with communication with healthcare providers and depression were associated with low adherence in women compared to men (300).

Alongside the gender difference that has been highlighted in the thesis findings, there were some patient factors and medication factors influencing the prescription of medications and the achievement of LDL-C and BP goals.

Diabetes diagnosis, polypharmacy and hyper-polypharmacy predicted prescribing of LLT. This may indicate that the prescribing of LLT in clinical practice is significantly influenced by the presence of co-morbidities and having frequent interactions with healthcare providers, in particular among those who are treated for primary prevention (213). CVD risk score was not associated with the prescription of LLT.

The studies in this thesis have demonstrated associations between specific patient demographic factors and achieving optimal control of LDL-C and BP. Patients' BMI influenced the control of LDL-C and BP, with overweight and obese people demonstrating lower likelihood of achieving the LDL-C control and BP control compared to people in a normal weight category. Previous studies reported a direct relationship between being overweight or obesity and hypertension (71,301,302), with a study suggesting that 40% of hypertension cases could be attributed to obesity (302). In addition, evidence showed a dose-response relationship of about 1 mmHg reduction in BP per a kilogram of weight loss among people with established hypertension (71). This emphasises the crucial impact of

lifestyle modification alongside pharmacological therapy in achieving optimal control of CVD risk factors such as LDL-C and BP and is consistent with guideline recommendations (24,60).

The overall findings in the thesis demonstrate suboptimal control of CVD risk factors, in particular dyslipidemia and BP in clinical practice across a wide age range of adults in both Ireland and Europe. This highlights the significant challenge in controlling CVD risk factors in clinical practice, which become even greater when applying the strict guideline recommended goals in the recent years (52,122,124). The optimal control of CVD risk factors cannot happen without focusing on tailoring antihypertensive and LLT medication according to the patients' CVD risk rather than the number of co-morbidities (272,285,303). Therefore, increasing prescribers' awareness about the latest guideline recommendations is essential. In addition, monitoring patients with frequent follow-up is needed to overcome clinical inertia and encourage adherence to antihypertensive and LLT medications (47,304). The provision of tailored, personalized interventions for medication adherence that are designed to help each individual to follow medical recommendations according to their clinical needs is recommended (299,305). Pharmacist interventions including delivering patients' education and healthcare provider educations, changing medications and patient reminders have demonstrated significant improvements in controlling high BP(306,307). A meta-analysis of 100 studies has reported a significant reduction in systolic BP -5.3 mmHg (95% CI -6.3,-4.4) and diastolic BP -2.3 mmHg (95% CI -2.9,-1.8) (307). Similarly, a meta-analysis of 12 studies has confirmed that pharmacists interventions resulted in significant improvements in BP control among people with diabetes and hypertension. The improvement involved the reduction of the mean systolic

BP -7.2 mmHg (95% CI -12.5,-1.9) and the mean diastolic BP -4.1 mmHg (95% CI -6.9,-1.4) (306). Medication reviews conducted by clinical pharmacists in a hypertension clinic have led to a significant increase in the prescribers' compliance with guideline recommendations among people with antihypertensive medications. The prescribers' acceptance rate of these recommendations has reached 59.1% (83). A cost-effectiveness analysis of pharmacist- interventions in the primary care setting shows that when pharmacists spent 2 hours every 9 months counselling and educating each patient about adverse events and medication adherence, a significant 6 mmHg reduction in systolic BP and 2.9 mmHg reduction in diastolic BP was observed (308). The intervention cost \$22.55 for each 1 percentage point improvement in BP control. In addition, fewer physician visits were reported in the intervention group, saving the physician time for more complex patients (308).

Clinician-patient discussion is essential in managing long-term conditions, in particular silent and/or symptomless conditions such as hypertension and dyslipidemia as the risks of treatment may appear to outweigh potential benefits (24). Therefore, involving patients in making decisions regarding their treatments and navigating treatment options with them is essential for ensuring their adherence to medications (309). Decision aids are one of the tools that help engage patients with their treatment plan. Decision aids include pamphlets, videos, or web-based resources that describe the options available to patients and outline the decisions to be made (310). These decision aids increase patients' knowledge and understanding of the benefits and harms of a treatment option, and help the patient to choose options that reflect what is necessary for them (310).

6.2. Strength and limitations:

This thesis provides insights into management of dyslipidaemia and hypertension in clinical settings in Ireland and Europe including the level of goal achievements, prescribing pattern of medications and adherence to medications among patients. The studies in the thesis included patients at different levels of CVD risk including people treated for primary prevention and people treated for secondary prevention. At present, there is no national electronic health care record in Ireland; therefore few datasets linking clinical parameters and medication data are available. The Mitchelstown Cohort Rescreen is one such dataset and while it is limited by being set in a single large primary care centre, it is enriched by its comprehensive data relating to the research question. In addition, Irish participants in the OPERAM clinical trial were patients of Cork University Hospital, a large Irish teaching hospital in serving a population of 1.1 million people in the South-west region of Ireland. The findings from the Mitchelstown Cohort Rescreen are consistent with findings from the Cork cohort of the OPERAM trial suggesting that CVD risk factors control remains a challenge across different healthcare settings. In addition, the consistency with the other three centers reflects the international context of the challenges in controlling CVD risk factors.

Adherence to antihypertensive medications and LLT was assessed using self-reported methods which may result in underestimation of non-adherence due to recall bias. However, self-reported assessments of medication adherence is a practical method for measuring adherence in clinical care because of their low cost, non-invasiveness and their flexibility in the timing and mode of administration. In the thesis, two self-reported methods were used. Medication adherence data was not available in chapter 3 as the

adherence measure used in the Mitchelstown Cohort Study rescreen was relevant to hypertension only. Therefore, the brief validated self-reported 3-item measure described by Voils *et al.*, was used to assess the extent of medication non-adherence to antihypertensive medications in chapter 4 and the Scale MMAS-8 was used to assess medication adherence in chapter 5. The 3-item survey developed by Voils *et al.* is validated for hypertensive populations (111). The MMAS-8 Scale has higher psychometric properties than the 4 items-MMAS.

One of the challenges in this thesis was missing data, which is a common challenge in medical and epidemiological research. Multivariate imputation by Chained Equation (MICE) was performed to handle missing data in chapters 4 and 5. MICE was chosen to address missing data in the datasets used in the thesis because it produces estimates and standard errors that are asymptotically unbiased and efficient. In addition, it can handle different variable types. The key concept of MICE is to use the distribution of observed data to estimate a set of plausible values for missing data. This happened in the first step, followed by analyzing each imputed dataset separately. The overall estimate is conducted by combining the estimates from all datasets and the variances-covariances matrix using Rubin's rule (311). This approach aims to limit the reduction in the statistical power due to small sample size and the selection bias that might arise within the collected data.

The research team sought to identify more recent datasets throughout the research period but no Irish dataset with post-2020 data was available during the research period that could address the aim and objectives of the thesis. While the datasets were collected independently and all the researchers involved in this thesis had no involvement in the data collection process, the professional contacts with the data collectors and data managers of

the Mitchelstown Cohort Study and OPERAM enabled clarification of methodology for collecting the variables and enhanced understanding of the datasets.

