Medicines Management Programme

Preferred Drugs

Statin monotherapy for the treatment of hypercholesterolemia and prevention of cardiovascular events in adults

Approved by:	Prof. Michael Barry, Clinical Lead, Medicines Management Programme (MMP).
Date approved:	24th July 2020
Version:	1.0

Table of Contents

Tables

Figures

List of abbreviations

ACC/AHA	American College of Cardiology/ American Heart Association
ACS	Acute coronary syndrome
ADR	Adverse drug reaction
Apo-A1	Apolipoprotein A-I
ASCVD	Atherosclerotic cardiovascular disease
ATC	Anatomical therapeutic chemical
BD	Twice daily
CAD	Coronary artery disease
CDS	Community drugs schemes
CHD	Coronary heart disease
CI	Confidence interval
CIMT	Carotid intima media thickness
CK	Creatine-kinase
CKD	Chronic kidney disease
CVD	Cardiovascular disease
CYP450	Cytochrome P450
DDD	Defined daily dose
DM	Diabetes Mellitus
DP	Drugs Payment
eGFR	Estimated glomerular filtration rate
ESC/EAS	European Society of Cardiology/ European Atherosclerosis Society
FH	Familial hypercholesterolaemia
FRS	Framingham risk score
GI	Gastrointestinal
GMS	General Medical Services
HDL-C	High-density lipoprotein cholesterol
HeFH	Heterozygous familial hypercholesterolaemia
HF	Heart failure
HoFH	Homozygous familial hypercholesterolaemia
HMG-CoA	3-hydroxy-3-methylglutaryl-coenzyme A

HPRA	Health Products Regulatory Authority
HR	Hazard ratio
hs-CRP	High sensitivity C-reactive protein
HSE	Health Service Executive
ICGP	Irish College of General Practitioners
INR	International normalised ratio
LDL-C	Low-density lipoprotein cholesterol
LFT	Liver function test
LTI	Long term Illness
MACE	Major adverse cardiovascular events
MHRA	Medicines & Healthcare products Regulatory Agency
MI	Myocardial infarction
MMP	Medicines Management Programme
NCPE	National Centre for Pharmacoeconomics
NICE	National Institute for Health and Care Excellence
NMIC	National Medicines Information Centre
OR	Odds ratio
PAV	Percent atheroma volume
PCERS	Primary Care Eligibility and Reimbursement Service
PCSK9	Proprotein convertase subtilisin/kexin type 9
RCT	Randomised controlled trial
RR	Relative risk
SCORE	Systemic Coronary Risk Estimation
SmPC	Summary of Product Characteristics
T1DM	Type 1 Diabetes Mellitus
T2DM	Type 2 Diabetes Mellitus
TC	Total cholesterol
TG	Triglycerides
UA	Unstable angina
ULN	Upper limit of normal
VLDL	Very low-density lipoprotein
WHO	World Health Organisation

Acknowledgements

The MMP wishes to acknowledge the staff of the National Medicines Information Centre (NMIC) and the National Centre for Pharmacoeconomics (NCPE) for their input and contributions to this document.

1. Purpose

The selection of a preferred statin by the Medicines Management Programme (MMP) is designed to support prescribers, in choosing a cost-effective medicine of proven safety and efficacy, in the management of patients with hypercholesterolaemia. Prescribers are encouraged to prescribe the preferred drug when initiating a statin and when there is a need to switch from one statin to another.

Simvastatin was selected as the MMP's preferred statin in April 2013. The purpose of this report is to review the choice of preferred statin in light of the current available evidence.

2. Scope

There are five oral statins which are licensed for use as monotherapy, and reimbursed in Ireland: atorvastatin, fluvastatin, pravastatin, rosuvastatin and simvastatin. These statins will be reviewed for the purpose of this document taking into account their role in the management of primary hypercholesterolaemia, homozygous familial hypercholesterolaemia and primary and secondary prevention of cardiovascular events. Simvastatin, rosuvastatin and atorvastatin are available as combined products with ezetimibe, and are also licensed for the treatment of hypercholesterolaemia. These combination products are outside the scope of this review.

Statin use in children is also outside the scope of this review.

3. Definitions

For the purpose of this report, the use of the word "statin" refers to the 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase inhibitors that are currently licensed for use in Ireland (atorvastatin, fluvastatin, pravastatin, simvastatin and rosuvastatin). The terms "statin" and "HMG-CoA reductase inhibitors" are used interchangeably throughout this document.

Unless otherwise stated, the associated cost refers to the reimbursed cost of the named HMG-CoA reductase inhibitors as listed on the Health Service Executive (HSE) Primary Care Eligibility and Reimbursement Service (PCERS) website in March 2020. Only reimbursed statins licensed for the treatment of primary hypercholesterolaemia, homozygous familial hypercholesterolaemia or the prevention of cardiovascular events are included in this review.

The Community Drug Schemes (CDS) referred to throughout this document include the Drug Payment (DP), Long Term Illness (LTI) and the General Medical Services (GMS)/medical card schemes. This data

is limited by its inability to capture prescriptions that are solely funded by the patient, and therefore are not reimbursed under any of the state-funded CDS e.g. prescriptions that fall below the co-payment threshold on the DP scheme.

The defined daily dose (DDD) is obtained for each drug using the anatomical therapeutic chemical (ATC) code. This code is a World Health Organisation (WHO) method for classifying drugs, based on the organ or system on which they act and their therapeutic, pharmacological and chemical properties.[1]

4. Consultation

A period of consultation was undertaken in relation to the identification of a preferred drug for statin monotherapy for the treatment of hypercholesterolaemia and prevention of cardiovascular events. Submissions from relevant stakeholders, including the pharmaceutical industry and professional bodies representing clinicians and healthcare professionals, were invited. This consultation period closed on 1st March 2019.

5. Preferred Statin

Atorvastatin is the preferred statin for the treatment of hypercholesterolaemia and prevention of cardiovascular events under MMP guidance.

6. Background

Cardiovascular disease (CVD), which includes coronary heart disease (CHD) and stroke, remains a leading cause of morbidity and mortality worldwide, despite improvements in outcomes.[2] The introduction of preventative measures, including smoking legislation has aided these improvements, yet an estimated 17.9 million people worldwide died from CVD in 2016, representing 31% of all global deaths.[2,3] Central statistics office figures indicate that circulatory disease accounted for 29% of all deaths in Ireland in 2017.[4] Disorders of cholesterol and lipoprotein metabolism are of great importance in atherosclerosis and coronary artery disease (CAD).[5]

Statins are the drugs of choice in the management of many lipid disorders.[6] Expenditure on statin monotherapy on the CDS was €47.83 million in 2017.[7] Expenditure has decreased in recent years due to generic substitution and reference pricing. However, in 2017, statins, as a drug-class, rated fifth-highest in terms of expenditure on the GMS scheme, with atorvastatin being the second most commonly prescribed drug on both the GMS and DP schemes and the fourth most commonly prescribed on the LTI scheme.[7]

Cholesterol is an essential molecule in humans, used to make steroid hormones, bile acids and vitamin D. It is also a vital part of cell membranes in the body. Most of the cholesterol in the body is synthesised in the liver and transported through the blood in lipoproteins. Excessively high levels of low-density lipoprotein cholesterol (LDL-C) increases the risk of atherosclerosis, heart disease and stroke.[8] In contrast, the high-density lipoprotein cholesterol (HDL-C) gathers up excess cholesterol and carries it to the liver where it is metabolised and excreted.

Hypercholesterolaemia is defined as the presence of high concentrations of cholesterol in the blood. Primary hypercholesterolaemia is associated with an underlying genetic cause and can be polygenic, where a number of genes interact with dietary and other factors including physical inactivity, or due to a specific gene defect, as in familial hypercholesterolemia (FH).[9]

FH is an inherited disorder, involving a single genetic mutation. It produces a clinically recognisable pattern that consists of severe hypercholesterolaemia due to the accumulation of LDL-C in the plasma, cholesterol deposition in tendons and occasionally in the skin, and a high risk of atherosclerosis manifesting almost exclusively as CAD.[10] The majority of patients with FH have inherited a defective gene from only one parent and therefore have heterozygous FH (HeFH). This condition is characterised by an elevated serum LDL-C, generally >4.9 mmol/L, which is responsible for a greater than 50% risk of CHD by the age of 50 years in men, and at least 30% in women by the age of 60 years.[9]

Occasionally a person will inherit a genetic defect from both parents. This is referred to as homozygous FH (HoFH) and is characterised by LDL-C levels of > 13 mmol/L.[9]

Lipid profile testing, along with other factors such as age, family history, cigarette smoking, diet, exercise, weight, blood pressure and diabetes, is used to determine the risk of CVD. The basic lipid blood test measures total cholesterol (TC), triglyceride (TG) levels, HDL-C and LDL-C.[11] Excess levels of TGs are a recognised risk factor for heart disease and stroke.[12] More extensive lipid profile testing

also examines very low-density lipoprotein (VLDL) cholesterol, non-HDL-C and the ratio of TC to HDL-C.[11]

Table 1: Normal cholesterol levels[12]

Cholesterol Breakdown	Cholesterol Level
Total Cholesterol	<5.0 mmol/L
LDL Cholesterol	<3.0 mmol/L
HDL Cholesterol	>1.0 mmol/L (men), >1.2 mmol/L (women)
Triglycerides	<1.8 mmol/L

Table 1 outlines normal cholesterol levels. Guidance issued by the European Society of Cardiology/ European Atherosclerosis Society (ESC/EAS) in 2019 suggests that patients who are considered to be at very-high-risk or high-risk of developing an atherosclerotic cardiovascular event should ideally have an LDL-C target of 1.4 or 1.8 mmol/L, respectively.[13]

Statins are the first-line pharmacological intervention for abnormal lipid profiles.[14] They work by inhibition of the enzyme HMG-CoA reductase, which is involved in the production of mevalonic acid in the cholesterol biosynthesis pathway.[15] By preventing the endogenous production of cholesterol, the expression of LDL receptors in liver cells is up-regulated, enhancing the clearance of the circulating LDL-C particles from the blood.[16] Although this is the primary biochemical effect of the HMG-CoA reductase inhibitors, there is also a slight reduction in plasma triglycerides and an increase in HDL-C.[17] These effects, in conjunction with cholesterol-independent (pleiotropic) cardio-protective effects, have resulted in statins being amongst the most highly prescribed medications worldwide.[16]

6.1 Statin classification

Although statins share a common mechanism of action, they differ in terms of their physicochemical structures, pharmacokinetic profiles, and lipid-modifying efficacy. The chemical structures of statins govern their water solubility, which in turn influences their absorption, distribution, metabolism and excretion.[18]

Table 2: Pharmacokinetic properties of statins[18]

	Atorvastatin	Fluvastatin	Pravastatin	Rosuvastatin	Simvastatin
Optimal time of dosing	Any time of day	Evening	Evening	Any time of day	Evening
Bioavailability (%)	12	24	18	20	5
Solubility	Lipophilic	Lipophilic	Hydrophilic	Hydrophilic	Lipophilic
Effect of food	Bioavailability decreased	Bioavailability decreased	Bioavailability decreased	No effect	No effect
Protein binding (%)	98	>98	~50	90	95-98
Active metabolites	✓	No	No	Minor	✓
Elimination half-life (hours)	14	1.2	1.8	19	2
CYP450 metabolism and isoenzyme	✓ 3A4	✓ 2C9	No	Limited	✓ 3A4
Renal excretion (%)	<5	6	20	10	13

Statins can be classified as natural or synthetic, according to their origin. Natural statins are secondary metabolites of fungi. Pravastatin and simvastatin are first-generation fungal-derived HMG-CoA reductase inhibitors. Atorvastatin, fluvastatin and rosuvastatin are fully synthetic statins.[19]

Upon oral administration, all statins are well absorbed from the intestine, though they undergo extensive first-pass metabolism within the liver, which reduces systemic bioavailability. The statins are administered as β-hydroxy-acids, except for simvastatin which is a pro-drug and requires hepatic metabolism to its active β-hydroxy state.[16]

Statins are further classified into hydrophilic and lipophilic groups based on tissue selectivity.[20] The lipophilicity of a drug influences its absorption and the hydrophilicity aids in excretion.[21] Atorvastatin, simvastatin and fluvastatin are lipophilic, while pravastatin and rosuvastatin are hydrophilic.[22]

6.1.1 Lipophilic statins

Lipophilic statins enter the cell by passive diffusion and are widely distributed in different tissues.[22] They have low systemic bioavailability due to extensive first-pass hepatic metabolism. Although this

effect can be desirable, the lipophilicity of these statins enables them to passively penetrate the cells of extrahepatic tissues, which may lead to undesirable side-effects.[23]

Lipophilic statins are susceptible to metabolism by the cytochrome P450 (CYP450) system, thus the use of concomitant medicines which inhibit CYP450 are likely to increase the concentration of statins and therefore, the possibility of side-effects including muscle toxicity.[24]

6.1.2 Hydrophilic statins

Hydrophilic molecules depend on an active transport process to enter the hepatocyte, thus hydrophilic statins are more hepatoselective because they are excluded by other tissues.[23] They are fnot significantly metabolised by CYP450 and are excreted largely unchanged. They are therefore less likely to participate in any clinically relevant drug-drug interactions due to CYP450.[25]

6.2 Statin intensity

Statins can be further subdivided based on their ability to reduce LDL-C. Statins may be of high-, moderate- or low-intensity depending on the percentage reduction they exert on LDL-C. The classification system varies slightly between advisory bodies (see section 7.3). In a document prepared by the Irish College of General Practitioners (ICGP) atorvastatin (≥ 40 mg) and rosuvastatin (≥ 20 mg) are considered to be high-intensity. Moderate-intensity statins include atorvastatin 10 mg/20 mg, rosuvastatin 5 mg/10 mg and simvastatin 20 mg/40mg.[26]

7. Selection Process

A number of key criteria were considered in the MMP statin selection process:

- **Licensed indications**
- **Clinical evidence**
    - Clinical efficacy and outcome data
- **Clinical guidelines**
- **Safety**
    - Adverse drug reactions
    - Cautions and contraindications
- **Drug interactions**
- **Patient factors**
    - Dosing
    - Administration

- **Cost**
- **National prescribing trends**

7.1 Licensed therapeutic indications

The licensed indications for statins in the treatment of adults are detailed in Table 3 below.

Table 3: Licensed indications for statin use in adults

	Atorvastatin[27]	Fluvastatin[28]	Pravastatin[29]	Rosuvastatin[30]	Simvastatin[31]
Primary hypercholesterolaemia	✓	✓	✓	✓	✓
Heterozygous familial hypercholesterolaemia	✓	✓	✓	✓	✓
Homozygous familial hypercholesterolaemia	✓			✓	✓
Mixed dyslipidaemia	✓	✓	✓	✓	✓
Prevention of cardiovascular events	✓	✓	✓	✓	✓
Reduction of post transplantation hyperlipidaemia			✓		

Statins, when indicated, should be used as an adjunct to diet, when response to diet and other non-pharmacological treatments (e.g. exercise, weight reduction) is inadequate.[27-31]

All five statins are licensed for the treatment of primary hypercholesterolaemia and prevention of cardiovascular events.

7.2 Clinical evidence

7.2.1. Clinical efficacy and outcome data

Statins are among the most studied drugs in CVD prevention. A number of large-scale trials have demonstrated that statins substantially reduce cardiovascular morbidity and mortality in both primary and secondary prevention, in both genders and in all age groups.[32] See Appendix A for information on clinical trials for individual statins.

