KCE REPORT 306

Federaal Kenniscentrum voor de Gezondheidszorg
Centre Fédéral d'Expertise des Soins de Santé
Belgian Health Care Knowledge Centre

STATINS FOR THE PRIMARY PREVENTION OF CARDIOVASCULAR EVENTS

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HEALTH TECHNOLOGY ASSESSMENT

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LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
ACAPS	Asymptomatic Carotid Artery Progression Study
AHA – ACC	American Heart Association – American College of Cardiology
ARD	Absolute Risk Difference
ASCOT-LLA	Anglo-Scandinavian Cardiac Outcomes Trial – Lipid Lowering Arm
ASCVD	Atherosclerotic Cardiovascular Disease Risk Algorithm (from AHA – ACC)
ASPEN	Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in Non-insulin Dependent Diabetes Mellitus
ASTRONOMER	Aortic Stenosis Progression Observation: Measuring Effects of Rosuvastatin
ATP III	Adult Treatment Panel III
BCFI – CBIP	Belgisch Centrum voor Farmacotherapeutische Informatie – Centre Belge d'Information Pharmacothérapeutique (Belgian Centre for Pharmaco-therapeutic Information – Belgium)
CAIUS	Carotid Atherosclerosis Italian Ultrasound Study
CARDS	Collaborative Atorvastatin Diabetes Study
CBA	Cost-Benefit Analyses
CEA	Cost-Effectiveness Analyses
CHD	Coronary Heart Disease (= IHD)
CI	Confidence Interval
CK	Creatine Kinase
CKD	Chronic Kidney Disease
CM – MC	Christelijke Mutualiteiten – Mutualités Chrétiennes (Christian Mutualities – Belgium)
CMA	Cost-Minimization Analyses
CRD	Centre for Review and Dissemination

CTG – CRM	Commissie Tegemoetkoming Geneesmiddelen – Commision de Remboursement des Médicament (Commission for the Reimbursement of Pharmaceuticals, Belgium)
CUA	Cost-Utility Analyses
CVD	Cardiovascular Disease
DALY	Disability-Adjusted Life Year
DDD	Defined Daily Dose
EPS	Echantillon Permanent – Permanente Steekproef (Permanent Sample, Belgium)
ESC – EAS	European Society of Cardiology – European Atherosclerosis Society
GRADE	Grading of Recommendations Assessment, Development and Evaluation working group
HEED	Health Economic Evaluations Database
HMG-CoA	3-hydroxy-3-methyl-glutaryl-coenzyme A
HOPE-3	Heart Outcomes Prevention Evaluation
HTA	Health Technology Assessment
HYRIM	Hypertension High Risk Management
ICER	Incremental Cost-Effectiveness Ratio
IHD	Ischaemic Heart Disease (= CHD)
IMA – AIM	Intermutualistisch Agentschap – Agence Intermutualiste (Inter Mutualist Agency, Belgium)
INAHTA	International Network of Agencies for Health Technology Assessment
JUPITER	Justification for the Use of Statins in Prevention: and Intervention Trial Evaluating Rosuvastatin
KAPS	Kuopio Atherosclerosis Prevention Study
KCE	Belgian Health Care Knowledge Centre (Kennis Centrum – Centre d'Expertise)
LDL	Low Density Lipoprotein

LDL-C	Low Density Lipoprotein Cholesterol
LDL-P	Low Density Lipoprotein Particle
LY	Life Year
LYG	Life-Year Gained
MEGA	Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese
METEOR	Measuring Effects on Intima-Media Thickness: an Evaluation of Rosuvastatin
MI	Myocardial Infarction
MPR	Mean Possession Ratio
NHS EED	National Health Service Economic Evaluation Database
NICE	National Institute for Health and Care Excellence (UK)
NIHDI	National Institute for Health and Disease Insurance (RIZIV – INAMI, Belgium)
NNH	Number Needed to Harm
NNT	Number Needed to Treat
PREVEND-IT	Prevention of Renal and Vascular Endstage Disease Intervention Trial
QALY	Quality-Adjusted Life Year
RR	Relative Risk
RIZIV – INAMI	National Institute for Health and Disease Insurance (= NIHDI, Belgium)
RCT	Randomized Controlled Trial
SBP	Systolic Blood Pressure
SCORE	Systemic Coronary Risk Estimation (European)
SHARP	Study of Heart and Renal Protection
SR	Systematic Review
TC	Total Cholesterol