6.3. Conclusion

This thesis provides a description of dyslipidemia and hypertension control among middle – to- older age adults in Irish and European settings across the spectrum of CVD risk level. The findings show a suboptimal control of these major risk factors. It highlights the considerable gap between guideline recommendations and applying these recommendations in clinical practice, especially the underutilization of LLT among older aged adults and among adults who were at very high risk and high risk without ASCVD. In addition, it highlights the underutilization of high potency statin and combination therapies despite the guideline recommendations. A similar pattern was evident with hypertension control, including a reluctance to prescribe combined antihypertensive formulations. This work highlights the influence of patient demographic factors, in particular age, sex, body mass index, education level, polypharmacy and patients' cardiovascular risk level on the control of these conditions. It stresses the importance of individualized medicines optimization based on each patient's CVD risk, and tailoring medication use to achieve optimal control of dyslipidemia and hypertension. Findings in the thesis show that medication adherence is a contributing factor that may enhance achieving the tight goals recommended in the latest guidelines. These findings encourage the frequent assessment of medication adherence and adherence support for patients,

especially those who are treated for primary CVD prevention to ensure optimal lipid and blood pressure control.

6.4. Future work

In the Irish context, future longitudinal studies are needed, due to the implementation of the CDM programme, which includes all adults with publicly funded general practice visits who have been diagnosed with a chronic disease, to monitor and assess the effectiveness of this intervention on CVD risk factors control. This would be facilitated by the introduction of a national electronic health record in Ireland. Comparison of Irish primary care data to the European/international data would highlight the differences in clinical practice and encourage the adoption of successful strategies. In addition, it will enhance the generalizability of the data and help in detecting the independent factors that could influence clinical outcomes so that intervention designs can be targeted to these particular populations.

Internationally, qualitative research is required to explore the challenges and/or barriers that prescribers encounter in primary care settings. In addition, qualitative research is required to explore patients' satisfaction level toward the healthcare provided in primary care settings and explore their perspectives about their management and incorporating pharmacists in clinical practice. Further qualitative research in collaboration with social scientists to explore the reasons behind the differences between men and women with regard to goal achievement, medication adherence and prescribing. Future research is needed to further identify behaviour change interventions for patients and prescribers. Such behaviour change techniques may be delivered by traditional methods or in recent times it has been suggested that Gen-AI tools such as GenAI-powered FAQs and AI-powered healthcare chatbots could be effective in delivering such interventions.

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APPENDICES

Appendix 1 Total cardiovascular risk assessment systems (27)

System	Risk	Variables
Framingham models	10-year risk of CHD events	Gender, age, TC, HDL-C, SBP, smoking status, diabetes, hypertensive treatment
Systematic Coronary Risk Estimation (SCORE)	10-year risk of CVD mortality	Gender, age, TC or TC/HDL-C ratio, SBP, smoking status
ASSIGN (CV risk estimation model from the Scottish Intercollegiate Guidelines Network)	10-year risk of first CVD event	Gender, age, TC, HDL-C, SBP, smoking (number of cigarettes), diabetes, area-based index of deprivation, family history
QRISK2	10-year risk of first CVD event	Gender, age, TC to HDL-C ratio, SBP, smoking status, diabetes, area-based index of deprivation, family history, BMI, antihypertensive treatment, ethnicity, rheumatoid arthritis, CKD stages 4–5, AF
Prospective Cardiovascular Munster Study (PROCAM)	Two separate scores calculate 10-year risk of major coronary events and cerebral ischaemic events	Age, gender, LDL-C, HDL-C, diabetes, smoking, SBP
Reynolds Risk Score	10-year risk of incident myocardial infarction, stroke, coronary revascularization, or CV death	Gender, age, SBP, smoking, high-sensitivity C-reactive protein, TC, HDL-C, family history of premature MI (parent aged <60 years), HbA1c if diabetic
CUORE	10-year risk of first CVD event	Age, gender, TC, HDL-C, diabetes, smoking, SBP, hypertensive treatment
Pooled Cohort equations	10-year risk of CVD event	Age, gender, TC, HDL-C, diabetes, smoking, SBP, hypertensive treatment, race
Globorisk	10-year risk of CVD mortality	Age, gender, smoking, SBP, diabetes, TC

AF, atrial fibrillation; BMI, body mass index; CHD, coronary heart disease; CKD, chronic kidney disease; CV, cardiovascular; CVD, cardiovascular disease; HbA1c, glycated haemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction, SBP, systolic blood pressure; TC, total cholesterol

Appendix 2 Systematic review protocol



Guideline adherence, medication adherence and goal attainment in the treatment of hypertension and dyslipidaemia in Irish populations: a systematic review

Rehab Elhiny, Linda M O'Keeffe, Elizabeth O. Bodunde, Stephen Byrne, Maria Donovan, Margaret Bermingham

To enable PROSPERO to focus on COVID-19 submissions, this registration record has undergone basic automated checks for eligibility and is published exactly as submitted.

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Citation 1 change

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<https://www.crd.york.ac.uk/PROSPERO/view/CRD42023422050>

REVIEW TITLE AND BASIC DETAILS

Review title

Guideline adherence, medication adherence and goal attainment in the treatment of hypertension and dyslipidaemia in Irish populations: a systematic review

Review objectives

What are the levels of guideline adherence among people diagnosed with hypertension and dyslipidaemia in Ireland ?

What are the levels of medication adherence among people diagnosed with hypertension or dyslipidemia in Ireland?

What are the levels of achievement of blood pressure and LDL-Cholesterol targets among people diagnosed with hypertension or dyslipidemia in Ireland?

SEARCHING AND SCREENING

Searches

This systematic review will follow The Preferred Reporting Items for Systematic Reviews and MetaAnalysis (PRISMA) 2020 checklist

Databases: Scopes, PubMed, CINAHL, Embase and WebScience

There will be no restriction on the language or the date of the publication.

Study design

It is expected that this review will identify studies using a wide range of research designs; observational studies including cohort studies, case-control studies, cross-sectional studies, and experimental studies including interventional studies in particular will be included. Systematic reviews, literature reviews, and meta-analyses, conference abstracts, articles without full texts available, and qualitative reports will be excluded.

ELIGIBILITY CRITERIA

Condition or domain being studied

Medication adherence, guideline adherence, and levels of blood pressure and LDL-Cholesterol goal attainment.

Population

Participants aged ≥ 18 years, diagnosed with hypertension or dyslipidemia and treated for these conditions, or treated for secondary prevention of cardiovascular disease with blood pressure or lipid-lowering medications.

Intervention(s) or exposure(s)

Prescriber adherence to guideline recommendations, medication adherence among people with hypertension or dyslipidemia, and blood pressure and LDL-Cholesterol goals attainment.

Comparator(s) or control(s) NA

Context

Studies in any setting in Ireland will be included.