Systematic reviews and meta-analyses which utilise pooled data from clinical trials, provide a means of assessing the general and comparative efficacy of statins, and were considered as part of the review process. These are outlined in table 4. Some large scale head-to-head comparative trials were also considered. These are outlined in table 5.

Relevant literature was identified by performing a search of the following databases: Cochrane Library, Embase and PubMed. The search terms used included comparative effectiveness, pharmacological comparison and comparative safety of statins/HMG-CoA reductase inhibitors.

Table 4: Summary of systematic reviews and meta-analyses for statins in the treatment of hypercholesterolaemia ¤ This list is not exhaustive

Study	Authors	Year	N	Population Included	Statins reviewed	Conclusion
Comparative effectiveness and safety of statins as a class and of specific statins for primary prevention of CVD: a systematic review and network meta-analysis of randomised trials with 94,283 participants[33]	Yebyo et al	2019	94,283 (40 trials)	Primary prevention	Atorvastatin Fluvastatin Lovastatin* Pravastatin Rosuvastatin Simvastatin	• All statins showed statistically significant risk reduction of CVD and all-cause mortality, while also associated with increased risk for certain harms. • The benefit-harm profile differed by statin type. • The drug-level network meta-analyses showed that atorvastatin and rosuvastatin were the most effective in reducing CVD events. • Atorvastatin had the best safety profile.
Comparison of the efficacy and safety of intensive-dose and standard-dose statin treatment for stroke prevention. A meta-analysis[34]	Wang et al	2016	120,970 (17 trials)	Primary & Secondary prevention	Atorvastatin Fluvastatin Pravastatin Rosuvastatin Simvastatin	• Intensive-dose statin treatment might be more favourable at preventing the occurrence of all-stroke incidences and fatal-stroke incidences than standard-dose statin treatment, especially for patients older than 65 years (all-stroke incidences). • The safety of intensive-dose statin treatment remains controversial. • Patients older than 65 years should receive careful monitoring, and caution should be exercised.
Lipophilic statin versus rosuvastatin (hydrophilic) treatment for heart failure: a meta-analysis and adjusted indirect comparison of randomised trials[35]	Bonsu et al	2016	10,966 (13 trials)	Secondary prevention	Atorvastatin Pitavastatin* Rosuvastatin Simvastatin	• Lipophilic statins were superior to hydrophilic rosuvastatin regarding all-cause mortality, cardiovascular mortality and hospitalisation for worsening heart failure. • Statin groups were comparable with regards to cardiovascular hospitalisations.
Comparative tolerability and harms of individual statins: a study-level network meta-analysis[36]	Naci et al	2013	246,955 (135 trials)	Primary & Secondary prevention	Atorvastatin Fluvastatin Lovastatin* Pitavastatin* Pravastatin Rosuvastatin Simvastatin	• Statins as a class resulted in significantly higher odds of diabetes mellitus and transaminase elevations. • Among individual statins, simvastatin and pravastatin seem safer and more tolerable than other statins.
Comparative effects of statins on major cerebrovascular events: a multiple-treatments meta-analysis of placebo-controlled and active-comparator trials[37]	Naci et al	2013	187,038 (61 trials)	Primary & Secondary prevention	Atorvastatin Fluvastatin Lovastatin* Pravastatin Rosuvastatin Simvastatin	• Overall, statins were associated with an 18% reduction in the relative odds of major cerebrovascular events. This was consistent across primary and secondary prevention populations. Findings were not sensitive to dose differentials of individual statins between trials. • The authors concluded that there is class effect with statins in preventing major cerebrovascular events.

Study	Authors	Year	N	Population included	Statins reviewed	Conclusion
Comparative benefits of statins in the primary and secondary prevention of major coronary events and all-cause mortality[38]	Naci et al	2013	199,721 (92 trials)	Primary & Secondary prevention	Atorvastatin Fluvastatin Lovastatin* Pravastatin Rosuvastatin Simvastatin	• Atorvastatin and fluvastatin were significantly more effective than rosuvastatin at reducing major coronary events at comparable doses. • Atorvastatin was significantly more effective than pravastatin and simvastatin for secondary prevention of major coronary events. • Primary prevention –no difference between statins (death, CVD event). • Across all populations, atorvastatin, fluvastatin and simvastatin had the highest overall probability of being the best treatment in terms of both outcomes.
Statins as a primary prevention: Which one is most effective? A systematic review and meta-analysis[39]	Figg et al	2013	1,439 (10 trials)	Primary prevention	Atorvastatin Fluvastatin Lovastatin* Pravastatin Rosuvastatin Simvastatin	• Population: Patients with T2DM and dyslipidaemia without prior CVD. • Atorvastatin and rosuvastatin were shown to be the most potent in reducing LDL-C and TGs. • Simvastatin showed the greatest increases in HDL-C. • Significance favouring statins for LDL-C and TG reductions but less evidence of significant effect of HDL-C improvement with all statins.
A systematic review and meta-analysis on the therapeutic equivalence of statins[40]	Weng et al	2010	Number of participa-nts not reported (75 studies)	Primary & Secondary prevention	Atorvastatin Fluvastatin Lovastatin* Pravastatin Rosuvastatin Simvastatin	• At comparable doses, statins are therapeutically equivalent in reducing LDL-C. • Rosuvastatin and atorvastatin at a daily dose of 20 mg or higher, were the only statins that could reduce LDL-C by more than 40%. • There was insufficient data to allow comparison between statins of CHD prevention and safety.

*lovastatin and pitavastatin are not currently licensed in Ireland

CVD: cardiovascular disease; CHD: coronary heart disease; T2DM: type 2 diabetes mellitus

There are very few head-to-head clinical trials which compare all or even most statins. Some compare two or three statins for clinical effectiveness and safety. Most meta-analyses include trials which primarily examine a statin versus placebo. The key findings from the meta-analyses and systematic reviews in Table 4 were as follows:

- Yebyo et al (2019) conducted a systematic review, meta-analysis and network meta-analysis to determine the comparative effectiveness and safety of statins (individually, and as a class) for primary prevention of CVD. The study considered six statins (atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin and simvastatin) for which trials on primary prevention were available. Forty trials were included: 33 were placebo-controlled and seven were head-to-head comparisons of statins; only one trial compared more than two statins. The majority of the trials tested low-dose (10/40) or moderate-dose (25/40) of statins. Only 5/40 trials used high-dose statins. (Low-/medium- and high-dose were defined according to the American College of Cardiology /American Heart Association guidance (ACC/AHA). See section 7.3.2). The primary outcomes of all trials were CVD events or all-cause mortality.

  In the pairwise meta-analysis, statins as a class, showed statistically significant risk reductions in non-fatal myocardial infarction (MI) (relative risk [RR] 0.62, 95% confidence interval (CI) 0.53-0.72), CVD mortality (RR 0.80, 95% CI 0.71-0.91), all-cause mortality (RR 0.89, 95% CI 0.85-0.93), non-fatal stroke (RR 0.83, 95% CI 0.75-0.92), unstable angina (RR 0.75, 95% CI 0.63-0.91) and composite major cardiovascular events (RR 0.74, 95% CI 0.67-0.81).

  The drug-level network meta-analysis showed that atorvastatin and rosuvastatin were the most effective in reducing CVD events. Atorvastatin showed statistically significant reductions in fatal and non-fatal MI, non-fatal stroke, all-cause mortality and unstable angina. Rosuvastatin showed statistically significant reductions in non-fatal MI, non-fatal stroke, all-cause mortality and CVD mortality.

  Statins, as a class were associated with a statistically significant increase in relative and absolute risks of myopathy, hepatic dysfunction and renal dysfunction. However, at drug-level, none of the individual statins demonstrated a statistically significant effect for myopathy, while fluvastatin demonstrated the only statistically significant effect for hepatic

dysfunction. The drug-level effect of rosuvastatin, but not atorvastatin, was statistically significant for renal dysfunction. Overall, the harm profile of the statins was diverse, with atorvastatin appearing to be the safest across all harm outcomes except diabetes for which atorvastatin and rosuvastatin showed the highest excess risk.

Limitations of the study included heterogeneity between CVD risk across the studies and lack of consistency in reported outcomes.[33]

- Wang et al (2016) conducted two meta-analyses to compare the efficacy and safety of intensive-dose and standard-dose statin treatment for stroke prevention. Trials which focused on both primary and secondary prevention of cardiovascular disease were included. The first meta-analysis (seven trials) compared intensive-dose statins with standard-dose or placebo; the second meta-analysis (10 trials) compared standard-dose with placebo. Standard-dose treatment was defined as a prescribed daily dose of atorvastatin ≤ 20 mg, simvastatin ≤ 60 mg, or rosuvastatin ≤ 10 mg, or any dose of pravastatin, lovastatin or fluvastatin. A daily dose that was higher than the standard dose was classified as intensive-dose statin treatment. All participants had certain risk factors for stroke, such as diabetes, smoking, previous unstable angina, or CVD.

  Intensive-dose statin treatment showed a statistically significant 21% reduction in RR for all stroke events compared with standard-dose (RR 0.79, 95% CI (0.71-0.87), p<0.00001). The reduction in RR was much greater in patients older than 65 years (RR 0.52, 95% CI 0.36- 0.74) than for those younger than 65 years (RR 0.82, 95% CI 0.74-0.92). High-dose statin treatment versus placebo demonstrated a significant reduction in the incidence of fatal stroke (RR 0.61, 95% CI 0.39-0.96) and a non-significant 5% reduction in haemorrhagic stroke (RR 0.95, 95% CI 0.35-2.55). The analysis of standard dose and placebo for prevention of fatal stroke events showed that the increase was not significant (RR 1.01, 95% CI 0.85-1.2). Likewise, the reduction in RR of haemorrhagic strokes was not significant (RR 0.96, 95% CI 0.91-1.01).

  The results of the meta-analysis of safety were not statistically significant, thus the authors concluded that more data is required to draw conclusions on the safety of intensive-dose statin treatment. The study was limited by heterogeneity in the patients' medication

standards and in baseline risk depending on how stroke was defined. Finally, because of a lack of safety data, standard-dose and intensive-dose statin treatment could not be considered for all secondary endpoints.[34]

- A systematic review and an adjusted indirect comparison meta-analysis conducted by Bonsu et al (2016) aimed to compare lipophilic and hydrophilic statin therapy on clinical outcomes of heart failure (HF). Atorvastatin, simvastatin and pitavastatin were the lipophilic statins evaluated against hydrophilic rosuvastatin. The review included 13 randomised controlled trials (RCTs) totalling 10,966 patients allocated to statin or placebo. Three of the included trials evaluated rosuvastatin in patients with HF. Atorvastatin was tested in 70% of the trials evaluating hydrophilic statins in HF. Lipophilic statins were associated with significantly lower incidence of all-cause mortality (odds ratio (OR) 0.50, 95 % CI (0.11-0.89); p=0.01), cardiovascular mortality (OR 0.61, 95% CI (0.25-0.97); p=0.009), hospitalization for worsening HF (OR 0.52, 95% CI (0.21-0.83); p=0.0005) compared with rosuvastatin treatment. However, reduction in cardiovascular hospitalisation (OR 0.80, 95% CI (0.31-1.28); p=0.36) among patients with HF was not statistically significant.

  The study was limited by the fact that rosuvastatin was the only hydrophilic statin included and the majority of lipophilic studies evaluated atorvastatin. Thus the meta-analysis may be interpreted in a more limited fashion as an indirect comparison of atorvastatin and rosuvastatin.[35]

- The objective of a network meta-analysis by Naci et al (2013) was to estimate the comparative tolerability and harms of individual statins using both placebo-controlled and active-comparator trials in primary and secondary prevention populations. The review included 55 two-armed placebo-controlled trials, and 80 two-armed or multi-armed active-comparator trials. No trial directly compared all seven statins with each other for drug-level or dose-level comparisons.

  When compared with placebo, individual statins were not significantly different than control in terms of myalgia, creatine kinase elevations, cancer, and discontinuations due to adverse

events. Statins, as a class, are generally safe with uncommon side-effects but are associated with significantly higher odds of diabetes mellitus and transaminase elevations compared with placebo. At dose-level comparisons, higher discontinuation rates were associated with higher doses of rosuvastatin and atorvastatin. Among individual statins, simvastatin and pravastatin were deemed to be safer and more tolerable than other statins.[36]

- A meta-analysis conducted by Naci et al (2013) sought to determine the effect of individual statins on major cerebrovascular events across all populations and within primary and secondary prevention groups. The study consisted of 51 two-armed placebo-controlled trials and the remaining 10 were two- or multi-armed active-comparator trials. No trial directly compared all six statins to each other. Across all populations, statin therapy was associated with a significant reduction in major cerebrovascular events when compared with placebo (OR 0.82, 95% CI 0.77-0.87), with no differences among individual statins.

  In the primary and secondary prevention populations, statin therapy was associated with a significant reduction in major cerebrovascular events (OR 0.80, 95% CI 0.71-0.91) and (OR 0.83, 95% CI 0.75-0.91) respectively. In the primary prevention population only atorvastatin and rosuvastatin had sufficient evidence for a significant benefit. In the secondary prevention population, only atorvastatin resulted in significantly few events as compared with placebo.
  For individual statins, significant risk reductions were achieved on major cerebrovascular events across all populations with atorvastatin (OR 0.74, 95% CI 0.63-0.85), pravastatin (OR 0.86, 95% CI 0.76-0.97) and simvastatin (OR 0.75, 95% CI 0.62-0.88) compared with placebo.

  Statins led to significant reductions in the risk of non-fatal strokes (OR 0.77, 95% CI: 0.71-0.85) but not of fatal strokes (OR 0.96, 95% CI: 0.80-1.15).

  Pooling of all trial results did not indicate a significant difference between statins in terms of major cerebrovascular events. Thus the authors concluded that there is a class effect with statins. The analysis was limited by the lack of head-to-head trials designed to capture differences in clinical outcomes as primary endpoints.[37]

- A further meta-analysis conducted by Naci et al (2013) compared the benefits of statins in the primary and secondary prevention of major coronary events and all-cause mortality. There were 92 trials included in the meta-analysis; this corresponded to 101 comparisons because some trials had more than two arms. There were 39 head-to-head statin trials and 62 trials comparing statin therapy to placebo. Only a small number of trials evaluated fluvastatin. No trial directly compared all six statins to each other. Most frequent comparisons occurred between pravastatin and placebo, atorvastatin and placebo, and atorvastatin and rosuvastatin. Primary outcomes were major coronary events and all-cause mortality.

  Across all populations, statins were significantly more effective than control in reducing all-cause mortality (OR 0.87, 95% CI 0.82-0.92) and major coronary events (OR 0.69, 95% CI 0.64-0.75). In terms of reducing major coronary events, atorvastatin (OR 0.66, 95% CI 0.48–0.94) and fluvastatin (OR 0.59, 95% CI 0.36–0.95) were significantly more effective than rosuvastatin at comparable doses. Atorvastatin was significantly more effective than pravastatin (OR 0.65, 95% CI 0.43-0.99) and simvastatin (OR 0.68, 95% CI 0.38-0.98) for secondary prevention of major coronary events. In primary prevention, statins significantly reduced deaths (OR 0.91, 95% CI 0.83-0.99), and major coronary events (OR 0.69, 95% CI 0.61-0.79) with no differences among individual statins. Across all populations, atorvastatin, fluvastatin and simvastatin had the highest overall probability of being the best treatment in terms of both outcomes.