UKPDS	United Kingdom Prospective Diabetes Study
USPSTF	U.S. Preventive Services Task Force
WOSCOPS	West of Scotland Prevention Study Group
WTP	Willingness To Pay
YLS	Years of Life Saved

SCIENTIFIC REPORT

1 BACKGROUND

Cardiovascular disease (CVD) remains a leading cause of morbidity and mortality, and despite improvements in CVD outcomes,[1] preventing CVD events remains important. First at population level by promoting healthy lifestyle behaviour but also at the individual level. In individuals with a moderate to high risk of developing CVD events or patients with established CVD this should be done first through tackling an unhealthy lifestyle (e.g. poor quality diet, physical inactivity, smoking) and by reducing increased levels of risk factors for CVD such as increased lipid or blood pressure levels.[1] Taking statins reduces the risk of CVD-associated morbidity and mortality mainly through their effects on lipids, although other mechanisms might be involved.[2] The 2016 ESC – EAS (European Society of Cardiology and European Atherosclerosis Society) guidelines for the management of dyslipidaemias recommend initiation of primary prevention of CVD with drug therapy in individuals depending upon the total CVD mortality risk as assessed with the (European) Systemic Coronary Risk Estimation (SCORE) and on the LDL-Cholesterol (LDL-C) level.[1] The NIDHI (RIZIV – INAMI) recommendations, using the same philosophy, recommend elevated levels of cholesterol AND a ≥ 5% ten-year risk of mortality assessed with SCORE as thresholds (see chapter 3 on statin use in Belgium). It is not the aim of this HTA report to discuss the different guidelines for statin use in detail.

Statins are the most frequently used drug category in our country (over 500 million DDD or almost 10% the total DDDs in 2017) and occupy the second position in terms of budget (over € 146 million or almost 5 % of the total drug budget in 2017).[a] The number of users (individuals who bought at least one conditioning over the year) is over 1.5 million. In a previous KCE report,[3] we demonstrated that the vast majority of statins use is for the primary prevention of CVD. This phenomenon was also described in other countries.[4]

a https://www.riziv.fgov.be/SiteCollectionDocuments/statistiek_farma_voorschrijvers_all_2017.pdf

In 2014, NIDHI (RIZIV – INAMI) published an extensive consensus document entitled [The rational use of lipid-lowering drugs] based on a comprehensive literature review and expert opinion.[5] The objective of the present KCE report is not to repeat this work, but to address three key questions not entirely covered by that consensus document.

1. The authors based their analysis mainly on two meta-analyses one from 2012 and a Cochrane review from 2013.[6, 7] It is important to check if more recent data on clinical benefit and harms have been published since. The authors of the consensus document also noted that meta-analyses had pooled trials where patients were included on the basis of combinations of criteria, and that poses a problem to estimate the efficacy of a statin in an individual patient. Therefore, we performed in this report a series of sensitivity analyses excluding specific trials on specific criteria.
2. The question of the cost-effectiveness of primary prevention of CVD by statins was not addressed in the consensus paper. As a result, NIHDI (RIZIV – INAMI) asked the KCE to review the evidence on the cost-effectiveness of the primary prevention of CVD by statins.
3. The 2016 ESC/EAS Guidelines also recommend that prescribing a statin should include a shared decision-making approach that engages the patient in a discussion before initiating treatment, especially when it is being considered for primary prevention of CVD.[1] A similar recommendation is also formulated in the Belgian Consensus paper.[5] Shared-decision making is a particular process of decision making by the patient and physician with the aim that the patient: [8]

- understands the risk or seriousness of the disease or condition to be prevented;
- understands the preventive service, including the risks, benefits, alternatives, and uncertainties;
- has weighed his or her values regarding the potential benefits and harms associated with the service;
- has engaged in decision making at a level at which he or she desires and feels comfortable.