OUTCOMES TO BE ANALYSED

Main outcomes

The primary outcomes are to determine (i) levels of guideline adherence among prescribers, (ii) the proportion of people who adhere to the anti-hypertensive and lipid lowering medications based on direct or indirect methods of estimating medication adherence, and (iii) to determine the proportion of people who could achieve the blood pressure and LDL-cholesterol goals based on guideline recommendations during the study.

Additional outcomes

Secondary outcomes include (i) identifying the tools used to measure the adherence and (ii) demographic factors influencing primary outcomes and (iii) comorbidities that influence the primary outcomes.

DATA COLLECTION PROCESS

Data extraction (selection and coding)

The results identified from the different database searches will be managed using reference management software (Zotero). Duplicates will be removed before the initial screening in the software. Titles and abstracts for the remaining articles will be screened by two authors, and at this stage irrelevant articles will be excluded. Two authors will independently screen all full text of the remaining articles against the inclusion criteria to identify studies eligible for inclusion and record the reasons for excluding the remaining articles. If disagreement occur at any stage, a decision will be taken based on a discussion between the reviewers or then through adjudication by another member of the research team. Data will be extracted by authors using a predefined data extraction worksheet in Microsoft Excel. The extracted data will be the article title, the first author name, year of publication, study objectives, study setting, study design, number of participants, participant mean age, participant gender (%), participants type i.e. hypertensive, hyperlipidemic, secondary prevention; guidelines used in the study, participant demographics, co-morbidities, and risk factors (%), target blood pressure or target LDL-cholesterol level, guideline adherence outcome, medication adherence outcome, blood pressure and LDL-cholesterol targets outcome.

Risk of bias (quality) assessment

The risk of bias will be assessed by the authors using the National Heart, Lung, and Blood Institute Quality Assessment Tool for Observational Cohort and Cross-sectional

Studies. The authors will provide quality appraisal of articles. One author will assess all articles and the second reviewer will assess a defined proportion of the articles. If disagreements arise, they will be resolved through discussion and referral to a third reviewer for adjudication if necessary. Studies will be included in the review regardless of the findings of the quality assessment but scores and quality of the articles selected will be considered and included in a data extraction table.

PLANNED DATA SYNTHESIS

Strategy for data synthesis

Narrative synthesis will be used as there will be multiple outcomes in this systematic review. The main reason for choosing the narrative approach is the presence of considerable heterogeneity between the primary studies including the study population, setting, study design, and outcomes.

Findings from the included articles will be grouped, narratively summarized and compared. Findings such as differences in the levels of medication adherence or goal attainment in primary care and secondary care, or according to age or sex, will be discussed. We will use the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) flow diagram to summarize the screening process during the review.

Analysis of subgroups or subsets Non planned.

REVIEW AFFILIATION, FUNDING AND PEER REVIEW

Review team members 1 change

- Ms Rehab Elhiny, Pharmaceutical Care Research Group, School of Pharmacy, University

College Cork, Cork, Ireland; Clinical Pharmacy Department, Faculty of Pharmacy, Minia University, Minia, Egypt.

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Integrative Epidemiology Unit at the University of Bristol, University of Bristol, Bristol, UK; Population Health Sciences, Bristol Medical School, University of Bristol, Bristol, UK.

- Ms Elizabeth O. Bodunde, School of Public Health, College of Medicine and Health, University

College Cork, Cork, Ireland. The Irish Centre for Maternal and Child Health Research, University College Cork, Cork, Ireland.

- Professor Stephen Byrne, Pharmaceutical Care Research Group, School of Pharmacy, University College Cork, Cork, Ireland.

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Review affiliation

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Funding source

Egyptian Government Scholarship for Postgraduate Studies.

Named contact

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TIMELINE OF THE REVIEW

Review timeline

Start date: 22 November 2022. End date: 01 September 2023

Date of first submission to PROSPERO

16 May 2023

Date of registration in PROSPERO

27 May 2023

CURRENT REVIEW STAGE

Publication of review results

The intention is to publish the review once completed. The review will be published in English

Stage of the review at this submission 1 change

Review stage	Started	Completed
Pilot work	✓	✓

Formal searching/study identification	✓	✓
Screening search results against inclusion criteria	✓	✓
Data extraction or receipt of IP	✓	✓
Risk of bias/quality assessment	✓	✓
Data synthesis	✓	✓
Review status		

The review is completed.

ADDITIONAL INFORMATION

PROSPERO version history

- Version 1.2 published on 23 Mar 2024
-
- Version 1.1 published on 27 May 2023
-

Version 1.0 published on 27 May 2023

Review conflict of interest None known

Country

Ireland

Medical Subject Headings

Cholesterol, LDL; Dyslipidemias; Goals; Guideline Adherence; Humans; Hypertension; Ireland

Revision note 1 change

A proportion meta-analysis is conducted to estimate the overall proportion of participants who attained the BP goals and LDL-C goals recommended by the guidelines.

Disclaimer

The content of this record displays the information provided by the review team. PROSPERO does not peer review registration records or endorse their content.

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Appendix 3 Search strategy adopted for each electronic database

1. Cardiovascular disease*
2. Heart disease*
3. Cerebrovascular disease*
4. Cerebrovascular disorder*
5. Coronary heart disease
6. Coronary artery disease
7. Ischemic heart disease
8. CAD
9. CVD
10. CHD
11. IHD
12. Stroke
13. Atherosclerosis
14. HTN
15. Hypertens*
16. High blood pressure
17. Systolic
18. Blood pressure
19. DBP
20. SBP
21. BP
22. Diastolic
23. Dyslipidemia
24. Hypercholesteremia
25. Hypercholesterolemia

26. Hyperlipidemia
27. Cholesterol
28. Lipoprotein*
29. LDL
30. ldl-cholesterol
31. Triglyceride*
32. Lipid*
33. HDL
34. Low density lipoprotein
35. Hypertriglyceridemia
36. apolipoprotein B
37. Apo-B
38. Patients Compliance
39. Patient Compliance
40. Medication adherence
41. Patient nonadherence
42. Patients non-adherence
43. Persistence
44. Patient constancy
45. Adherence
46. Concordance
47. Compliance
48. Patient noncompliance
49. Medication nonadherence
50. Guideline adherence
51. Guideline compliance
52. Guideline implementation
53. Underutilization evidence-based therapies

54. Guideline nonadherence
55. Guideline directed medical therapies
56. GDMT
57. Target* achieve*
58. Goal* achieve*
59. Target* attain*
60. Goal* attain*
61. Therapeutic goal
62. Ireland
63. Republic of Ireland
64. Irish
65. Northern Ireland

Search strategy		Terms
Group A	Each group searched separately, then combined together with “OR”	#1#2#3#4#5#6#7#8#9#10#11#12#13
		#14#15#16#17#18#19#20#21#22
		#23#24#25#26#27#28#29#30#31#32#33#34#35#36#37
Group B	Each group searched separately, then combined together with “OR”	#38#39#40#41#42#43#44#45#46#47#48#49
		#50#51#52#53#54#55#56
		#57#58#59#60#61
Group C	Combined together with “OR”	#62#63#64#65
“AND”		
Group A, B & C were combined together with		