  The trial was limited by a number of factors; heterogeneity ranged from low to moderate across various pair-wise meta-analyses of statins versus controls, there were limited head-to-head statin trials and some of the older trials were prone to bias.[38]

- A systematic review and meta-analysis conducted by Figg et al (2013) focused on statins as a primary prevention method to determine which statin is most effective in improving LDL-C, HDL-C and TG levels in patients with type 2 diabetes mellitus (T2DM). The systematic review evaluated 10 studies: atorvastatin and simvastatin were evaluated in three studies, rosuvastatin was evaluated in one study and three studies evaluated more than one statin, collectively consisting of rosuvastatin, atorvastatin, simvastatin, pravastatin, fluvastatin and

lovastatin. Primary outcomes were LDL-C, HDL-C and TG levels after statin treatment and whether targets set by the American Diabetes Association were achieved.

Atorvastatin and rosuvastatin were shown to be the most potent in reducing LDL-C and TGs. Simvastatin demonstrated the greatest improvements in HDL-C compared to other statins. Studies investigating atorvastatin presented the most adverse events although the number of participants affected was minimal. Simvastatin was reported as well tolerated. There were conflicting reports of tolerability associated with rosuvastatin. Another study reported mild side-effects for all statins studied (atorvastatin, pravastatin, simvastatin and lovastatin). The authors concluded that patients with T2DM with high LDL-C and TGs may benefit from high doses of atorvastatin or rosuvastatin as a primary preventative treatment. Patients with less high-risk profiles may benefit from treatment with simvastatin.

This systematic review and meta-analysis was limited by the small number of studies included and heterogeneity in the patient population (some studies included overweight participants and others varied in the length of time since diagnosis of diabetes).[39]

- A systematic review and meta-analysis by Weng et al (2010) compared the efficacy and safety profiles of different statins at different doses to determine the therapeutically-equivalent doses of statins to achieve a specific level of LDL-C lowering. Eligible patients were over 18 years of age and used statins as a monotherapy for hyperlipidaemia. The study included 75 RCTs representing 140 paired statin comparisons: 62 studies compared two different statins, four studies compared three different statins, six studies compared four different statins and three studies compared five different statins.

  The results showed that at comparable doses, statins are therapeutically equivalent in reducing LDL-C. Statins at equivalent doses provide similar effects on HDL and TG. The only two statins that could reduce LDL-C by more than 40% were rosuvastatin and atorvastatin at daily doses of ≥ 10 mg and ≥ 20 mg respectively. There was insufficient data to allow comparisons of CHD prevention and safety.[40]

Table 5: Head to head statin trials in prevention of cardiovascular events

¤ This list is not exhaustive

Trial	Trial design	Agent	Study population	Follow-up, years	Result
Pitt et al, 2012 (LUNAR)[41]	Open-label, multicentre, parallel-group, prospective RCT	Rosuvastatin 20/40 mg vs atorvastatin 80 mg daily	825 adult patients with CAD hospitalised for acute coronary syndrome	0.23	Rosuvastatin 40 mg had significantly greater efficacy at reducing LDL-C than atorvastatin 80 mg (46.8% vs 42.7% p=0.02); LDL-C reduction with rosuvastatin 20 mg similar to atorvastatin 80 mg. Increase in HDL-C greater with both rosuvastatin 40 mg (11.9%, p<0.001) and 20 mg (9.7%, p<0.01) than atorvastatin 80 mg (5.6%).
Nicholls et al, 2011 (SATURN)[42]	Multicentre, double-blind RCT	Rosuvastatin 40 mg/daily vs. atorvastatin 80 mg/daily	1039 patients with coronary disease	2	Both resulted in significant regression of coronary atherosclerosis. Similar degree of regression of percent atheroma volume (PAV).
Saku et al, 2011 (PATROL)[43]	Multicentre, prospective RCT	Atorvastatin 10 mg/daily vs. rosuvastatin 2.5 mg daily vs. pitavastatin 2 mg daily	302 patients with risk factors for CAD and elevated LDL-C levels	0.333	No difference between these three statins in terms of safety and efficacy.
Leiter et al, 2007 (POLARIS)[44]	Multicentre, double-blind, RCT	Rosuvastatin 40 mg/daily vs. atorvastatin 80 mg/daily	871 high-risk patients with hypercholesterol-aemia	0.5	Mean reduction in LDL-C of 56% in patients receiving rosuvastatin versus 52% in patients receiving atorvastatin (p< 0.001) (Primary end point at 8 weeks).
Pedersen et al, 2005 (IDEAL)[45]	Multicentre, open-label, blinded end-point RCT	Atorvastatin 80 mg/daily vs. simvastatin 20 mg/daily	8,888; age ≤80 years, history of MI (secondary prevention)	4.8	No significant ↓ in coronary events with atorvastatin 80 mg, [hazard ratio (HR) 0.89; 95% CI (0.78-1.01); p=0.07]. Reduction in secondary composite end point of a major cardiovascular event including stroke in atorvastatin group (HR 0.83; 95% CI(0.71-0.98); p=0.02).
Nissen et al, 2004 (REVERSAL)[46]	Multicentre, double-blind RCT	Pravastatin 40 mg/daily vs. atorvastatin 80 mg/daily	654 patients aged 30-75 years who required coronary angiography for a clinical indication	1.5	For the primary end point, progression of coronary atherosclerosis occurred in the pravastatin group (2.7%; 95% CI, 0.2-4.7%; p =0.001) compared with baseline. Progression did not occur in the atorvastatin group (−0.4%; 95% CI (−2.4-1.5%); p= 0.98) compared with baseline.
Cannon et al,2004 (PROVE-IT)[47]	Multicentre, double-blind RCT	Pravastatin 40 mg/daily vs. atorvastatin 80 mg/daily	4,162 patients hospitalised for ACS within 24 hours of ACS	2	3.9% Absolute risk reduction in primary outcome (composite of all-cause mortality, MI, UA hospitalisation, revascularization, stroke) with atorvastatin 80 mg ; relative risk reduction of 15%

Trial	Trial design	Agent	Study population	Follow-up, years	Result
Jones et al, 2003 (STELLAR)[48]	Multicentre, parallel-group, open-label RCT	Rosuvastatin 10/20/40/80 mg/daily (80 mg not reported) vs Atorvastatin 10/20/40/80 mg/daily vs Simvastatin 10/20/40/80 mg/daily vs Pravastatin 10/20/40 mg/daily	2431 adults with hypercholesterolaemia defined as LDL-C 160-250 mg/dl and TG levels < 400 mg/dl	0.12	Rosuvastatin 10-40 mg has greater efficacy than atorvastatin 10-80 mg, simvastatin 10-80 mg and pravastatin 10-40 mg for achievement of Adult Treatment Panel III LDL-C and non-HDL-C goals, European LDL-C goals, and Canadian LDL-C and triple goals. The percentage of patients who reported adverse events were similar among trials.
Ballantyne et al, 2003 (CHESS)[49]	Multicentre, double-blind, parallel-dose RCT	Simvastatin 80 mg/daily vs. atorvastatin 80 mg/daily	917 patients with hypercholesterolaemia	0.4	Simvastatin 80 mg increased HDL-C and apolipoprotein (apo-AI) significantly more than atorvastatin 80 mg. Significantly fewer hepatic transaminase elevations occurred in patients treated with simvastatin.
Brown et al, 2002[50]	Multicentre, parallel-group, double-blind RCT	Rosuvastatin 5/ 10 mg/daily vs pravastatin 20 mg/daily vs simvastatin 20 mg/daily	477	1	At 12 weeks, % LDL-C ↓after rosuvastatin 5/10 mg were 39.1% and 47.4%, respectively, and were significantly different ($p<0.05$) from LDL-C ↓ after 20 mg pravastatin (26.5%) and 20 mg simvastatin (36.4%). After 52 weeks, more rosuvastatin–treated patients remained at their starting dose than simvastatin or pravastatin-treated patients.
Dart et al, 1997[51]	Multicentre, double-blind RCT	Atorvastatin 10 mg/daily vs simvastatin 10 mg/daily	177 patients with hypercholesterolaemia	1	Greater ↓ from baseline in LDL-C, VLDL, TG and apo-B with atorvastatin 10 mg. 46% of patients reached target LDL-C by week 16 with atorvastatin 10 mg (vs 27% with simvastatin 10 mg). No difference in safety between statins.

ACS: acute coronary syndrome CAD: Coronary artery disease RCT: randomised controlled trial UA: unstable angina

Atorvastatin is the statin of choice in terms of efficacy under MMP review.

Atorvastatin and rosuvastatin are the preferred treatment options for patients requiring large reductions in LDL-C e.g. > 50%

7.3 Clinical guidelines for the prevention and treatment of cardiovascular events

In recent years, a number of organisations have published guidelines for primary prevention of atherosclerotic cardiovascular disease (ASCVD) using statin therapy including the ESC/EAS, the National Institute for Health and Care Excellence (NICE) and the ACC/AHA. All guidelines emphasise lifestyle changes as a first-line intervention and agree that statin therapy is the mainstay for patients requiring lipid-lowering medications. Even though all guidelines reflect the same evidence-base, they differ significantly in their recommendations.

7.3.1 2019 ESC/EAS

The 2019 ESC/EAS Guidelines for the Management of Dyslipidaemia state that LDL-C is causal to ASCVD and thus remains the primary target for intervention. Individual LDL-C targets are set at < 1.8 mmol/L in high-risk and < 1.4 mmol/L in very-high-risk patients. For both of these patient groups, these targets, as well as a minimum reduction of 50% from baseline, should be achieved with treatment. A high-intensity regimen is defined in the ESC/EAS guidelines, as the dose of a statin that, on average, reduces LDL-C by ≥ 50%; moderate-intensity therapy is defined as the dose expected to reduce LDL-C by 30-50%.[13]

Individual LDL-C targets are based on global risk, as defined by the Systemic Coronary Risk Estimation (SCORE) risk system. SCORE estimates the 10-year cumulative risk of a first fatal atherosclerotic event (heart attack, stroke or other occlusive arterial disease, including sudden cardiac death).

Statins are the mainstay of pharmacotherapy to lower LDL-C levels and prevent CVD. The guidelines recommend that hypercholesterolaemia should be treated with the highest recommended statin dose or highest tolerable dose to reach the goal.[13]

Table 6: ESC/EAS guideline (2019) for the management of dyslipidaemia

Risk Category	Definition	LDL-C Targets	Intervention
Very High Risk	• Documented CVD • Diabetes mellitus (DM) with target organ damage, ≥ 3 major risk factors or early onset T1DM** of long duration • Severe chronic kidney disease (CKD) (eGFR≠ < 30 mL/min/1.73 m^2) • Calculated SCORE ≥ 10% for 10-year risk of fatal CVD • FH with ASCVD or with another major risk factor	< 1.4 mmol/L and a reduction of ≥ 50% from baseline LDL-C levels	• Lifestyle & concomitant drug intervention if LDL-C > 1.4 mmol/L (secondary prevention)* or > 1.8 mmol/L (primary prevention) • *Consider* drug intervention if LDL-C < 1.4 mmol/L (secondary prevention)* or if > 1.4 (primary prevention)
High Risk	• Markedly elevated single risk factors, in particular TC > 8 mmol/L, LDL-C > 4.9 mmol/L or blood pressure ≥ 180/110 mmHg • Patients with FH without other major risk factors • Patients with DM without target organ damage, with DM-duration ≥ 10 years or other risk factors • Moderate CKD (GFR 30-59 mL/min/1.73 m^2) • A calculated SCORE ≥5% and < 10% for 10-year risk of fatal CVD	< 1.8 mmol/L and a reduction of ≥ 50% from baseline LDL-C levels	• Lifestyle & concomitant drug intervention if LDL-C ≥ 2.6 mmol/L • *Consider* drug intervention if LDL-C ≥ 1.8 mmol/L (uncontrolled)
Moderate Risk	• Young patients with DM-duration < 10 years without other risk factors • SCORE ≥ 1% and < 5% for 10-year risk of fatal CVD	< 2.6 mmol/L	• Lifestyle intervention. • *Consider* drug intervention if LDL-C ≥ 2.6 mmol/L (uncontrolled) • Concomitant drug intervention if LDL-C ≥ 4.9 mmol/L
Low Risk	SCORE < 1% for 10-year risk of fatal CVD	< 3.0 mmol/L	• Lifestyle intervention. • *Consider* drug intervention if LDL-C ≥ 3.0 mmol/L (uncontrolled) • Concomitant drug intervention if LDL-C ≥ 4.9 mmol/L

*All secondary prevention is considered to be very high risk **T1DM: Type 1 Diabetes Mellitus ≠eGFR: estimated glomerular filtration rate

The updated 2019 guidelines advise that if the goals are not achieved with the maximum tolerated dose of statin, combination with ezetimibe is recommended. For secondary prevention, for patients at very-high risk not achieving their goal on a maximum tolerated dose of statin and ezetimibe, a combination with a proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor is recommended.[*] For very-high-risk FH patients (i.e. those with ASCVD or with another major risk factor) who do not achieve their goals on a maximum tolerated dose of statin and ezetimibe after 4-6 weeks, a combination with a PCSK9 inhibitor is recommended.

Table 7 illustrates the achievable reductions of LDL-C depending on the therapeutic approach chosen.

Table 7: Achievable levels of LDL-C as a function of therapeutic approach

Achievable LDL-C levels with different therapeutic strategies					
	Moderate-intensity statins		High-intensity statins		
Starting LDL-C, (mmol/L)		**Plus ezetimibe**		**Plus ezetimibe**	**Plus PCSK9 inhibitor**
4.5	3.2	2.5	2.3	1.6	0.9
4.3	3.0	2.4	2.2	1.5	0.9
4.0	2.8	2.2	2.0	1.4	0.8
3.7	2.6	2.0	1.9	1.3	0.7
3.5	2.5	1.9	1.8	1.2	0.7
3.2	2.2	1.8	1.6	1.1	0.6
3.0	2.1	1.7	1.5	1.1	0.6
2.7	1.9	1.5	1.4	0.9	0.5
2.5	1.8	1.4	1.3	0.9	0.5
2.2	1.5	1.2	1.1	0.8	0.4
1.9	1.3	1.0	1.0	0.7	0.4

The guidelines also recommend statins as the drug of choice for reducing CVD risk in high-risk individuals with hypertriglyceridaemias.

Treatment of dyslipidaemias with statins is recommended for older persons, according to the risk level, in those aged ≤ 75 years. Initiation of statin treatment for primary prevention in older people aged ≥ 75 years may be considered for those at high-risk or above.[13]

[*] In Ireland, PCSK9 inhibitor, evolocumab, is reimbursed under the High Tech Arrangement in line with the HSE-Managed Access Protocol

7.3.2 2018 ACC/AHA

In 2013, the ACC and the AHA published joint guidelines on the treatment of blood cholesterol to reduce ASCVD risk in adults. The recommendations arose from consideration of evidence derived from RCTs, and systematic reviews and meta-analyses of RCTs. Four patient cohorts were identified for whom the evidence demonstrated a reduction in ASCVD events with a good margin of safety from moderate-or high-intensity statin therapy.[52] These groups were further stratified in the guidelines which were updated in 2018.