Whether or not the overall benefit-harm balance justifies the use of a medication for an individual patient cannot be determined by a guidelines committee, a health care system, or even the attending physician. Instead, it is the individual patient who has a fundamental right to decide whether or not taking a drug is worthwhile.[9] This requires an evidence-informed and patient-centred approach.[8, 10, 11]

This last question will be specifically addressed in a follow-on report on this Health Technology Assessment report, dedicated to the development of a Belgian decision aid. This decision aid is due to appear in 2019.

2 OBJECTIVES

As a consequence of the arguments brought forward in chapter 1, the research questions for this Health Technology Assessment (HTA) report are:

1. What is the historical and current use of statins in Belgium, both overall as in individual users?
2. What is the scientific evidence on the benefits and harms of using statins in the primary prevention of CVD events in individuals without underlying additional risk factors?
3. What is the scientific evidence on the cost-effectiveness of statins in the primary prevention of CVD events without underlying additional risk factors?

This report is meant to be an HTA, not a clinical guideline on CVD risk reduction in primary prevention. For guidelines, the reader can refer to the 2016 ESC – EAS guidelines for the management of dyslipidaemias (will be updated in 2019),[1] the Belgian Consensus Document published in 2014,[5] or the NICE clinical guideline published in 2014 and updated in 2016.[12] A further update of this latter guideline is planned.

In a follow-on report the development of a decision aid tool will be described.

3 HISTORICAL AND CURRENT STATIN USE IN BELGIUM

3.1 Introduction

Statins (also known as HMG-CoA reductase inhibitors) are a class of lipid-lowering medications. Statins proved to reduce the relative risk for cardiovascular disease (CVD), CVD events and mortality similarly in all individuals, but the absolute risk reduction is much greater in those who are at high risk of CVD events. Statins are used both in the primary and secondary prevention of CVD.

Clinical practice guidelines generally recommend, in primary prevention, that people first apply *'lifestyle modification'*, including a cholesterol-lowering diet and physical exercise and stop smoking, before they start using statins. Statins or other pharmacologic agents may afterwards be prescribed for those who do not meet their lipid-lowering goals through lifestyle changes only.

At the end of the previous century several statins came onto the market at a very high price. In April 1994, the results of a Merck-sponsored secondary prevention trial, the Scandinavian Simvastatin Survival Study (the 4-S study), were reported.[13] Researchers tested simvastatin, sold by Merck as Zocor, on 4444 patients with high cholesterol and existing heart disease. After five years, the study concluded the patients saw a 35% reduction in their cholesterol, and their risks of dying from a myocardial infarction were reduced by 42%. At that moment several other pharmaceutical companies were developing similar products.

Because of the high price, reimbursement of statins was initially restricted to selected patients at high risk. Since 2003, and due to patent expirations, generic alternatives became increasingly available leading to a sharp decline of prices. As a consequence, the necessity for a strict control of the reimbursement of statins diminished and reimbursement rules were softened over the years. This led to a marked increase in the volumes consumed.

Statins are prescribed for many Belgian patients and the cost for individuals and third-party payers is still substantial. In 2017 the total budget for reimbursement of all pharmaceuticals dispensed in public pharmacies in Belgium was over € 3 billion. Almost 5% of this budget (almost € 150 million) was spend on statins.[b]

Statins are the main lipid modifying agents used, but sometimes they are used in combination with other agents, separately or in combination products. In this chapter we consider all statins, either alone or in combination preparations.

3.2 Methods

3.2.1 Global data

To obtain global data we used the *official documents and reports* of RIZIV – INAMI on the regulation, volumes and cost of statin use as available on their website (www.riziv.fgov.be). These documents report the historic use (i.e. purchase) of statins in Belgium since 1997.