Appendix 4 The National Heart, Lung, and Blood Institute Quality Assessment Tool for Observational Cohort and Cross-sectional Studies

Study	1	2	3	4	5	6	7	8	9	10	11	12	13	14	Quality Rating
The Davinci,2022 (52)	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	NR	NA	No	Fair (9)
M. Dunne,2013 (122)	Yes	Yes	NR	Yes	No	Yes	Yes	Yes	Yes	No	Yes	NR	NR	No	Fair (8)
Peter Hayes, 2019 (150)	Yes	Yes	yes	Yes	Yes	Yes	No	Yes	NR	No	yes	NA	NA	Yes	Fair (9)
Paul Dillon,2018(148)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	CD	No	Yes	Good (12)
San Kim, 2017(151)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	yes	NR	Yes	No	Good(12)
Stephen Murphy, 2015 (147)	Yes	Yes	CD	Yes	No	Yes	Yes	Yes	CD	Yes	CD	NR	CD	Yes	Fair (8)
James M. G. Curneen,2022(149)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NR	No	Yes	Good (12)
Paul Dillon,2019(152)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	NR	Yes	Yes	Good(12)
Caroline A. Walsh, 2019(146)	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	CD	Yes	NR	Yes	Yes	Good (11)

Study	1	2	3	4	5	6	7	8	9	10	11	12	13	14	Quality Rating
Margaret Bermingham, 2011 (143)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NR	NA	Yes	Good (12)
Danielle Ní Chróinín, 2018 (49)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	NA	NR	Yes	Good (11)
Catriona Murphy, 2015 (142)	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	yes	NA	Yes	NR	NA	Yes	Fair (10)
Kornelia Kotsevaa,2009(51)	Yes	Yes	CD	No	Yes	Yes	No	Yes	Yes	CD	Yes	NR	NA	No	Fair (7)
Ifeanyi Okechukwu,2007 (153)	Yes	Yes	Yes	Yes	Yes	CD	Yes	CD	Yes	No	Yes	CD	NA	Yes	Fair (9)
Kornelia Kotseva,2016(50)	Yes	Yes	Yes	No	No	Yes	No	Yes	Yes	NA	Yes	NR	Yes	No	Fair (8)
K. Kotseva,2007 (141)	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	NA	Yes	NR	NA	Yes	Fair (10)
Renata Cí'fkova',2019 (89)	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Yes	NA	NR	Yes	Fair (9)
Anselm K. Gitt, 2016(138)	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	NA	Yes	NR	NA	No	Fair (8)

Study	1	2	3	4	5	6	7	8	9	10	11	12	13	14	Quality Rating
Brendan Buckley,2009(124)	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	CD	Yes	CD	Yes	Yes	Good (11)
Conor McCaughey, 2022 (139)	Yes	Yes	NR	Yes	Yes	Yes	Yes	Yes	Yes	CD	Yes	NR	NA	No	Fair (9)
A.A Syed, 2010(154)	Yes	Yes	Yes	Yes	No	Yes	CD	No	No	No	Yes	NR	NA	No	Fair (6)
Keating,2022(145)	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	CD	No	CD	NR	NA	No	Fair (7)
Kotseva, 2001(140)	Yes	Yes	Yes	No	No	Yes	No	Yes	Yes	NA	Yes	NR	NA	Yes	Fair (8)

Appendix 5 Population categories, LDL-cholesterol goals, and statin subcategories.

	Population category	Cardiovascular disease risk category	Criteria
2012 European Guidelines on cardiovascular disease prevention in clinical practice: The Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice	Secondary prevention group	Very high-risk	1. ischemic heart disease 2. acute MI 3. atherosclerosis 4. PAD 5. cerebrovascular diseases (stroke and transient ischemic attack)
	People with diabetes	Very high-risk	Type I & Type II with one or more risk factors (such as smoking, total cholesterol >8mmol/L, Systolic BP >180mmHg)
		High-risk	Type I & Type II with no risk factors
	People with estimated	Very high-risk	Severe impairment eGFR <30ml/min/1.73m ²

	glomerular filtration rate (eGFR)	High-risk	Moderate impairment: eGFR $\geq 30 - < 60$ ml/min/1.73 m ²
	Primary prevention	People were categorized based on their score into: 1. Very high-risk 2. High-risk 3. Low moderate risk	Score algorithm for people aged ≤ 65 years
			The updated 10 year-risk estimate of fatal and non-fatal cardiovascular diseases (SCORE2 and SCORE2-OP)
			The updated 10 year-risk estimate of fatal and non-fatal cardiovascular diseases (SCORE2-OP)
2011 ESC/EAS Guidelines for the management of dyslipidemia	LDL-cholesterol goals	Very high-risk	LDL-cholesterol < 1.8 mmol/L
		High-risk	LDL-cholesterol < 2.5 mmol/L
		Low-moderate risk	LDL-cholesterol < 3.0 mmol/L
2016 ESC/EAS guidelines for the management of dyslipidemia		Very high-risk	LDL-cholesterol < 1.8 mmol/L
		High-risk	LDL-cholesterol < 2.6 mmol/L
		Low-moderate risk	LDL-cholesterol < 3 mmol/L
2019 ESC/EAS guidelines for the management of dyslipidemia		Very high-risk	LDL-cholesterol < 1.4 mmol/L
		High risk	LDL-cholesterol < 1.8 mmol/L

		Low-moderate risk	LDL-cholesterol <2.6mmol/L
2013 ESH/ESC Guidelines for the management of arterial hypertension	systolic & diastolic BP	<140/90	Adults with no diabetes
		<140/85	People with diabetes
2024 ESC Guidelines for the management of elevated blood pressure and hypertension	systolic & diastolic BP	120 –129/70 –79	Entire population
	Statin subcategories		
2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults	High-intensity statin		atorvastatin 40mg-80mg
			rosuvastatin 20 (40) mg
	Moderate-intensity statin		atorvastatin 10 (20) mg
			rosuvastatin (5)10 mg
			simvastatin 20 – 40 mg
			pravastatin 40 (80) mg
			lovastatin 40 mg
			fluvastatin XL 80 mg
			fluvastatin 40 mg BID
			pitavastatin 2 – 4 mg
	Low-intensity statin		simvastatin 10 mg
			pravastatin 10 – 20 mg
			lovastatin 20 mg

Appendix 6 Variables used in multivariable multiple imputation models

Variable	Type of variable	Model used to predict missing data
Marital status	Categorical (2 categories)	n/a, complete cases
Sex	Categorical (2 categories)	n/a, complete cases
Age categories	Categorical (4 categories)	n/a, complete cases
Systolic BP	Continuous	n/a, complete cases
Diastolic BP	Continuous	n/a, complete cases
Smoking status	Categorical (3 categories)	n/a, complete cases
Body mass index categories	Categorical (3 categories)	n/a, complete cases
Diabetes	Categorical (2 categories)	n/a, complete cases
Polypharmacy	Categorical (3 categories)	n/a, complete cases
Statin therapy	Categorical (2 categories)	n/a, complete cases