Table 8: ACC/AHA guideline (2018) on treatment of blood cholesterol[53]

Category of patients likely to receive benefit from statin therapy	Statin Therapy
Primary Prevention	
No ASCVD; age 40-75 years; LDL-C ≥4.9 mmol/L*	High-intensity statins
No ASCVD; age 40-75 years; Diabetes, LDL-C 1.8-4.9 mmol/L	Moderate-intensity statins; Use high-intensity statins if patient has multiple ASCVD risk factors or is 50-75 years of age.
No ASCVD or diabetes; aged 40-75 years; LDL-C 1.8-4.9 mmol/L	High-intensity statins if 10-year ASCVD risk ≥20%; Moderate-intensity statins if 10-year ASCVD risk ≥ 7.5% - <20%; Possible moderate-intensity statins if 10-year ASCVD risk 5-7.5% following risk discussion for statin benefit.
Secondary Prevention	
Clinical ASCVD	Maximum tolerated statins if patient is **very high risk;** High intensity statins if patient has stable ASCVD, aged ≤ 75 years; High or moderate-intensity statin if patient has stable ASCVD, aged > 75 years.

* Exclude secondary causes including hypothyroidism, alcoholism, nephrotic syndrome, drugs etc.

Estimations for 10-year and lifetime risks for ASCVD, defined as coronary death or nonfatal MI, or fatal or nonfatal stroke, are calculated using a tool developed by the ACC/AHA Risk Assessment Work Group.

Patients were classified as very high-risk if they had a history of multiple major ASCVD events, or one major ASCVD event and multiple high-risk conditions.

Table 9: ACC/AHA definition of very high-risk for future ASCVD events[53]

Major ASCVD Events
Recent acute coronary syndrome (within the past 12 months)
History of MI (other than recent acute coronary syndrome event listed above)
History of ischaemic stroke
Symptomatic peripheral arterial disease (history of claudication with ankle brachial index <0.85, or previous revascularization or amputation)
High-Risk Conditions
Age ≥ 65 years
Heterozygous familial hypercholesterolaemia
History of prior coronary artery bypass surgery or percutaneous coronary intervention outside of the major ASCVD event(s)
Diabetes Mellitus
Hypertension
Chronic kidney disease (eGFR 15-59 mL/min/1.73 m^2)
Current smoking
Persistently elevated LDL-C (LDL-C ≥ 2.6 mmol/L) despite maximally tolerated statin therapy & ezetimibe
History of congestive heart failure

eGFR: estimated Glomerular Filtration Rate

Table 10: Classification of statin therapy by intensity under ACC/AHA guidance[53]

	High-Intensity Statin Therapy	Moderate-Intensity Statin Therapy	Low-Intensity Statin Therapy
LDL-C Lowering*	≥50%	30% to 49%	<30%
Primary Statins	Atorvastatin 40-80 mg Rosuvastatin 20-40 mg	Atorvastatin 10-20mg Rosuvastatin 5-10 mg Simvastatin 20-40 mg Pravastatin 40–80 mg Fluvastatin XL 80 mg Fluvastatin 40 mg bd	Simvastatin 10 mg Pravastatin 10-20 mg Fluvastatin 20-40 mg

*Reduction in LDL-C that should be achieved with the dosage listed below each intensity. All doses are daily unless otherwise indicated BD: twice daily

7.3.3 2016 NICE

NICE guidance (Clinical guideline 181- Cardiovascular disease: Risk assessment and reduction, including lipid modification) advises using non-HDL cholesterol, rather than LDL-C levels, to measure lipid levels but no goal is set for atherogenic cholesterol, other than noting that non-HDL-C levels should ideally be reduced by approximately 40% following statin treatment for a period of three months (primary and secondary prevention). Non-HDL-C is defined as total cholesterol minus HDL-C.

Statins are classified slightly differently under NICE guidance compared with the ACC/AHA guidelines: A statin which reduces LDL-C by 20%-30% is considered to be a low-intensity statin, by 31%-40% is a medium-intensity statin and above 40% is a high-intensity statin. Thus, atorvastatin 20/40/80 mg, simvastatin 80 mg and rosuvastatin 10/20/40 mg are all considered to be high-intensity statins under NICE guidance.

Table 11: Percentage reduction in LDL-C with statin therapy under NICE Guidance[54]

Reduction in LDL cholesterol					
Dose (mg/day)	**5**	**10**	**20**	**40**	**80**
Fluvastatin	-	-	21%	27%	33%
Pravastatin	-	20%	24%	29%	-
Simvastatin	-	27%	32%	37%	42%
Atorvastatin	-	37%	43%	49%	55%
Rosuvastatin	38%	43%	48%	53%	-

The NICE guideline recommends that the decision to start statin therapy should be made after an informed discussion between the clinician and the patient. Once the decision to prescribe a statin has been made, the guideline recommends using a statin of high intensity and low acquisition cost.

NICE guidance specifically recommends atorvastatin for the treatment and prevention of CVD, as seen in Table 12 below. Alternative high-intensity statins are rosuvastatin 10-40 mg daily and simvastatin 80 mg. The Medicines & Healthcare products Regulatory Agency (MHRA) however, have advised that simvastatin 80 mg is associated with an increased risk of myopathy and should only be considered in people with severe hypercholesterolaemia and high risk of cardiovascular complications who have not achieved their treatment goals on lower doses, when the benefits are expected to outweigh the potential risk.[54]

The guideline also notes that the clinical outcomes of the only study that compared atorvastatin with rosuvastatin for the prevention of CVD (SATURN, 2011) were inconclusive. Thus, in light of higher cost of rosuvastatin, atorvastatin was recommended as the most cost-effective high-intensity statin.

The guidance does not include patients with FH.

Table 12: NICE guideline (2016) on lipid modification therapy for the prevention of CVD[54]

Patient Category	Recommended Statin Therapy
Primary prevention	
Patients with type 1 diabetes **and:** age > 40 years **or** have diabetes > 10 years **or** have established Diabetic Kidney Disease **or** have other CVD risk factors	Atorvastatin 20 mg daily
Patients with T2DM **and** ≥ 10% 10-year risk of developing CVD; risk estimated using QRISK2*	Atorvastatin 20 mg daily
Patients with chronic kidney disease	Atorvastatin 20 mg daily
Patients with ≥ 10% 10-year risk of developing CVD; risk estimated using QRISK2*	Atorvastatin 20 mg daily
Patients ≥ 85 years old, if appropriate	Atorvastatin 20 mg daily
Secondary prevention	
Patients with established CVD	Atorvastatin 80 mg daily
Patients with chronic kidney disease	Atorvastatin 20 mg daily

*A person's 10-year risk of CVD can be used to inform treatment decisions, such as lifestyle advice or drug treatment. QRISK2 is the recommended formal risk assessment tool to assess CVD risk for the primary prevention of CVD in people up to and including the age of 84 years. QRISK2 is an online assessment tool for estimating the 10-year risk of having a cardiovascular event, in people who do not already have heart disease.

7.3.4 Irish guidelines

The HSE National Diabetes Model of Integrated Care 2018 recommends using LDL-C as the primary target in lipid management for people with T2DM.

Table 13: Target LDL-C for T2DM patients as per HSE National Diabetes Model of Integrated Care

T2DM patients likely to receive benefit from statin therapy	Target LDL-C
No ASCVD; Age > 40 years; ≥ 1 CV risk factors	≤ 2.5 mmol/L
ASCVD	≤ 1.8 mmol/L

Statin therapy is advised except for people < 40 years with low risk of cardio- or cerebrovascular disease, people planning pregnancy or who are pregnant.

In people with T2DM treated with maximum dose statins, who do not reach target LDL-C, a reduction of > 50% in LDL-C from baseline is an alternative therapeutic goal. While LDL-C remains the primary target, desirable HDL-C levels are ≥ 1.0 mmol/L in men and ≥ 1.3 mmol/L in women.

Desirable fasting serum TGs are ≤ 1.7 mmol/L.

The National Diabetes Model of Integrated Care 2018 has two first line statin-therapy options: simvastatin and atorvastatin. However the guidelines note that both agents are proven in diabetes but simvastatin is the first-line treatment due to its cost effectiveness over atorvastatin.[55]

Atorvastatin is the statin of choice in terms of clinical guidelines under MMP review.

7.4 Safety

7.4.1 Adverse drug reactions

Concerns over the safety of statins have increased since the voluntary withdrawal of cerivastatin from the world market in 2001. Table 14 illustrates the common (≥ 1 in 100 to < 1 in 10) adverse-effects of individual statins as a result of their individual properties. A full list of adverse drug reactions (ADRs) for each drug can be found in the individual Summary of Product Characteristics (SmPC) available at www.hpra.ie. There were no very common (≥ 1 in 10) adverse events listed for the five statins below.

Safety evidence from the systematic reviews and meta-analyses (Section 7.2.1) was also considered in this section of the review.

Table 14: Common adverse events associated with statin use

	Atorvastatin[27]	Fluvastatin[28]	Pravastatin[29]	Rosuvastatin[30]	Simvastatin[31]
Abnormal LFTs*	✓				
Allergic reactions	✓				
Asthenia				✓	
Blood creatine kinase ↑	✓	✓			
Blood transaminases ↑		✓			
Dizziness				✓	
Epistaxis	✓				
GI disturbance**	✓	✓		✓	
Headache	✓	✓		✓	
Hyperglycaemia	✓			✓	
Insomnia		✓			
Musculoskeletal & connective tissue disorders	✓			✓	
Nasopharyngitis	✓				
Pharyngolaryngeal pain	✓				

*LFT: Liver Function Test

** GI: gastrointestinal

7.4.2 Contraindications and cautions

Prescribers are required to regularly monitor all patients when prescribing a statin where caution is advised and to avoid prescribing statins where they are deemed contraindicated. The SmPC of the individual statin should be consulted for guidance on cautions and contraindications, available at www.hpra.ie.

Contraindications

Statin use is contraindicated in patients:

- with hypersensitivity to the active substances or any excipients listed;
- with active liver disease, or unexplained, persistent elevations in serum transaminases;
- during pregnancy and breast-feeding;
- with concomitant use of certain medicines (see section 7.5).

Cautions

Hepatic disorders: There have been rare post-marketing reports of fatal and non-fatal hepatic failure in patients taking statins. Liver function tests should be performed before initiation of treatment and when clinically indicated. (Particular care should be taken with daily doses of simvastatin 80 mg and rosuvastatin 40 mg). Elevated serum transaminases warrant close patient monitoring and potentially discontinuation of the statin. Statins are contraindicated in active liver disease (e.g. viral hepatitis) and should be used with caution in patients who consume substantial quantities of alcohol and/or have a history of liver disease.[27-31]

Renal effects: Proteinuria has been observed in patients treated with higher daily doses of rosuvastatin, in particular 40 mg. Increases in urine protein, detected by dipstick, were seen in < 1% of patients at some time during treatment with 10 mg and 20 mg daily, and in approximately 3% of patients treated with 40 mg daily. Haematuria has also been observed in patients treated with rosuvastatin and clinical trial data shows that the occurrence is low.[30]

Muscle disorders: The HMG-CoA reductase inhibitors may occasionally affect skeletal muscle causing myalgia and myopathy which, on rare occasions (≥ 1/10,000, < 1/1,000), progresses to rhabdomyolysis. Rhabdomyolysis is potentially a life-threatening condition characterised by elevated creatine-kinase (CK) levels (> 10 times upper limit of normal (ULN)), myoglobinaemia and

myoglobinuria which may lead to renal failure.[27] Statins should be prescribed with caution in patients with pre-disposing factors for rhabdomyolysis. If CK levels are significantly elevated (> 5 times ULN) at baseline, treatment should not be started. Patients should be made aware of possible serious side-effects and should report inexplicable muscle pain, weakness or cramps, particularly if associated with malaise or fever.[27-31]

Diabetes mellitus: There is some evidence to suggest that statins raise blood glucose and produce a level of hyperglycaemia where formal diabetes care is appropriate. Patients should be monitored appropriately, but usually, statin therapy should not be discontinued.[27-31]

A meta-analysis by Thakker et al (2016) showed that statins, as a class, increase the risk of diabetes by 12%. In the network meta-analysis, high-dose atorvastatin was associated with the highest risk of diabetes, followed by rosuvastatin.[56]

Interstitial lung disease: Cases of interstitial lung disease have been reported with some statins, particularly with long-term therapy. Symptoms include dyspnoea, non-productive cough and deterioration in health. Statin therapy should be stopped if this is suspected.[27-31]

Lactose intolerance: Patients with hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption are advised not to take atorvastatin, pravastatin, simvastatin and rosuvastatin.[27,29-31]

Cognitive function: Post-marketing reports of statins have implicated a reversible cognitive impairing effect in some patients. In contrast, Phase III clinical trials used for drug approval did not report any significant increase in cognitive impairment in statin users versus placebo. However, the clinical trials were not originally designed to detect cognitive impairment. Re-evaluations of the statin clinical trial data have also found no effect on cognition but case-reports and studies have continued to suggest statins can cause cognitive impairment in some patients.[57]

Note: Safety data from the meta-analyses and systematic reviews was also considered in this section of the review.

There are no significant differences between statins in terms of safety under MMP review.

7.5 Drug interactions

Below is an overview of potential drug-drug/ drug-substance interactions that may occur with HMG-CoA reductase inhibitors. This list is not exhaustive and it is advisable to consult the SmPC of the individual statins for a comprehensive list of drug interactions at www.hpra.ie.

- **Products metabolised by cytochrome P450:**

Concomitant administration of medicinal products that are metabolised by CYP450 enzymes may lead to increased plasma concentrations of the statin and an increased risk of myopathy and rhabdomyolysis.

i. Macrolide antibiotics

A risk of increased statin exposure leading to myopathy has been observed with the concurrent use of statins and macrolides. The SmPC's for **atorvastatin** and **pravastatin** advise caution when used concomitantly with macrolides.[27,29] Concomitant use of erythromycin or clarithromycin with **simvastatin** is contraindicated.[31]

ii. Calcium channel blockers

Concomitant administration of verapamil or diltiazem with **simvastatin** increases the risk of myopathy and rhabdomyolysis. Concomitant use of amlodipine with **simvastatin** increases the risk of myopathy. The SmPC for **simvastatin** states that the dose should not exceed 20 mg daily in patients receiving concomitant medication with any of these calcium channel blockers.[31]
A lower maximum dose of **atorvastatin** should be considered when co-administering with CYP3A4 inhibitors.[27]

iii. Amiodarone

The SmPC for **atorvastatin** advises caution, and consideration of a lower dose of atorvastatin when used in combination with amiodarone. [27] The dose of **simvastatin** should not exceed 20 mg daily.[31]

iv. Protease inhibitors

The SmPC's for **atorvastatin** and **rosuvastatin** suggest that their concomitant use with protease inhibitors should be avoided if possible.[27,30] Inhibitors e.g. nelfinavir, boceprevir and telaprevir are contraindicated with **simvastatin**.[31]

v. Fibrates

The use of fibrates alone is occasionally associated with myopathy. An increased risk of muscle related adverse events have been reported when fibrates are co-administered with statins.[29] The risk of these events may be increased with the concomitant use of **atorvastatin** and fibric acid derivatives. The SmPC states that if concurrent use cannot be avoided, the lowest dose of atorvastatin to achieve the therapeutic objective should be used and the patient monitored appropriately.[27] The SmPC for **fluvastatin** urges caution in combination with fibrates.[28] Concomitant use of gemfibrozil and **simvastatin** is contraindicated.[31] The combination of gemfibrozil and **pravastatin** or **rosuvastatin** is not recommended. **Rosuvastatin 40 mg** is contraindicated with concomitant use of a fibrate.[29,30]

vi. Azole antifungals

The SmPC for atorvastatin advises caution when co-administering with azole antifungals**.**[27] The use of itraconazole, ketoconazole, posaconazole or voriconazole is contraindicated with **simvastatin**.[31]

vii. Ciclosporin

The SmPC for **atorvastatin** advises that use with ciclosporin should be avoided. If concurrent use cannot be avoided, the dose of **atorvastatin** should not exceed 10 mg daily.[27] Starting and maintenance dose of **fluvastatin** should be as low as possible when combined with ciclosporin.[28] Clinical and biochemical monitoring of patients receiving concomitant **pravastatin** and ciclosporin is recommended. Treatment should begin with 20 mg **pravastatin** daily and titration to 40 mg should be done with caution.[29] Concurrent administration with **simvastatin** and **rosuvastatin** is contraindicated.[30,31]

viii. Grapefruit juice

Large amounts of grapefruit juice very markedly increase **simvastatin** exposure and moderately increase **atorvastatin** exposure. The SmPC for **simvastatin** states that concomitant use should be avoided. Smaller amounts of grapefruit juice and separating administration by 12 hours reduces the effect with **atorvastatin.** [58]