3.2.2 Individual data

Permanent sample (EPS)

To obtain more detail on the characteristics of users, adherence and information on whether statins are used for primary vs. secondary prevention, we have used data from the *'permanent sample'*. In Belgium, registered inhabitants, in principle, have a compulsory health insurance provided through one of the seven national sickness funds and funded by social security contributions withhold on wages and other earnings. For all sickness funds healthcare reimbursement data of their members can be gathered into databases at IMA – AIM (Intermutualistisch Agentschap – Agence Intermutualiste), according to a legal framework, meaning that no informed consent is required. From this population a sample was selected (random selection stratified for age and gender). Sample proportion was 1/40 among subjects younger than 65 and 1/20 among subjects aged 65 years and older. This sample contains approximately 300 000 individuals that are followed since 2002. The sample is updated yearly to compensate for mortality and aging and new members are added according to the same sample size rules. The resulting database is referred to as *'échantillon permanent – permanente steekproef'* (EPS). For all the individuals in the sample demographic and socio-economic information is collected in addition to detailed information on health care expenditures.

KCE has a legal right to use those anonymised data for specific study purposes with an a-priori internal control by our data managers and a-posteriori control by the technical cell governing the EPS.

Selection of EPS data and extrapolation to the total population

We used the permanent sample (EPS) to obtain more detailed information on the profile of the users taking statins, stopping statins alive or stopping statins because of death.

Data were selected and analysed according to the following rules:

For data selection the index date was defined as the date of the first ambulatory statin dispensation with a quantity ≥1 packaging (ATC level 4 = C10AA).

For the analysis, the selection filters applied on the database were all patients with a delivery of at least 1 packaging of a lipid modifying agent (ATC level 2 = C10) in ambulatory care. It includes statin (ATC level 4 = C10AA), other lipid modifying agent (fibrates - ATC level 4 =C10AB, bile sequestrant - ATC level 4 =C10AC, nicotinic acid - ATC level 4 =C10AD, other lipid modifying agent - ATC level 4 =C10AX) and associations (ATC level 3 =C10B).

[b] Source: RIZIV – INAMI statistics pharmaceuticals 2017. https://www.riziv.fgov.be/SiteCollectionDocuments/statistiek_farma_voorschrijvers_all_2017.pdf

Patients who used antidiabetic or cardiovascular drugs were identified with the prescription ATC code: for antidiabetic drugs: ATC level 2 = A10 (insulin and analogues, blood glucose lowering drugs other than insulins and other drugs used in diabetes) and CV drugs: ATC level 2 = C07 (beta blocking agents), C08 (calcium channel blockers) and C09 (agents acting on the renin-angiotensin system).

All analysis were realized with the SAS software version 7.1. Since the sample proportion is known (1/40 among subjects younger than 65 and 1/20 among subjects aged 65 years and older), this permits to extrapolate the data to the Belgian population. This extrapolation was realized thanks to the SAS survey procedure.

To check the validity of this extrapolation we test the concordance of the extrapolated data with the official data published by RIZIV – INAMI.

Concordance of the extrapolated data with RIZIV – INAMI data

The exact number of users and the number of DDD's for the three main statins were reported in the TOP 25 RIZIV – INAMI (NIDHI) report for 2016[c]. Table 1 and Table 2 report the total number of users and the number of DDD's comparing registered data and extrapolated data from EPS

Table 1 – Number of users of the three major statins in Belgium 2016 (thousand users)

	NIDHI data (TOP 25)	Extrapolated from EPS [95% CI]
Simvastatin	612.1	585.5 [579.2 to 591.7]
Atorvastatin	481.8	453.3 [447.3 to 459.3]
Rosuvastatin	286.6	272.9 [268.0 to 277.8]

Table 2 – Consumption of the three major statins in Belgium 2016 (million DDD)

	NIDHI data (TOP 25)	Extrapolated from EPS [95% CI]
Simvastatin	161.6	159.7 [158.4 to161.0]
Atorvastatin	185.8	182.2 [180.4 to 184.0]
Rosuvastatin	120.7	121.1 [118.4 to 123.8]

We conclude from those numbers that these extrapolated EPS data give a relatively good estimate of the level of consumption of statins by comparing them to the full numbers. Therefore we feel that those EPS data can confidently be used to analyse consumption modes of statin in the Belgian population.