Variable	Type of variable	Model used to predict missing data
Education level	Categorical (3 categories)	Ordinal logistic regression
Number of antihypertensives	Categorical (3 categories)	Multinomial logistic regression
Medication classes	Categorical (4 categories)	Multinomial logistic regression
Question 1	Ordered categories (5 categories)	Ordinal logistic regression
Question 2	Ordered categories (5 categories)	Ordinal logistic regression
Question 3	Ordered categories (5 categories)	Ordinal logistic regression
Average score	Continuous	Passive imputation
Medication non-adherence	Categorical (2 Categories)	Passive imputation

Appendix 7 Patients' characteristics based on goal achievements using the imputed and observed data based on the systolic BP and diastolic BP cut off level in the 2013 European Society of Cardiology (ESC)/ European Society of Hypertension guidelines (ESH) goals(69)

Variables	% of the imputed data	Achieved goals		Didn't achieve goals	
		Imputed data (N = 362) (63.8%)	Observed data (N = 217) (67.8%) (without imputation)	Imputed (N = 205) (36.2%)	Observed (N = 103) (32.2%) (without imputation)
Age in years		67.1 (0.28)	67.3 (0.37)	66.6 (0.35)	66.4 (0.53)
Body mass index (BMI) (Kg/m ²)		29.7 (0.25)	29.7 (0.3)	30.8 (0.73)	31.4 (1.4)
Systolic BP (mmHg)		122.2 (0.54)	122.0 (0.67)	152.4 (0.92)	152.4 (1.29)
Diastolic BP (mmHg)		72.7 (0.40)	73.1 (0.53)	83.6 (0.75)	83.1 (1.03)
Diabetes		13.2	13.3	14.6	10.6
Male		53.8	52.5	62.9	61.1
Smoking status (n,%)					
Current smoker		7.2	5.1	10.2	9.7
Former smoker		40.3	43.3	41.5	42.7
Non-smoker		52.4	51.6	48.2	47.5

Marital status (n,%)					
Single		26.2	22.5	26.3	26.2
Coupled		73.7	77.4	73.6	73.7
Education level (n,%)					
Primary level	7.7%	32.3	32.7	31.6	29.1
Second level		47.8	47.0	44.0	45.6
Third level		19.7	20.3	24.4	25.2
Antihypertensive intensities (n,%)					
Monotherapy		54.4	50.6	53.6	43.6
Dual therapy		32.3	33.2	29.2	35.9
Triple therapy		11.6	14.3	13.2	18.4
More than triple therapy		1.6	1.8	3.9	1.9
Antihypertensive regimen (n,%)					
Free equivalent combination		55.7	56.1	53.6	62.1
Single pill combination (SPC)		29.0	28.0	23.1	22.4
Free equivalent + SPC		15.1	15.8	23.1	15.5
Antihypertensive Class					

Renin angiotensin aldosterone system inhibitor		72.1	80.6	69.2	72.8
Beta- blockers		37.2	33.2	30.2	27.2
Calcium channel blocker		16.2	16.5	28.2	31.1
Diuretic		9.4	9.6	8.7	11.6
Alpha blockers		0.5	0.46	1.4	1.94
Medication adherence (n,%)					
Adherent		67.4	76.0	61.1	70.8
Non-adherent		32.5	23.9	38.9	29.1

Appendix 8 Patients' characteristics based on BP goal achievements using the imputed data and observed data based on the systolic BP and diastolic BP cut off level in the 2024 ESC Guidelines for the management of elevated blood pressure and hypertension(60)

	Achieved goals		Did not achieve goals	
	Imputed data (N = 218)	Observed data (N = 130)	Imputed data (N = 349)	Observed data (N = 190)
Age in years (mean, SE)	67.5 (0.35)	68.2 (0.44)	66.5 (0.28)	66.2 (0.40)
Body mass index (BMI) (kg/m ²) (mean, SE)	29.6 (0.34)	29.9 (0.39)	30.4 (0.45)	30.5 (0.77)
Systolic BP (mmHg) (mean, SE)	116.6 (0.55)	116.8 (0.70)	143.4 (0.81)	142.0 (1.12)
Diastolic BP (mmHg) (mean, SE)	70.0 (0.42)	81.2 (0.53)	70.1 (0.55)	80.9 (0.69)
Diabetes (n,%)	13.7	13.8	13.7	11.5
Male (n,%)	56.8	56.2	57.3	54.7
Smoke status (n,%)				
Current smoker	7.7	4.6	8.6	7.9
Former smoker	39.4	43.1	41.5	43.2

Non smoker	52.7	52.3	49.9	48.9
Education level (n,%)				
Primary level	31.2	33.1	33.0	30.5
Second level	50.3	48.5	43.6	45.3
Third level	18.5	18.5	23.3	24.2
Marital status (n,%)				
Single	26.6	25.4	26.0	22.6
Coupled	73.9	74.6	73.9	77.4
Medication adherence (n,%)				
Adherent	61.7	80.0	70.6	70.5
Non adherent	38.3	20.0	29.3	29.5

Appendix 9 Medication non-adherence among participants using the imputed data and observed data

			Imputed data					Observed data				
Item	Adherence statement	% of missing data	Strongly disagree	Disagree	Neutral	Agree	Strongly Agree	Strongly disagree	Disagree	Neutral	Agree	Strongly Agree
1	Over the past 7 days, I took all doses of my BP medications	29.8	56 (9.8)	8 (1.6)	3 (0.5)	28 (4.9)	472 (83.3)	25 (7.8)	4 (1.3)	2 (0.6)	11 (3.4)	278 (86.8)
2	Over the past 7 days, I missed or skipped at least one dose of my BP medications	35.6	428 (75.5)	21 (3.7)	16 (2.8)	14 (2.4)	88 (15.6)	266 (83.1)	7 (2.2)	6 (1.9)	6 (1.9)	35 (10.9)

3	Over the past 7 days, I wasn't able to take all of my BP medications	36.6	471 (83.0)	10 (1.7)	6 (1.0)	5 (1.0)	75 (13.3)	282 (88.1)	3 (0.9)	2 (0.6)	1 (0.3)	32 (10.0)
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Appendix 10 OPERAM Analysis Plan

OPERAM Analysis Plan (AP) Submission Form

Instructions: please complete the entire form (3-5 pages max.) and send it by email to katharina.jungo@biham.unibe.ch for review by the Publication Committee (PC).

To be filled in by OPERAM PC Coordinator:

Date of approval: 26.08.2024 AP number: AP48

Type of subproject proposal

(Select the most appropriate type)

Sub-study not using OPERAM trial data (systematic review,

Sub-Study embedded in the main trial, using OPERAM data

If yes, type of data used: Cross-sectional

Yes meta-analysis, etc.)