- **Other interactions**

Colchicine

Use with caution in combination with statins due to reports of myopathy and rhabdomyolysis.[58] The 2016 AHA statement on drug-drug interactions with statins states that coadministration of colchicine with rosuvastatin, fluvastatin or pravastatin is reasonable when clinically indicated. Dose reductions may be considered for atorvastatin and simvastatin given the potential for interactions mediated by both CYP3A4 and permeability glycoprotein pathways.[59]

Colestyramine

Colestyramine slightly reduces **pravastatin** exposure when given at the same time, and has minimal effect when administration is separated. An online interaction tool advises separation of administration.[58] The SmPC for **fluvastatin** states that administration should be at least four hours after colestyramine.[28]

Ezetimibe

The incidence of rhabdomyolysis may be increased with concomitant use of ezetimibe and statins. However, no extra precautions are needed on the concurrent use of ezetimibe and a statin compared with those recommended for either drug alone. Patients should be carefully monitored and should be told to report any signs of myopathy and possible rhabdomyolysis.[58]

Fusidic acid

The risk of myopathy including rhabdomyolysis may be increased by concomitant administration of systemic fusidic acid with statins. If treatment with systemic fusidic acid is necessary, the statin should be discontinued throughout the duration of the fusidic acid treatment and for a further seven days after cessation.[27-31]

Lenalidomide

Rhabdomyolysis has been reported in patients taking lenalidomide with **pravastatin.** Other statins might be associated with the same risk.[58]

Rifampicin

The effects of rifampicin on statin exposure depend on whether rifampicin is administered as a single dose or steady-state and whether the drugs are given together or separated. Prudent monitoring of the outcome of concurrent use is recommended.[58]

Vitamin K antagonists

The initiation of treatment or dosage up-titration of HMG Co-A reductase inhibitors in patients treated concomitantly with vitamin K antagonists (e.g. warfarin) may result in increased International Normalised Ratio (INR) values. Discontinuation or dose decreases may result in a decrease in INR. Appropriate monitoring of INR in these patients is advised.[27-31]

Fluvastatin, pravastatin and rosuvastatin have favourable drug interaction profiles under MMP review.

7.6 Patient factors

7.6.1 Dosing and administration

The HMG-CoA reductase inhibitors considered in this review are taken once daily.[27-31]

Table 15: Dosing and administrations of individual statins

Drug	Dose	Frequency	Administration
Atorvastatin	10-80 mg/day	Once daily	Swallow whole, with or without food
Fluvastatin	80 mg/day	Once daily	Swallow whole with a glass of water, with or without food. Once daily dose taken in the evening.
Pravastatin	10-40 mg/day	Once daily	Swallow whole preferably in the evening, with or without food
Rosuvastatin	10-40 mg/day	Once daily	Swallow whole at any time of the day, with or without food
Simvastatin	5-80 mg/day	Once daily	Swallow whole in the evening, with or without food

HMG-CoA reductase inhibitors should be swallowed whole, with water. Concomitant food intake does not affect absorption. Atorvastatin and rosuvastatin can be taken at any time of the day, irrespective of meals.[27,30] Hepatic cholesterol synthesis is maximal between midnight and 2am; therefore statins with a half-life of 4 hours or less (simvastatin, immediate release fluvastatin and pravastatin) should be taken in the evening.[60]

Atorvastatin and rosuvastatin are the preferred statins with regard to dosing and administration under MMP review.

7.7 Cost

Value for money is a consideration when choosing a preferred statin. It is also a consideration for patients who pay for their medicines. A drug of lower acquisition cost is preferable unless a more expensive drug has a proven advantage in terms of either safety or efficacy.

Figure 1 illustrates the PCERS reimbursed cost price comparison of 28 dosage units of each statin. The most expensive statin in terms of reimbursed cost price is rosuvastatin 40 mg (€11.48). The least expensive is simvastatin 10 mg (€1.96). Prices are correct as of 01/03/2020.[61]

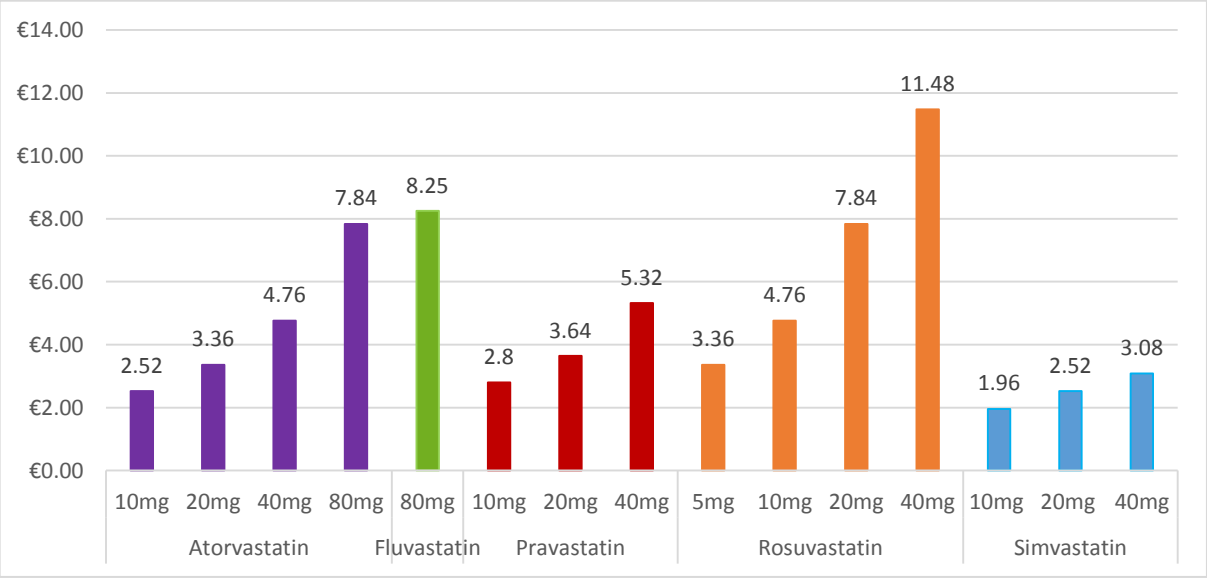

Figure 1: PCERS reimbursed cost of 28 dosage units of each statin (March 2020)

The cost of individual statins can also be compared using the defined daily dose (DDD), as identified by the WHO-collaborating-centre for drug statistics methodology.[1] In the case where the DDD is not available as a single-dose preparation, the combination of tablets that make up the dose is used e.g. the DDD for simvastatin is 30 mg, therefore the PCERS reimbursed cost of a 10 mg and a 20 mg tablet is used to calculate the cost per DDD per month. The DDD can sometimes be a dose that is rarely or never prescribed e.g. fluvastatin 60 mg is not available in Ireland, thus ¾ of the PCERS reimbursed cost of XL 80 mg tablet was used to calculate the DDD. This is solely used to calculate the DDD for comparative purposes and may not be a true representation of daily dosing.

Table 16: Defined daily dose for each statin[1]

Drug	Defined daily dose (DDD)
Atorvastatin	20 mg
Fluvastatin	60 mg
Simvastatin	30 mg
Pravastatin	30 mg
Rosuvastatin	10 mg

Figure 2 shows the typical reimbursement cost per month (28 days) exclusive of pharmacist fees and mark-up of available statins based on the DDD. Atorvastatin is the least expensive statin using this method.

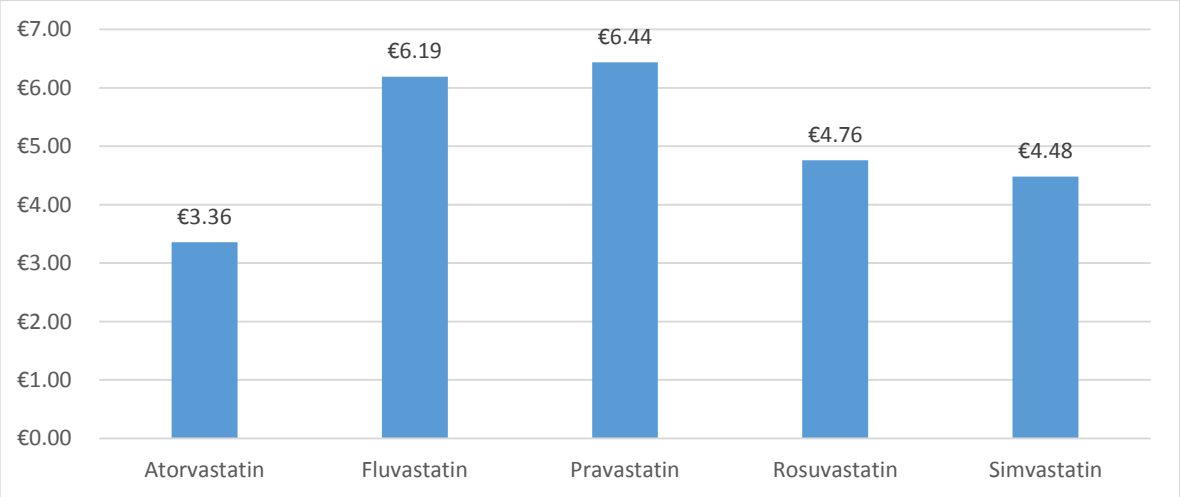

Figure 2: PCERS reimbursed cost of 28 dosage units based on defined daily dose (March 2020)

Comparison of the cost of individual statins of the same intensity is also useful in determining the most cost-effective statin. The costs of low-, medium- and high-intensity statins (as defined by ACC/AHA) are compared in tables 17, 18 and 19 below.[61]

Table 17: Cost comparison of low-intensity statins

Low-intensity statin	Cost per 28-day supply
Pravastatin 10 mg/day	€2.80
Pravastatin 20 mg/day	€3.64
Simvastatin 10 mg/day	€1.96

Table 18: Cost comparison of medium-intensity statins

Medium-intensity statin	Cost per 28-day supply
Atorvastatin 10 mg/day	€2.52
Atorvastatin 20 mg/day	€3.36
Fluvastatin 80 mg/day	€8.25
Pravastatin 40 mg/day	€5.32
Rosuvastatin 5 mg/day	€3.36
Rosuvastatin 10 mg/day	€4.76
Simvastatin 20 mg/day	€2.52
Simvastatin 40 mg/day	€3.08

Table 19: Cost comparison of high-intensity statins

High-intensity statin	Cost per 28-day supply
Atorvastatin 40 mg/day	€4.76
Atorvastatin 80 mg/day	€7.84
Rosuvastatin 20 mg/day	€7.84
Rosuvastatin 40 mg/day	€11.48

Atorvastatin and simvastatin are the statins of choice with regard to cost under MMP guidance.

Atorvastatin is the least expensive statin using the Defined Daily Dose as a cost-comparison method.

7.8 National prescribing trends in Ireland

Figure 3 below represents the total volume of claims (number of prescriptions) reimbursed by the PCERS for each of the statins on the CDS from January- December 2018. The largest volume is attributed to atorvastatin, at 58.6% of total volume reimbursed. This is followed by rosuvastatin, pravastatin, simvastatin and fluvastatin.[62]

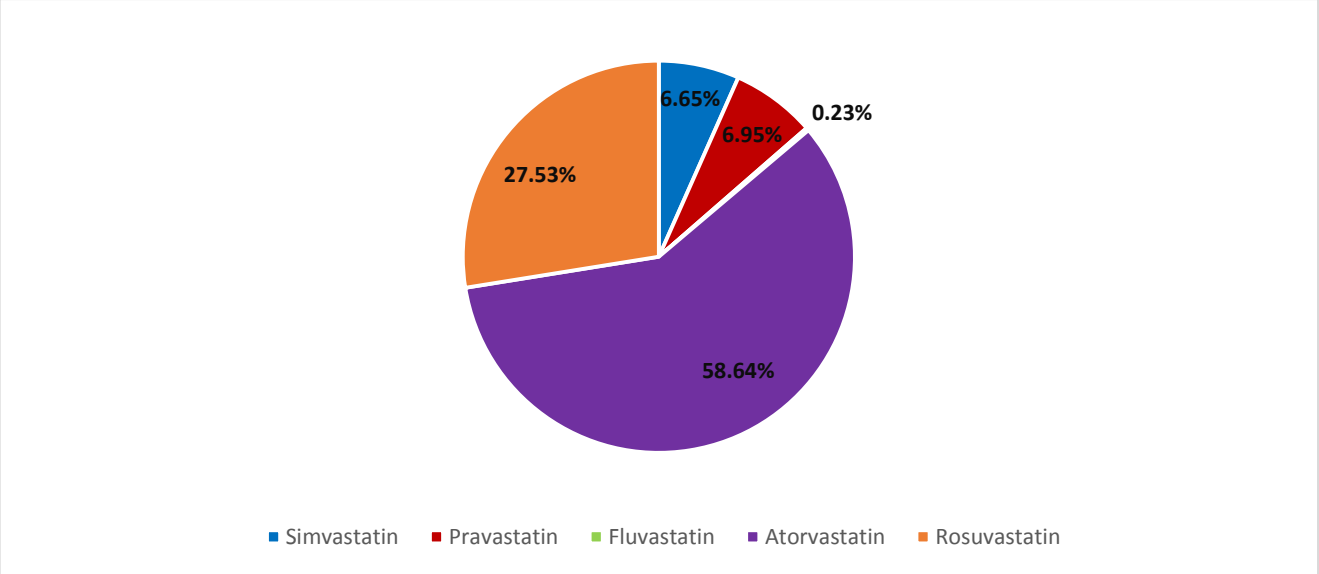

Figure 3: Distribution of statin claims based on number of prescriptions reimbursed by PCERS on the Community Drug Schemes, January to December 2018

7.8.1 Expenditure trends

Following a slight decline in total expenditure on atorvastatin on the GMS scheme in early 2015, total expenditure on each of the statins has remained relatively constant over the last three years. The highest expenditure on this scheme, has consistently been on atorvastatin, corresponding with the largest number of prescriptions reimbursed and the largest cohort of patients receiving statin therapy. Expenditure on rosuvastatin dropped by almost half in August 2018 following the revision of reference pricing by the HSE. However it increased slightly the following month and remained steady at approximately €800,000 per month for the rest of 2018. (figure 4).[62]