Yes

X
x

No

X

No

Longitudinal

Title

Relationship between self-reported medication adherence and cardiovascular risk control in hospitalized older adults

Proposed Writing Group

(Indicate potential investigators/authors for this project)

First author: Rehab Elhiny			
Senior author: Prof Stephen Byrne			
OPERAM sponsor* (if senior author not part of OPERAM): Prof Stephen Byrne			
Statistical analysts + site of analysis: Cork			
Provisional list of co-authors: From Original OPERAM team:			
<ul style="list-style-type: none"> • UCL: Prof. Anne Spinewine, Dr. Olivia Dalleur • UCC: Prof Denis O'Mahony, Prof Stephen Byrne • Bern: Prof Nicolas Rodondi, Dr Luise Adam • Utrecht: Prof Wilma Knol, Dr Geert Lefeber 			
From this research team:			
<ul style="list-style-type: none"> • Dr. Margaret Bermingham, Dr. Maria Donovan, Dr. Linda O'Keeffe 			
In case of trial data, sites (single or multicenter): Multicentre			
Other source of funding in addition to OPERAM (if any): -			
Ethical committee approval (if needed): -			
Has the AP been circulated to all co-authors for feedback, letting them 10 days to comment?			
Yes	☒	No	☐

* WP leader or other GA members

Has the internal OPERAM website been checked for overlap between sub- ☒ X ☐ No ☐ studies? Yes

Background

(Explain briefly why this study is innovative with respect to prior studies done in this field)

Despite the improvement in the outcomes of cardiovascular disease (CVD), more patients are surviving their first cardiovascular event and are at high risk of recurrence (1). Age is one of the non-modifiable risk for CVD (2). According to the American Heart Association (AHA), the incidence of CVD almost doubles in older adults, increasing from 40% among people 40-59 years to 75% and then further to 86% among people aged 60-79 years and 80 years respectively (2,3). CVD prevention interventions must be delivered to individuals who are at moderate to very high risk of a cardiovascular event, to individuals with established cardiovascular diseases, as well as to people with diabetes who are categorized as being at high to very high risk of CVD (1,4). CVD prevention interventions in this context means controlling critical risk factors such as increased low-density lipoprotein cholesterol (LDL-C) levels and increased blood pressure levels (1,4,5). Previous studies suggested that achieving low-density lipoprotein (LDL-C) targets is noticeably suboptimal among patients treated as part of either primary or secondary prevention strategies (6–10). Similarly, international and Irish data reported sub-optimal control of blood pressure among antihypertensive people (9,(11,12). Poor medication adherence is a challenging factor that leads to the suboptimal control of blood pressure and LDL-C (13). Adherence to the lipid lowering treatment (LLT) such as statins is one of the contributing factors to achieving the clinical guideline goals; however, statins discontinuation or LLT non-adherence was reported in various European studies including Ireland (14–17). Similarly, suboptimal adherence to antihypertensive medications is also reported in previous studies (18).

In a systematic review of 25 studies, including 12,628 hypertensive participants, 45% were non-adherent to antihypertensive medications, and of the 2606 participants with uncontrolled hypertension, 84% were non-adherent based on the self-reported Morisky Medication Adherence Scale (8 items-MMAS) (18). A study conducted in the U.S. reported a relationship between antihypertensive medication adherence and goal attainments; however, evidence linking medication adherence and LDL-C or BP goal attainments is sparse in both the Irish and the international context (19).

Study Hypotheses/Specific aims

(List the study hypotheses and specific aims of this subproject)

- | | |
|--|---|
| <p>Aim:</p> <ol style="list-style-type: none"> 1. | <p>Using multi-centre clinical trial data, the Morisky Medication Adherence Scale (8 item) questionnaire (MMAS-8) will be used to assess the level of adherence to antihypertensive medications and lipid lowering therapies.</p> |
|--|---|

2. Determine the proportion of people achieving the LDL-C and BP recommended guideline goals based on their medical conditions (co-morbidities) and their cardiovascular risk score.
3. Assess the factors related to achieving the guideline goals and the adherence to medications such as gender, number of medicines, number of co-morbidities.

Methods

(Describe the methods you plan to use to address the study hypothesis/questions, in particular, if you need specific variables from the OPERAM project to accomplish your goals)

Study design (Please indicate whether it is cross-sectional, longitudinal, etc.)

Multicentre cross-sectional observational study

Study population with inclusion/exclusion criteria you intend to include

People in all the trial sites with MMAS-8 data at index of hospitalization

Outcome(s) (If applicable, please be as specific as possible)

1. Cardiovascular Risk Score (SCORE) will be estimated for people who are treated for primary prevention (people with no existing cardiovascular diseases at index hospitalisation). The 10-year risk of fatal and non-fatal cardiovascular diseases will be calculated for people aged 70+ (SCOREOP). The score will be calculated using software STATA by incorporating the factors of age, sex, systolic blood pressure, smoking status, total cholesterol level, HDL level and diabetes status. People with diabetes will be assigned to high risk or very high risk in the presence of any other cardiovascular

disease/proteinuria. People with eGFR <30 ml/min/ 1.73m^2 will be assigned to very high risk group and people with eGFR 30-59 ml/min/ 1.73 m^2 .

2. Proportion of patients at moderate, high, and very high-risk achieving LDL-C, BP and blood glucose/ HbA1c targets will be determined in accordance to the latest guideline recommendations relevant to the OPERAM data; 2016 ESC/EAS, 2013 ESH/ESC guidelines & 2012 European Guidelines on cardiovascular disease prevention in clinical practice (The LDL-C goals will be specified based on the estimated cardiovascular risk for each patient. 2016 ESC/EAS recommended LDL-C targets will be used (LDL-C <1.8 mmol/L for very high risk; LDL-C <2.5 mmol/L for high risk; LDL <3 mmol/L for low-moderate risk). 2013 ESH/ESC guidelines for management of arterial hypertension recommended blood pressure (BP) targets (Systolic BP (SBP) $<140\text{mmHg}$ for people at low-moderate risk of CVD, people with previous stroke, TIA, people with coronary heart diseases (CHD), and people with diabetes; diastolic blood pressure (DBP) <90 mmHg except for people with diabetes who should target DBP $<85\text{mmHg}$. Blood glucose/HbA1c $<7.0\%$ (<53 mmol/mol) and/or fasting blood glucose <7.0 mmol/L (125 mg/dl)
3. Identification of factors related to target achievement i.e. medication adherence from the 8-item MMAS, beliefs about medicines (BMQ-General, if available).
4. Identifying factors related to medication adherence such as number of medicines and number of co-morbidities.

Predictor(s), Exposure(s) (If applicable, please be as specific as possible)

Trial sites:

Centres of Bern (Switzerland), Utrecht (The Netherlands), Brussels (Belgium) and Cork (Ireland).

Index hospitalization (Stay);Type of admission; main symptoms, main reasons for admission; number of co-morbidities; number of drugs.

All Diagnosis data (ICD-10 code).

Medication list (ATC-2016 code).

Demographics (gender, date of birth, weight, height, Ethnos, other Ethnos, Highest level of education, smoking status and history, alcohol consumption).