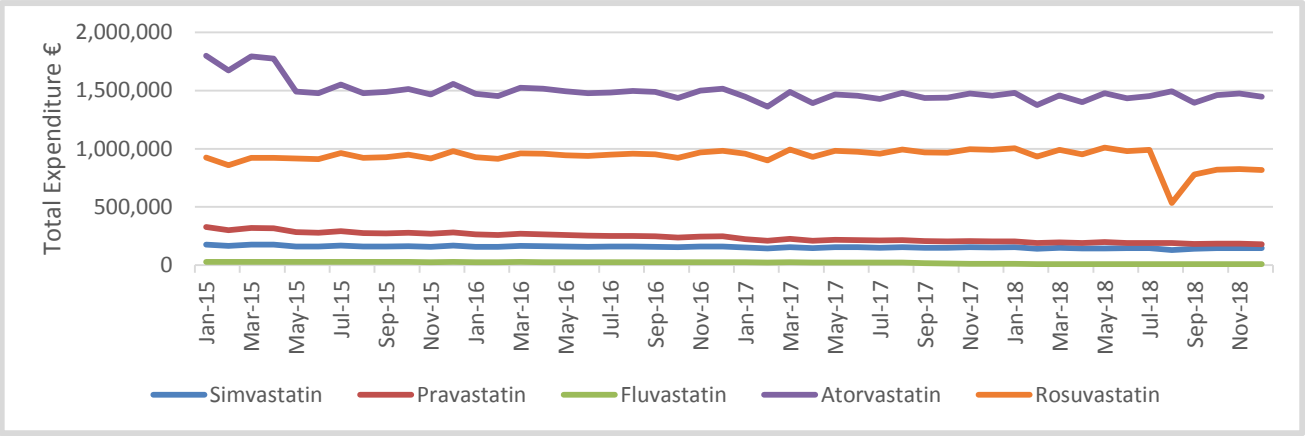

Figure 4: Total monthly expenditure for each statin on the GMS scheme, January 2015- December 2018

Total statin expenditure on CDS accounted for €45.8 million in 2018. Within that, the largest spend was on atorvastatin (€24.4 million), followed by rosuvastatin (€16 million), pravastatin (€2.96 million), simvastatin (€2.33 million) and fluvastatin (€143,000), respectively (figure 5).[62]

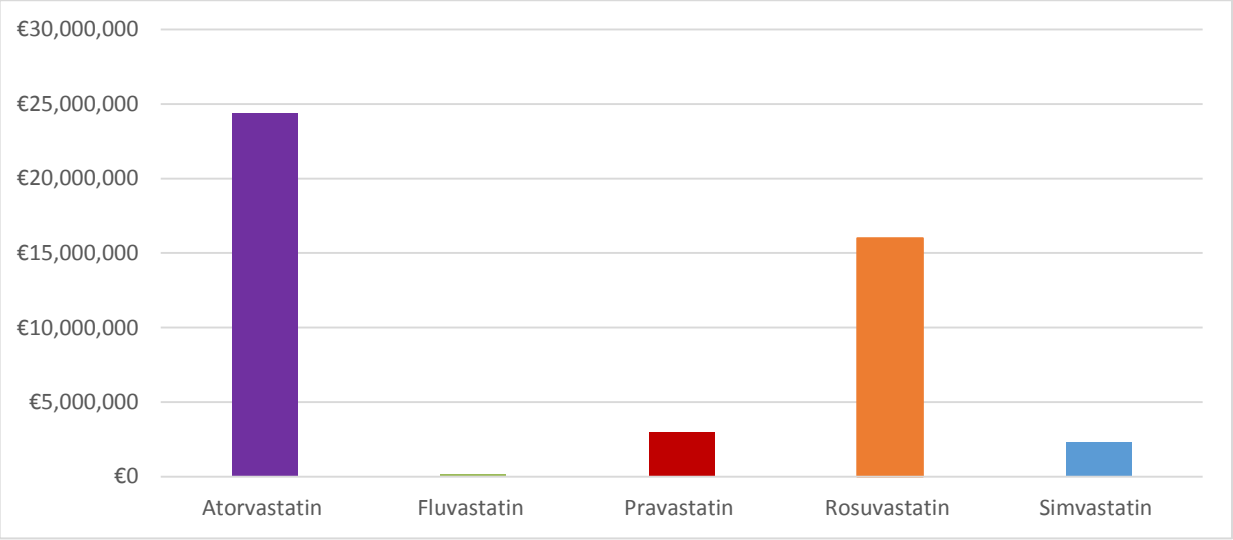

Figure 5: Total statin expenditure on Community Drug Schemes, 2018

When expenditure by strength of statin was examined, rosuvastatin 10 mg accounted for the largest outlay of statin expenditure on the CDS in 2018 corresponding to a spend of approximately €8.3 million. This was followed by atorvastatin 10 mg (€7.6 million), atorvastatin 20 mg (€7.5 million) and atorvastatin 40 mg (€7 million) (figure 6).[62]

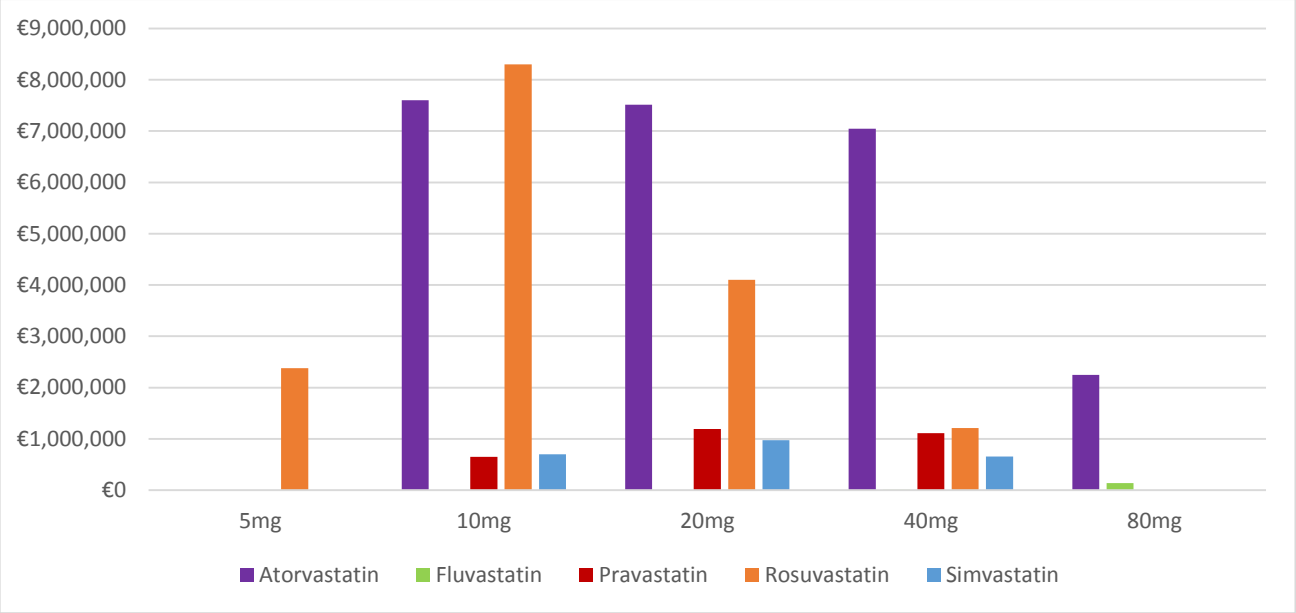

Figure 6: Total statin expenditure on Community Drug Schemes by strength, 2018

7.8.2 Patient demographics

Atorvastatin 10 mg was associated with the highest numbers for patients receiving statins on the GMS scheme in 2018 (21.5%). This was followed by atorvastatin 20 mg (19%), rosuvastatin 10 mg (14.8%) and atorvastatin 40 mg (14.6%) (table 20).[62]

Note: This data refers to strength of tablet only, rather than dose e.g. a patient could be prescribed 40 mg atorvastatin but be taking two of the 20 mg tablets.

Table 20: Percentage of patients on each strength of individual statin on the GMS scheme in 2018

Percentage of patients on each statin dose on the GMS scheme in 2018						
	5 mg	**10 mg**	**20 mg**	**40 mg**	**80 mg**	**Total**
Atorvastatin	N/A	21.5	19.0	14.6	3.7	**58.8%**
Fluvastatin	N/A	N/A	0.0	0.0	0.2	**0.2%**
Pravastatin	N/A	1.9	3.0	2.2	N/A	**7.1%**
Rosuvastatin	5.4	14.8	5.2	1.3	N/A	**26.7%**
Simvastatin	N/A	2.5	3.0	1.7	N/A	**7.2%**
TOTAL						**100%**

Analysis of patient numbers on individual statins showed that simvastatin 20 mg accounted for the majority of simvastatin dispensing (41%). The other statins associated with the highest patient

numbers were: Pravastatin 20 mg (41% of pravastatin dispensing), fluvastatin 80 mg (97% of fluvastatin dispensing), atorvastatin 10 mg (36% of atorvastatin dispensing) and rosuvastatin 10 mg (55% of rosuvastatin dispensing).[62]

7.8.3 Prescribing trends by statin intensity

Figure 7 illustrates the distribution of low-, medium- and high-intensity statins, as defined by the ACC/AHA guidelines, on all CDS in 2018. The vast majority of statins dispensed belong to the medium-intensity-statin group (69%). High-intensity statins are the second-largest group at 24% and, finally, 7% of all statins prescribed on the CDS in 2018 belonged to the low-intensity statin group.

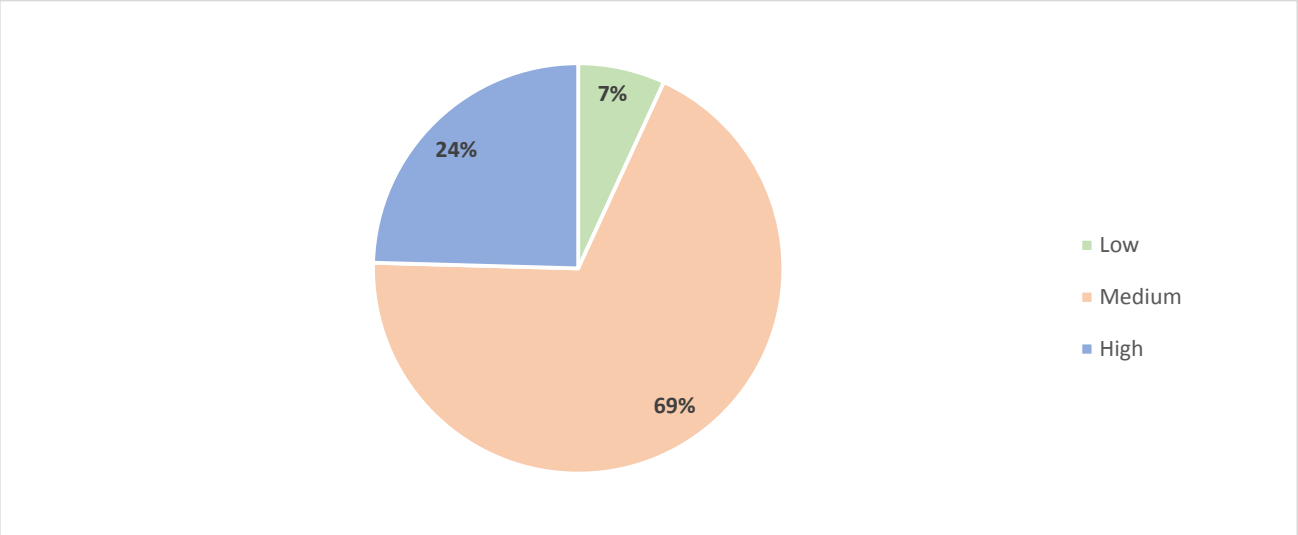

Figure 7: Distribution of low-, medium- and high-intensity statins on Community Drug Schemes 2018

Breakdown of claims by strength were similar between schemes (figures 8 and 9 below). This was observed for the higher intensity statins also, where the percentage of claims was almost identical between high-intensity atorvastatin on the GMS scheme and on the DPS/LTI. Slight differences were observed for rosuvastatin where the percentage of claims for rosuvastatin 20 mg was 18.9% for the GMS scheme and 22.7% for the DP and LTI schemes combined. Figures for rosuvastatin 40 mg were 4.85% (GMS) and 6.5% (DPS/LTI). (These values are a percentage of total rosuvastatin claims).