Clinical parameters LDL-C/HDL-C/Triglycerides/total cholesterol/ systolic and diastolic BP/ blood glucose and creatinine levels/eGFR/Albumin/Albumin (Urine).

Other variables needed – Baseline variables, covariates, etc. (If applicable, please be as specific as possible)

Compliance aid, Health economics baseline (formal care), hospitalizations, length of stay, “SHIM” including (Are you using your medications independently; Are you using dosage system; Are you experiencing problems taking your medications)

Planned analyses (Provide a brief description of the statistical analyses)

We will use descriptive statistics to describe LDL-C, BP and blood glucose/HbA1c goal achievements using the Irish OPERAM data and then perform a comparative analysis using data from the other 3 OPERAM trial sites across European countries. Chi-

square tests will be used to identify significant differences between the categorical determinants such as achievements of LDL-C, BP and blood glucose/HbA1c goals and medication adherence among all eligible patients followed by a Tukey's HSD post-hoc test (p-values < 0.05 are considered significant).

Lifestyle factors such as smoking and alcohol consumption may affect the achievement of LDL-C and BP targets. Socioeconomic status and education may affect people behavior about medications and medications adherence. Multivariate regression model can be conducted to adjust these factors.

The association between number of co-morbidities and number of drugs (poly-pharmacy) and medication adherence will be determined using multivariate logistic regression presented as regression coefficient (β) 95% CI, at index hospitalisation

We will perform subgroup analyses with patients with primary prevention and secondary prevention, and people with diabetes.

Potential overlap with other OPERAM sub-studies and how it will be addressed/

avoided (Please check the internal OPERAM website for ongoing and planned OPERAM sub-studies (<https://operam2020.tp21.com/s/ba186e94-5f00-4142-bfd3-4e4c97e32228/wiki/page/list>) and do not hesitate to reach out to Katharina Jungo (katharina.jungo@biham.unibe.ch) if you have any questions)

[Statin therapy in multimorbid older patients with polypharmacy- a cross-sectional analysis of the Swiss OPERAM trial population - PubMed \(nih.gov\)](#)

The study examined the inappropriate use of statin therapy in the population and assessed it with a number of patients characteristics.

While our study aims to assess the same population who are on statin therapy, the perspective of our potential study is different. The main aim of the study is to assess the adherence using the self-reported MMAS and the relationship of adherence to target LDL-C and BP achievement, which has not previously been studied to our knowledge. We will collaborate with the first and senior author of the above paper on this proposed study, to avoid any overt overlap.

Project Timeline (Indicate the presumed date when the project will be completed, including planned abstract submission)

Data collection: No additional data apart from the already collected data
Data analysis: 08/2024-12/2024
Submission of the manuscript: Summer 2025

Expected workload (on a patient basis, including number of patients) for each

participating partner (in case of a sub-study embedded in trial)

No additional workload is expected of this sub-study for the study sites.

Appendix 11 Variables used in multivariable multiple imputation models

Variables	Percent missing	Type of variable	Model used
Age	0	Continuous variable	Regular variable
Sex	0	Categorical variable (2 categories)	Regular variable
Diabetes diagnosis	0	Categorical variable (2 categories)	Regular variable
Hypertension diagnosis	0	Categorical variable (2 categories)	Regular variable
Site	0	Categorical variable (4 categories)	Regular variable
Lipid therapy	0	Categorical variable (2 categories)	Regular variable
Hospital ward	0	Categorical variable (24 categories)	Regular variable
Total cholesterol	63.2 %	Continuous variable	predictive-mean matching
Triglycerides	64 %	Continuous variable	predictive-mean matching
HDL-C	63.7%	Continuous variable	predictive-mean matching
LDL-C	64%	Continuous variable	predictive-mean matching
Estimated glomerular filtration rate (eGFR)	12.2%	Continuous variable	predictive-mean matching
Education level	1.2%	Categorical variable	Ordered logistic regression
Body mass index (BMI)	7.9%	Continuous variable	Regression
Smoke status	0.2%	Categorical variable	Logistic regression

Item 1-MMAS	4.7%	Categorical variable	Logistic regression
Item2- MMAS	4.7%	Categorical variable	Logistic regression
Item3- MMAS	4.8%	Categorical variable	Logistic regression
Item4- MMAS	5.0%	Categorical variable	Logistic regression
Item5 – MMAS	5.0%	Categorical variable	Logistic regression
Item6- MMAS	4.8%	Categorical variable	Logistic regression
Item7 -MMAS	4.7%	Categorical variable	Logistic regression
Item8 -MMAS	4.7%	Ordinal variable	Ordered logistic regression
Achieved LDL-C goals according to 2016 ESC/EAS guidelines	64%	Categorical variable (2 categories)	Passive imputation
Achieved LDL-C goals according to 2019 ESC/EAS guidelines	64%	Categorical variable (2 categories)	Passive imputation
MMAS categories	5%	Categorical variable (3 categories)	Passive imputation

Appendix 12.Participants demographic factors using the imputed and observed data

	Imputed		Observed	
	Lipid therapy N =1,153 (57.5%)	No lipid therapy N =855 (42.4%)	Lipid therapy N = 373 (57.3%)	No lipid therapy N = 277 (42.6%)
Age in years (mean ±SD)	78.7 (0.17)	80.2 (0.22)	78 (0.29)	79.9 (0.30)
LDL-C (mmol/L) (mean ±SD)	1.7 (0.035)	2.4 (0.04)	1.7 (0.04)	2.4 (0.05)
BMI (Kg/m ²) (mean ±SD)	27.4 (0.16)	26.2 (0.20)	27.3 (5.11)	26.11 (5.4)
Sex (n,%)				
Male	708 (61.4)	400 (47.1)	250 (67.0)	144 (51.9)
Female	445 (38.5)	450 (52.9)	123 (32.9)	133 (48.0)
Body mass index (n/%)				
Underweight	23 (1.9)	52(6.1)	16 (5.7)	11 (2.9)
Normal weight	358 (31.1)	334(39.3)	104 (37.5)	111 (29.7)
Overweight	483 (41.8)	281(33.0)	102 (36.8)	160 (42.9)
Obese	289 (25.1)	183(21.5)	55 (19.8)	91 (24.4)
Smoking status (n,%)				
Current smoker	104 (9.1)	54 (6.3)	21 (7.5)	38 (10.2)
Education level (n,%)				
Under high school	345 (29.9)	257 (30.1)	65 (17.4)	42 (15.2)
High school level	534 (46.4)	387 (45.2)	222 (59.5)	163 (58.8)
University level	274 (23.7)	210 (24.6)	86 (23.1)	72 (25.9)
Morbidities (n,%)				