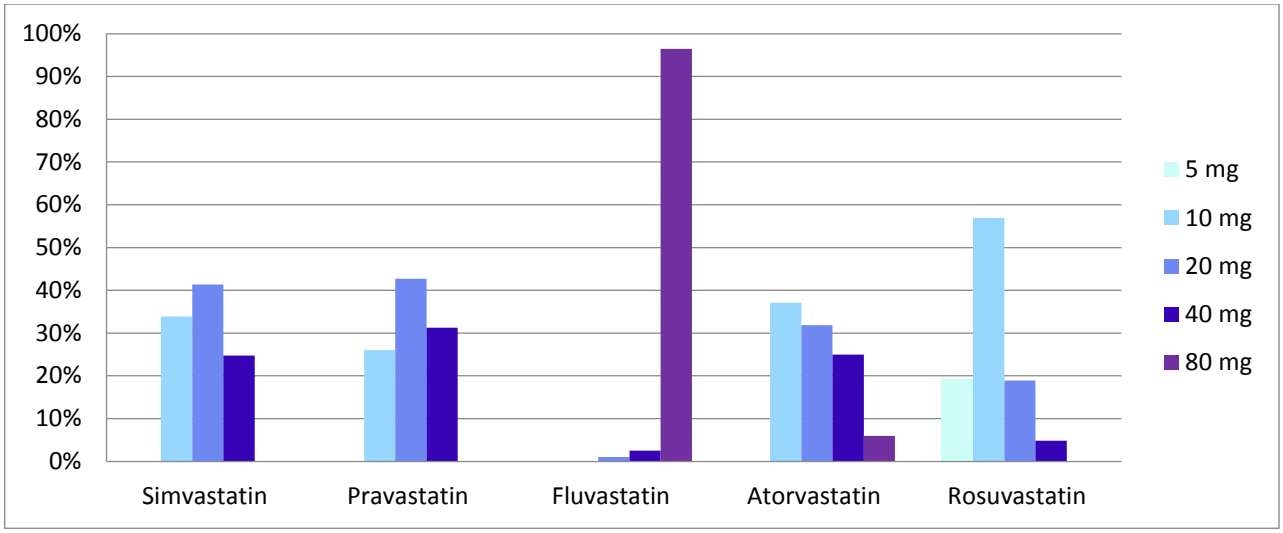

Figure 8: Percentage of claims in each strength-GMS 2018

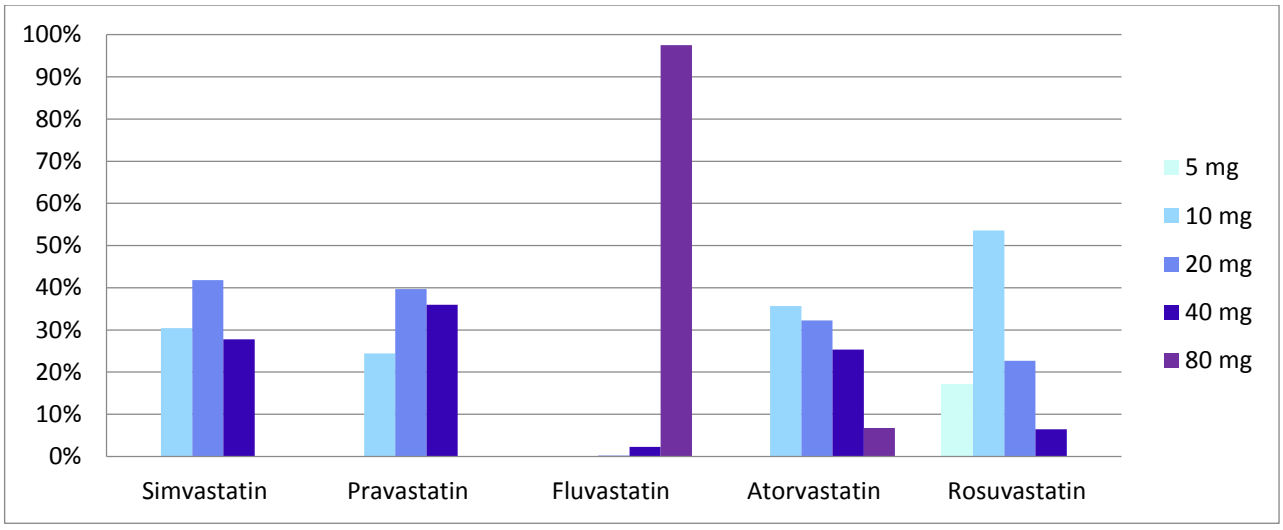

Figure 9: Percentage of claims in each strength-DPS/LTI 2018

7.8.4 Prescribing trends by age

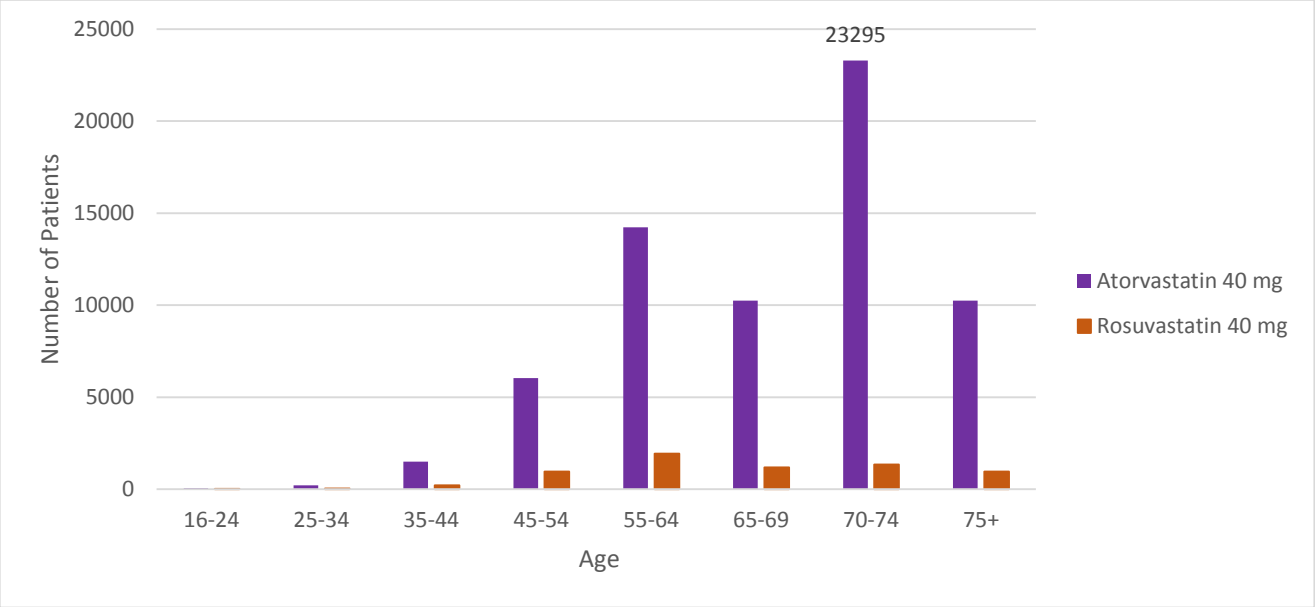

Figure 10: Number of adult patients on high-intensity statins on Community Drug Schemes in 2018, as differentiated by age

Patients aged between 70 and 74 years represent the largest percentage of patients on high-intensity statins (31%), followed by those aged 55-64 (24%), 65-69 years (16%) and 75 years and older (15%). 10.5% of high-intensity statin users are aged between 45 and 54 years (figure 10).[62] Within each age bracket, atorvastatin 40 mg was consistently associated with the highest patient numbers.

Atorvastatin is the statin of choice in terms of national prescribing trends and market-share under MMP guidance.

8. Conclusion

Atorvastatin is the preferred statin monotherapy for the treatment of hypercholesterolaemia and prevention of cardiovascular events under MMP guidance

- ✓ Atorvastatin is licensed for primary hypercholesterolaemia and prevention of cardiovascular events
- ✓ Atorvastatin has once daily dosing for all indications
- ✓ Atorvastatin can be taken at any time of the day
- ✓ Atorvastatin has favourable clinical efficacy data
- ✓ Atorvastatin and simvastatin have the lowest acquisition costs
- ✓ Atorvastatin holds 58% of market share in Ireland (2018)
- ✓ Atorvastatin has a range of dosage strengths which allow patients move from low to medium or high intensity treatment as required
- ✓ Atorvastatin is a potential treatment option for patients requiring a large decrease in LDL-C
- ✓ Atorvastatin is recommended by NICE for the treatment of hypercholesterolaemia & prevention of cardiovascular events

References

1. WHO Collaborating Centre for Drug Statistics methodology ATC/DDD Index. Available at https://www.whocc.no/atc_ddd_index/?code=C10AA. [Accessed June 13, 2018].

2. Piepoli MF, Hoes AW, Agewall S, et al. 2016 European Guidelines on Cardiovascular Disease Prevention in Clinical Practice. *Eur Heart J* 2016; 37:2315-2381.

3. WHO | Cardiovascular diseases (CVDs). WHO. Published 2018. Available at: https://www.who.int/health-topics/cardiovascular-diseases/#tab=tab_1 [Accessed September 27, 2018].

4. Central Statistics Office. *Vital Statistics Yearly Summary 2017*. [s.n.]; 2017. Available at https://www.cso.ie/en/releasesandpublications/ep/p-vsys/vitalstatisticsyearlysummary2017/ [Accessed June 12, 2018].

5. Superko HR. Hypercholesterolemia and Dyslipidemia. *Curr Treat Options Cardiovasc Med*. 2000;2(2):173-187.

6. McKenney JM. Pharmacologic Characteristics of Statins. *Clin Cardiol*. 2003;26(4 Suppl 3):III32-8. doi:10.1002/clc.4960261507

7. Primary Care Reimbursement Service. *Statistical Analysis of Claims and Payments 2017*. Accessed December 19, 2018. www.hse.ie

8. The Familial Hypercholesterolemia Foundation. How to Lower Your Elevated LDL Cholesterol. Available at: https://thefhfoundation.org/lower-elevated-ldl-cholesterol [Accessed June 12, 2018].

9. NICE [STA]:June 2012. Mipomersen for the Prevention of Cardiovascular Events Due to Homozygous or Severe Heterozygous Familial Hypercholesterolaemia. Available at https://www.nice.org.uk/guidance/gid-tag437/documents/hypercholesterolemia-mipomersen-final-scope2 [Accessed June 12, 2018].

10. Marais AD. Familial hypercholesterolaemia. *Clin Biochem Rev*. 2004;25(1):49-68.

11. How to Understand a Lipid Panel | ForeverHealth.com. Available at: https://www.foreverhealth.com/blogs/forever-health/69756741-how-to-understand-a-lipid-panel [Accessed June 13, 2018]

12. Irish Nutrition and Dietetic Institute. How To Manage Cholesterol. Published 2013. Available at https://www.indi.ie/diseases,-allergies-and-medical-conditions/heart-health/530-how-to-manage-cholesterol.html [Accessed June 12, 2018]

13. Mach F, Baigent C, Catapano AL, et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk: The Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society. *Eur Heart J*. 2020;41:111-188

14. NICE [CG181]: July 2014. Lipid Modification. Cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease. Available at https://www.nice.org.uk/guidance/cg181/evidence/lipid-modification-update-

full-guideline-243786637 [Accessed September 27, 2018].

15. Mas E, Mori TA. Coenzyme Q 10 and Statin Myalgia: What is the Evidence? Curr Atheroscler Rep 2010;12(6):407-413.

16. McFarland A, Anoopkumar-Dukie S, Arora D, et al. Molecular Mechanisms Underlying the Effects of Statins in the Central Nervous System. *Int J Mol Sci*. 2014;15(11):20607-20637.

17. Rang H, Dale M, Ritter J, Flower R. *Rang and Dale's Pharmacology*. 6th ed. Churchill Livingstone Elsevier; 2007. Accessed June 11, 2018. https://www.cmecde.com/rang-and-dale-pharmacology-7th-edition-download-pdf/

18. Schachter M. Chemical, pharmacokinetic and pharmacodynamic properties of statins: an update. *Fundam Clin Pharmacol*. 2005;19(1):117-125.

19. Matusewicz L, Meissner J, Toporkiewicz M, et al. The effect of statins on cancer cells—review. *Tumour Biol*. 2015;36(7):4889-4904

20. Kim MC, Ahn Y, Jang SY, et al. Comparison of Clinical Outcomes of Hydrophilic and Lipophilic Statins in Patients with Acute Myocardial Infarction. *Korean J Intern Med*. 2011;26(3):294-303.

21. Maji D, Shaikh S, Solanki D, et al. Safety of statins. *Indian J Endocrinol Metab*. 2013;17(4):636-646.

22. Bonsu KO, Kadirvelu A, Reidpath DD. Lipophilic versus hydrophilic statin therapy for heart failure: a protocol for an adjusted indirect comparison meta-analysis. *Syst Rev*. 2013;2(1):22. doi:10.1186/2046-4053-2-22

23. Gazzerro P, Proto MC, Gangemi G, et al. Pharmacological actions of statins: a critical appraisal in the management of cancer. *Pharmacol Rev*. 2012;64(1):102-146.

24. Dalakas MC. Toxic and drug-induced myopathies. *J Neurol Neurosurg Psychiatry*. 2009;80:832-838.

25. Medsafe. Statins and CYP Interactions. Published 2014. Available at https://www.medsafe.govt.nz/profs/PUArticles/March2014StatinsAndCYPInteractions.htm [Accessed June 8, 2018].

26. Irish College of General Practitioners. Quality and Safety in Practice Committee. *Good Practice Points: Cardiovascular Disease Prevention*.; 2020. Available at https://www.icgp.ie/ [Accessed June 22, 2020].

27. Atorvastatin (Lipitor®) 40mg Tablets (Pfizer). Summary of Product Characteristics. Available at https://www.medicines.ie/ [Accessed June 14, 2018].

28. Fluvastatin (Lescol®) XL 80mg Tablets (Novartis). Summary of Product Characteristics. Available at https://www.medicines.ie/ [Accessed June 14, 2018].

29. Pravastatin (Lipostat®) 10mg, 20mg, 40mg Tablets (BMS Pharmaceuticals). Summary of Product Characteristics. Avaiable at https://www.medicines.ie/ [Accessed June 14, 2018].

30. Rosuvastatin (Crestor®) 5mg,10mg, 20mg, 40mg Tablets (Astra Zeneca). Summary of Product Characteristics. Available at https://www.medicines.ie/ [Accessed June 14, 2018].

31. Simvastatin (Zocor®) 10mg, 20mg, 40mg Tablets (MSD Ltd). Summary of Product Characteristics. Available at https://www.medicines.ie/ [Accessed June 14, 2018].

32. Catapano AL, Graham I, De Backer G, et al. 2016 ESC/EAS Guidelines for the Management of Dyslipidaemias. *Eur Heart J*. 2016;37(39):2999-3058.

33. Yebyo HG, Aschmann HE, Kaufmann M, et al. Comparative effectiveness and safety of statins as a class and of specific statins for primary prevention of cardiovascular disease: A systematic review, meta-analysis and network meta-analysis of randomized trials with 94,283 participants. *Am Heart J*. 2019;210:18-28.

34. Wang J, Chen D, Li D-B, et al. Comparison of the efficacy and safety of intensive-dose and standard-dose statin treatment for stroke prevention. *Medicine (Baltimore)*. 2016;95(39):e4950.

35. Bonsu KO, Reidpath DD, Kadirvelu A. Lipophilic Statin Versus Rosuvastatin (Hydrophilic) Treatment for Heart Failure: a Meta-Analysis and Adjusted Indirect Comparison of Randomised Trials. *Cardiovasc Drugs Ther*. 2016;30(2):177-188.

36. Naci H, Brugts J, Ades T. Comparative Tolerability and Harms of Individual Statins. *Circ Cardiovasc Qual Outcomes*. 2013;6(4):390-399.

37. Naci H, Brugts JJ, Fleurence R, et al. Comparative effects of statins on major cerebrovascular events: a multiple-treatments meta-analysis of placebo-controlled and active-comparator trials. *QJM An Int J Med*. 2013;106(4):299-306.

38. Naci H, Brugts JJ, Fleurence R, et al. Comparative benefits of statins in the primary and secondary prevention of major coronary events and all-cause mortality: a network meta-analysis of placebo-controlled and active-comparator trials. *Eur J Prev Cardiol*. 2013;20(4):641-657.

39. Figg G, Jervis A, Champion S,et al. Statins as a Primary Prevention: Which One is Most Effective? A Systematic Review and Meta-Analysis. J Cardiovasc Dis Diagn 2013, 1:2.

40. Weng T-C, Yang Y-HK, Lin S-J, et al. A systematic review and meta-analysis on the therapeutic equivalence of statins. *J Clin Pharm Ther*. 2010;35(2):139-151.

41. Pitt B, Loscalzo J, Monyak J, et al. Comparison of Lipid-Modifying Efficacy of Rosuvastatin Versus Atorvastatin in Patients With Acute Coronary Syndrome (from the LUNAR Study). *Am J Cardiol*. 2012;109(9):1239-1246.

42. Nicholls SJ, Ballantyne CM, Barter PJ, et al. Effect of Two Intensive Statin Regimens on Progression of Coronary Disease. *N Engl J Med*. 2011;365(22):2078-2087.

43. Saku K, Zhang B, Noda K. The PATROL Trial Investigators. Randomized Head-to-Head Comparison of Pitavastatin, Atorvastatin, and Rosuvastatin for Safety and Efficacy (Quantity and Quality of LDL). *Circ J*. 2011;(75)6:1493-1505

44. Leiter LA, Rosenson RS, Stein E, et al. Efficacy and safety of rosuvastatin 40 mg versus atorvastatin 80 mg in high-risk patients with hypercholesterolemia: Results of the POLARIS study. *Atherosclerosis*. 2007;194(2):e154-e164.

45. Pedersen TR, Faergeman O, Kastelein JJP, et al. High-Dose Atorvastatin vs Usual-Dose

Simvastatin for Secondary Prevention After Myocardial Infarction;The IDEAL Study: A Randomized Controlled Trial. *JAMA*. 2005;294(19):2437-2445

46. Nissen SE, Nicholls SJ, Sipahi I, et al. Effect of Very High-Intensity Statin Therapy on Regression of Coronary Atherosclerosis. *JAMA*. 2006;295(13):1556-1565.

47. Cannon CP, Braunwald E, McCabe CH, et al. Intensive versus Moderate Lipid Lowering with Statins after Acute Coronary Syndromes. *N Engl J Med*. 2004;350:1495-1504.

48. Jones PH, Davidson MH, Stein EA, et al. Comparison of the efficacy and safety of rosuvastatin versus atorvastatin, simvastatin, and pravastatin across doses (STELLAR* Trial). *Am J Cardiol*. 2003;92(2):152-160.