Diabetes	425 (36.8)	200 (23.4)	140 (37.5)	80 (28.8)
Hypertension	726 (65.3)	463 (54.5)	227 (60.9)	139 (50.2)
Cardiovascular risk (n,%)				
Primary prevention	400(34.6)	534 (62.4)	85 (22.8)	140 (50.5)
Secondary prevention	753(65.3)	321 (37.5)	288 (77.2)	137 (49.5)
2016 ESC/EAS goals(n,%)				
Achieved goals	781 (67.5)	463 (49.1)	250 (67.0)	117 (42.2)
Didn't achieve goals	372 (32.4)	387 (50.9)	123 (32.9)	160 (57.7)
2019 ESC/EAS goals (n,%)				
Achieved goals	487 (42.3)	209 (24.5)	52 (18.7)	152 (40.7)
Didn't achieve goals	666(57.7)	646 (75.5)	225 (81.2)	221 (59.2)
MMAS questionnaire (n,%)				
Low /medium adherence	625 (54.2)	-	218 (58.5)	-
High adherence	528 (45.7)	-	155 (41.5)	-

Appendix 13 Prescribing pattern and LDL-C control across four European centers

	Imputed data				Observed data			
	Louvain (N=388)	Utrecht (N=452)	Bern (N = 822)	Cork (N =346)	Louvain (N = 87)	Utrecht (N = 55)	Bern (N = 471)	Cork (N = 373)
Primary prevention (n,%)	234(60.5)	193(42.6)	325(39.5)	181 (47.6)	42 (48.3)	14 (25.4)	156 (33.1)	13 (35.1)
Secondary prevention (n,%)	153(39.4)	258(57.3)	497(60.4)	165(47.6)	45 (51.7)	41 (74.5)	315 (66.8)	24 (64.8)
On lipid lowering therapy (n,%)	222 (57.2)	285(63.1)	416(50.6)	230 (66.4)	56 (64.4)	39 (70.9)	249 (52.8)	29 (78.4)
Statin monotherapy	189 (85.1)	264(92.6)	387(93.0)	215(93.4)	45 (51.8)	34 (61.8)	234 (49.6)	24 (64.8)
Dual therapy	23 (10.3)	14(4.9)	23(5.5)	12(5.2)	7 (8.1)	55 (5.5)	13 (2.7)	4 (10.8)
Non-statin	10 (4.5)	6.9(2.4)	6(1.4)	3 (1.3)	4 (4.6)	2 (3.6)	2 (0.42)	1 (2.7)

Achieved 2016 goals (n,%)	175(78.8)	196(68.8)	283(67.9)	125(54.4)	49 (87.5)	14 (35.9)	172 (69.1)	13 (44.8)
Primary prevention	97(90.3)	79(89.2)	89(88.3)	76(73.8)	20 (40.8)	6 (42.8)	44 (25.6)	6 (46.2)
Secondary prevention	78(68.2)	117(59.6)	193(61.3)	49(38.6)	29 (59.2)	8 (57.1)	128 (74.4)	7 (53.8)
Achieved 2019 goals (n,%)	183(47.2)	137(48.1)	164(39.3)	64(27,7)	37 (66.1)	8 (20.5)	96 (38.5)	4 (13.7)
Primary prevention	73(68.5)	59(65.9)	49(48.7)	38 (37.6)	18 (48.6)	4 (50.0)	20 (20.8)	1 (25.0)
Secondary prevention	49(42.9)	78(40.0)	115(36.4)	26 (19.6)	19 (51.4)	4 (50.0)	76 (79.2)	3 (75.0)

Appendix 14 Predictors of goal achievements among people with prescribed LLT based on the observed data (N =373)

Predictors of achieving 2016 goals	Odds ratio	95% confidence interval	P-value
Age: <80 years	Reference		
Age ≥ 80 years	1.61	0.95, 2.72	0.076
Sex: Male	Reference		
Female	0.68	0.33, 0.77	0.002
BMI: Normal weight	Reference		
Underweight	4.05	0.44,36.7	0.213
Overweight	0.92	0.52,1.64	0.777
Obese	1.08	0.54,2.15	0.815
Smoking status: non – smoker	Reference		
Current	1.22	0.54,2.75	0.625
Education level: High school level	Reference		
Less than high school	0.59	0.29,1.20	0.147
Post secondary level	0.89	0.48,1.65	0.720
Morbidities	Reference		
Diabetes	1.63	0.96,2.74	0.067
Hypertension	0.89	0.54,1.48	0.676
Cardiovascular risk			
Primary prevention	7.10	3.19,16.1	0.000
Morisky categories: low/medium adherence			
High adherence	1.07	0.65,1.75	0.784
Centre: Bern			
Louvain	0.07	0.02,0.22	0.000
Utrecht	0.31	0.12,0.78	0.014

Predictors of achieving 2016 goals	Odds ratio	95% confidence interval	P-value
Cork	0.09	0.02,0.32	0.000

Appendix 15 Predictors for LDL-C goal achievements among people with prescribed lipid lowering therapies according to the 2019 ESC/EAS guidelines using observed data

Predictors of LDL-C goal achievements ESC 2019	Odds ratio	95% confidence interval	P-value
Age: <80 years			
Age ≥80 years	1.64	0.76, 1.73	0.481
Sex: Male			
Female	0.57	0.34, 0.80	0.004
BMI: Normal weight			
Underweight	1.85	0.48,7.19	0.369
Overweight	1.05	0.61,1.82	0.851
Obese	0.94	0.49,1.81	0.867
Smoking status: non – smoker			
Current	0.94	0.39,1.37	0.344
Education level: School level			
below school level	0.59	0.46,1.16	0.192
University level	0.78	0.46,1.19	0.230
Cardiovascular risk: Secondary prevention			
Primary prevention	2.12	1.21,3.73	0.008
Morbidities:			
Diabetes	1.32	0.82,2.13	0.257
Hypertension	0.94	0.58,1.52	0.808
Morisky categories: Low/ medium adherence			
High adherence	1.28	0.81,2.03	0.289
Centre: Bern			
Louvain	3.42	1.71,6.82	0.000
Utrecht	0.44	0.18,1.04	0.062
Cork	0.26	0.08,0.85	0.025

Appendix 16. Predictors for medication adherence among people with prescribed lipid lowering therapies using Morisky Medication Adherence Scale using observed datasets

Predictors of medication adherence	Odds ratio	95% confidence interval	P-value
Age: <80 years Reference			
Age $\geq$ 80 years	0.98	0.88, 1.48	0.318
Sex: Male Reference			
Female	1.09	0.73, 1.26	0.815
BMI: Normal weight Reference			
Underweight	1.21	0.33, 4.40	0.765
Overweight	1.09	0.65, 1.82	0.741
Obese	1.02	0.55, 1.86	0.954
Smoking status: non – smoker Reference			
Current	0.94	0.44, 1.08	0.104
Education level: high School level Reference			
Below high school level	1.49	0.80, 2.77	0.205
Post secondary school level	0.89	0.51, 1.55	0.691
Morbidities Reference			
Diabetes	0.73	0.46, 1.16	0.193
Hypertension	0.67	0.43, 1.05	0.082
Cardiovascular risk: Secondary prevention			
Primary prevention	0.87	0.51, 1.49	0.629
Center: Bern			
Louvain	0.78	0.39, 1.54	0.479
Utrecht	2.67	1.28, 5.55	0.009
Cork	0.98	0.42, 2.31	0.974