49. Ballantyne CM, Blazing MA, Hunninghake DB, et al. Effect on high-density lipoprotein cholesterol of maximum dose simvastatin and atorvastatin in patients with hypercholesterolemia: Results of the Comparative HDL Efficacy and Safety Study (CHESS). *Am Heart J*. 2003;146(5):862-869.

50. Brown WV, Bays HE, Hassman DR, et al. Efficacy and safety of rosuvastatin compared with pravastatin and simvastatin in patients with hypercholesterolemia: A randomized, double-blind, 52-week trial. *Am Heart J*. 2002;144(6):1036-1043.

51. Dart A, Jerums G, Nicholson G, et al. A multicenter, double-blind, one-year study comparing safety and efficacy of atorvastatin versus simvastatin in patients with hypercholesterolemia. *Am J Cardiol*. 1997;80(1):39-44.

52. Stone NJ, Robinson JG, Lichtenstein AH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2014;129(25 Suppl 2):S1-45.

53. Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/ AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation. 2019;139:e1082-e1143

54. NICE [CG181]: July 2014. Cardiovascular Disease: Risk Assessment and Reduction, Including Lipid Modification.Available https://www.nice.org.uk/guidance/cg181/resources/cardiovascular-disease-risk-assessment-and-reduction-including-lipid-modification-pdf-35109807660997 [Accessed June 13, 2018]

55. Irish College of General Practitioners. *Model of Integrated Care for Patients with Type 2 Diabetes. A Guide for Health Care Professionals (Clinical Management Guidelines)*.; 2018. Available at https://www.hse.ie/eng/services/list/2/primarycare/east-coast-diabetes-service/management-of-type-2-diabetes/model-of-integrated-care-for-patients-with-type-2-diabetes-%E2%80%93-a-guide-for-health-care-professionals.pdf [Accessed July 1, 2019].

56. Thakker D, Nair S, Pagada A, et al. Statin use and the risk of developing diabetes: a network meta-analysis. *Pharmacoepidemiol Drug Saf*. 2016;25(10):1131-1149.

57. Schultz BG, Patten DK, Berlau DJ. The role of statins in both cognitive impairment and protection against dementia: a tale of two mechanisms. *Transl Neurodegener.* 2018: 7:5

58. Stockley's Interactions Checker. 2018. Available online at https://www.medicinescomplete.com/#/ [Accessed June 27, 2018]

59. Wiggins BS, Saseen JJ, Page RL, et al. Recommendations for Management of Clinically Significant Drug-Drug Interactions With Statins and Select Agents Used in Patients with Cardiovascular Disease: A Scientific Statement from the American Heart Association. Circulation 2016;134(21):e468-495

60. National Medicines Information Centre (NMIC). Update on Lipid-Lowering Therapies. *Natl Med Inf Cent Bull*. 2006;12(4). Available at http://www.stjames.ie/GPsHealthcareProfessionals/Newsletters/NMICBulletins/NMICBulletins2006/Update%20on%20Lipid-Lowering%20Therapies%20Vol.12%20No.4%202006.pdf [Accessed June 14, 2018].

61. HSE PCRS Reimbursable Items. Available at https://www.sspcrs.ie/druglist/pub [Accessed March 5, 2019].

62. PCRS database-total expenditure on statins (January 2015- December 2018). On file.

63. Knopp RH, d'Emden M, Smilde JG, et al. Efficacy and Safety of Atorvastatin in the Prevention of Cardiovascular End Points in Subjects With Type 2 Diabetes: The Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in Non-Insulin-Dependent Diabetes Mellitus (ASPEN). *Diabetes Care*. 2006;29(7):1478-1485.

64. The Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) Investigators. High-Dose Atorvastatin after Stroke or Transient Ischemic Attack. *N Engl J Med*. 2006;355(6):549-559.

65. LaRosa JC, Grundy SM, Waters DD, et al. Intensive Lipid Lowering with Atorvastatin in Patients with Stable Coronary Disease. *N Engl J Med*. 2005;352(14):1425-1435.

66. Wanner C, Krane V, März W, et al. Atorvastatin in Patients with Type 2 Diabetes Mellitus Undergoing Hemodialysis. *N Engl J Med*. 2005;353(3):238-248.

67. Sever PS, Dahlöf B, Poulter NR, et al. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial—Lipid Lowering Arm (ASCOT-LLA): a multicentre randomise. *Lancet*. 2003;361(9364):1149-1158.

68. Colhoun HM, Betteridge DJ, Durrington PN, et al. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. *Lancet*. 2004;364(9435):685-696.

69. Schwartz GG, Olsson AG, Ezekowitz MD, et al. Effects of Atorvastatin on Early Recurrent Ischemic Events in Acute Coronary Syndromes;The MIRACL Study: A Randomized Controlled Trial. *JAMA*. 2001;285(13):1711-1718.

70. Serruys PWJC, Feyter P de, Macaya C, et al. Fluvastatin for Prevention of Cardiac Events Following Successful First Percutaneous Coronary Intervention. A Randomized Controlled Trial. *JAMA*. 2002;287(24):3215-3222.

71. West SM, Herd AJ, Ballantyne CM, et al. The Lipoprotein and Coronary Atherosclerosis Study (LCAS): Design, methods, and baseline data of a trial of fluvastatin in patients without severe

hypercholesterolemia. *Control Clin Trials*. 1996;17(6):550-583

72. Shepherd J, Blauw GJ, Murphy MB, et al. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. *Lancet*. 2002;360(9346):1623-1630.

73. The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Major Outcomes in Moderately Hypercholesterolemic, Hypertensive Patients Randomized to Pravastatin vs Usual Care: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT-LLT). *JAMA* 2002;288(23):2998-3007.

74. Sacks FM, Pfeffer MA, Moye LA, et al. The Effect of Pravastatin on Coronary Events after Myocardial Infarction in Patients with Average Cholesterol Levels. *N Engl J Med*. 1996;335(14):1001-1009.

75. Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. Prevention of Cardiovascular Events and Death with Pravastatin in Patients with Coronary Heart Disease and a Broad Range of Initial Cholesterol Levels. *N Engl J Med*. 1998;339(19):1349-1357.

76. Nakamura H, Arakawa K, Itakura H, et al. Primary prevention of cardiovascular disease with pravastatin in Japan (MEGA Study): a prospective randomised controlled trial. *Lancet* 2006;368(9542):1155-1163.

77. Shepherd J, Cobbe SM, Ford I, et al. Prevention of Coronary Heart Disease with Pravastatin in Men with Hypercholesterolemia. *N Engl J Med*. 1995;333(20):1301-1308.

78. Fellström BC, Jardine AG, Schmieder RE, et al. Rosuvastatin and Cardiovascular Events in Patients Undergoing Hemodialysis. *N Engl J Med*. 2009;360(14):1395-1407.

79. Kjekshus J, Apetrei E, Barrios V, et al. Rosuvastatin in Older Patients with Systolic Heart Failure. *N Engl J Med*. 2007;357(22):2248-2261.

80. Ridker PM, Danielson E, Fonseca FAH, et al. Rosuvastatin to Prevent Vascular Events in Men and Women with Elevated C-Reactive Protein. *N Engl J Med*. 2008;359(21):2195-2207.

81. Crouse JR, Raichlen JS, Riley WA, et al. Effect of Rosuvastatin on Progression of Carotid Intima-Media Thickness in Low-Risk Individuals With Subclinical Atherosclerosis. *JAMA*. 2007;297(12):1344-1353.

82. Scandinavian Simvastatin Survival Study Group. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet*. 1994;344(8934):1383-1389.

83. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol-lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet*. 2002;360:7-22.

84. Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH) Collaborative Group. Intensive lowering of LDL cholesterol with 80 mg versus 20 mg simvastatin daily in 12,064 survivors of myocardial infarction: a double-blind randomised trial. *Lancet*. 2010; 376(9753):1658-1669.

Appendix A: Statin clinical trials

¤ This list is not exhaustive

Trial	Trial design	Agent	Study population	Follow-up, years	Result
ASPEN (2006) Knopp et al[63]	Multicentre, double-blind	Atorvastatin 10 mg/daily vs. Placebo	2,410; Type 2 diabetics without high LDL-C levels (1^{y} prevention)	4.25	No significant ↓in 1^{y} composite endpoint. ↓ Fatal and nonfatal MI by 27% (2^{y} endpoint)
SPARCL (2006) Amerenco et al[64]	Multicentre, randomised double-blind	Atorvastatin 80 mg/daily vs. placebo	4731; Previous stroke without PAD	4.9	↓ CVE and strokes, slight ↑ in incidence of haemorrhagic stroke
TNT (2005) LaRosa et al[65]	Multicentre, prospective, double-blind RCT	Atorvastatin 80 mg vs. atorvastatin 10 mg/daily	10,001; clinically evident CHD (2^{y} prevention)	4.9	80 mg group had 22% RR in 1^{y} outcome of death from CHD, nonfatal MI, fatal or nonfatal stroke compared with 10 mg
4D (2005) Wanner et al[66]	Multicentre, prospective, double-blind RCT	Atorvastatin 20 mg/daily vs. Placebo	1255, Type 2 diabetics receiving maintenance haemodialysis	4	No significant effect on 1^{y} endpoint of cardiovascular death, non-fatal MI and stroke
ASCOT-LLA (2004) Sever et al[67]	Multicentre, double-blind RCT	Atorvastatin 10 mg/daily vs. Placebo	10,305; hypertension with ≥3 CVD risk factors, average or lower cholesterol (1^{y} prevention)	3.3	↓Non-fatal MI and CHD-related death by 36% vs placebo
CARDS (2004) Colhoun et al[68]	Multicentre RCT	Atorvastatin 10 mg/daily vs. placebo	2,838 Type 2 diabetics without high LDL-C levels, ≥ 1 risk factor (1^{y} prevention)	4	↓ in cardiovascular events by 37% ↓in stroke risk by 48% ↓in all-cause mortality by 27%
MIRACL (2001) Schwartz et al[69]	Multicentre, randomised, double-blind	Atorvastatin 80 mg/daily vs. placebo	3086; CHD (unstable angina or non-Q-wave acute MI)	0.33	2.6 % absolute reduction, 16% relative reduction (RR) in 1^{y} composite endpoint
LIPS (2002) Serruys et al[70]	Multicentre, double-blind RCT	Fluvastatin 80 mg/daily vs. placebo	1677 patients with CHD following PCI (2^{y} prevention)	3.9	5.3% Absolute risk reduction with fluvastatin in risk of MACE
LCAS (1996) West et al[71]	Double-blind RCT	Fluvastatin 40 mg/daily vs. placebo (a quarter of patients were also randomly assigned to open-label cholestyramine)	429 patients aged 35-75 years with CHD (2^{y} prevention)	2.5	23.9% ↓mean LDL in all fluvastatin patients (± cholestyramine), ↓ 3.8% placebo (±cholestyramine) ↓22.5% fluvastatin only
PROSPER (2002) Shepherd et al[72]	Multicentre, double-blind RCT	Pravastatin 40 mg/daily vs. Placebo	5804; aged 70-82 with history of, or risk factors for, cardiovascular disease	3.2	34% ↓LDL-C 19% ↓coronary events 24% ↓CHD mortality
ALLHAT-LLT (2002) Allhat officers[73]	Multicentre, randomised, open-label	Pravastatin 40 mg/daily vs. usual care	10,355; hypertension with ≥1 CHD risk factor, moderate hypercholesterolaemia (1^{y} prevention)	4.8	↓TC 17% (pravastatin) vs 8% (usual care) No significant difference for all-cause mortality or combined fatal and nonfatal CHD

CARE (1996) Sacks et al[74]	Multicentre, randomised, double-blind	Pravastatin 40 mg/daily vs. placebo	4,159 previous MI (2^{y} prevention)	5	↓fatal coronary heart disease or MI 24% ↓stroke risk 31%
LIPID (1998) Lipid Study group[75]	Multicentre, randomised double-blind	Pravastatin 40 mg/daily vs. placebo	9,014 CHD (2^{y} prevention)	6.1	24% ↓RR of CHD death Lower incidence of all cardiovascular outcomes (pravastatin)
MEGA (2006) Nakamura et al[76]	Open-label, blinded RCT	Pravastatin 10-20 mg/daily vs. Diet	7832 patients with a body weight of ≥40kg, hypocholesterolaemia ; (1y prevention)	5.3	↓TC 11% pravastatin group vs 2% diet group, MI/UA/sudden cardiac death/coronary revascularization↓ 33%
WOSCOPS (1995) Shepherd et al[77]	Multicentre, randomised double-blind	Pravastatin 40 mg/daily vs. Placebo	6595 MEN aged 45-64 with hypercholesterolaemia (1^{y} prevention)	4.9	↓ TC 20%, MI/CHD death 31%, death 22%
AURORA (2009) Fellstrom et al[78]	Multicentre, double-blind RCT	Rosuvastatin 10 mg/daily vs. placebo	2,776; age 50-80 undergoing haemodialysis	3.8	↓ 42.9% LDL vs. 1.9% No significant difference in 1^{y} outcome of MI, stroke or CV death
CORONA (2007) Kjekshus et al[79]	Multicentre, double-blind, RCT	Rosuvastatin 10 mg/daily vs. placebo	5011; age ≥ 60 years with chronic HF with ejection fraction of ≤ 0.40 (2^{y} prevention)	3	No significant difference in 1^{y} composite outcome of cardiovascular death, nonfatal MI or nonfatal stroke.
JUPITER (2008) Ridker et al[80]	Multicentre, double-blind, RCT	Rosuvastatin 20 mg/daily vs. Placebo	17,802 with NO history of CVD (1^{y} prevention) but with a hs-CRP of ≥ 2mg/L	1.9	↓ hs-CRP 37%, MI/stroke/arterial revascularization/UA/ cardiovascular death 44%
METEOR (2007) Crouse et al[81]	Multicentre, double-blind, RCT	Rosuvastatin 40 mg/daily vs. Placebo	984 with either age as the only CHD risk or a 10-year FRS <10%, modest CIMT thickening and elevated LDL	2	Statistically significant ↓ rate of progression of maximum CIMT with rosuvastatin
4S (1994) Pedersen et al[82]	Multicentre, double-blind, RCT	Simvastatin 20 mg/daily vs. Placebo (simvastatin ↑ to 40 mg if TC > 200 mg/dL)	4444; Prior MI and/or angina (2^{y} prevention)	5.4	3.3% ↓ absolute risk reduction in all-cause mortality ↓ Mean changes in TC and LDL-C 25% and 35%, respectively ↑HDL-C of 8%
HPS(2007) HPS Collaborative Group[83]	Multicentre, double-blind RCT	Simvastatin 40 mg/daily vs. Placebo	20,536; age 40-80 years with CAD, occlusive arterial disease or diabetes	5	Significant↓ in all-cause mortality (12.9% vs 14.7%) with simvastatin Significant ↓ of ~one quarter in first event rate for non-fatal MI, fatal/non-fatal stroke and coronary/non coronary revascularisation
SEARCH (2010) Armitage et al[84]	Multicentre, double-blind RCT	Simvastatin 20 mg vs. simvastatin 80 mg/daily	12,064;history of previous MI	6.7	6% proportional reduction in major vascular events with 80 mg; ↑ in myopathy (80 mg)

CIMT:carotid intima media thickness; FRS: Framingham risk score; hs-CRP: high sensitivity C-reactive protein MACE: major adverse cardiovascular events