Definitions used in analysis.

User: Each person who purchased at least 1 packaging of statin during the period of consideration.

New user: Each person who purchased at least 1 packaging of statin during the period of consideration with no statin delivering in the previous 365 days. Because data were available from 2002, new users are only defined from year 2003 onwards. Please note that a same person can be counted several times as a new user provided that at least one year elapses during 2 purchases.

Medication Possession Ratio (MPR): defined as the ratio of the number of tablets purchased divided by the number of days during the period of use. It is the measure of adherence, defined as a MPR ≥80%.

Regular User: new user with a MPR ≥ 80% and more than one statin packaging recorded.

[c] Source: http://www.inami.fgov.be/SiteCollectionDocuments/infospot-2017-03-nl.pdf

Occasional User: New user who is not a regular user.

Defaulter: Regular user who stopped statin use during at least 3 months after the period theoretically covered by the last refill recorded.

Quitter: Occasional user who did stop definitely the statin.

Switcher: Consumer of different statin molecules within a defined period of time.

Major Statin: The statin mostly used (in tablet numbers) during the period considered in the case of more than one type of statin delivering.

Statin Dose according to the NICE classification: (dose in mg) low dose statin (fluvastatin 20, fluvastatin 40, simvastatin 10, pravastatin 10, pravastatin 20, pravastatin 40), medium dose statin (atorvastatin 10, fluvastatin 80, simvastatin 20, simvastatin 40, rosuvastatin 5) and high dose statin (atorvastatin 20, atorvastatin 40, atorvastatin 80, simvastatin 80, rosuvastatin 10, rosuvastatin 20, rosuvastatin 40).

Weak socio-economic status: include patients who benefit the "Verhoogde tegemoetkoming - Intervention majorée" (https://www.inami.fgov.be/fr/themes/cout-remboursement/facilite-financiere/Pages/intervention-majoree-meilleur-remboursement-frais-medicaux.aspx)

Secondary prevention: Secondary prevention, for the purpose of this report, is defined as prevention after an occurred cardiovascular event (heart infarction, ischemic strokes or coronary artery diseases). As hospital data were not available, only an estimate of patients taking statin for secondary prevention could be done. For this purpose, patients who were hospitalized in hospitals with a cardiovascular care unit B (B1, B2, B3) and who were hospitalized in service with a code 210 (diagnosis and surgical treatment), 220 (diagnosis and medical treatment), 490 (Intensive care unit) et 610 (cardio pulmonary diseases) have been selected. The patient has been considered in secondary prevention if the difference of hospitalisation date and first date of statin is within 365 days.

Primary prevention: patients who are not in secondary prevention.

3.3 Statins available on the Belgian market

3.3.1 Statins

Five of the eight statin molecules are currently marketed in Belgium, see Table 3 (Source: Belgisch Centrum voor Farmacotherapeutische Informatie – Centre Belge d'Information Pharmacothérapeutique (BCFI – CBIP) www.bcfi.be and NIHDI (RIZIV – INAMI) www.riziv.fgov.be). Both sources were initially consulted in December 2017 and checked again in October 2018. Cerivastatin was previously marketed in Belgium but withdrawn in 2001 due to safety concerns.

For four of those five statins generic alternatives are now available. The sole exception is fluvastatin that is only marginally used in Belgium. Until recently there was no generic equivalent for rosuvastatin (Crestor®) but this changed in January 2018.

Table 3 – Statins on Belgian Market and availability of generic alternatives

ATC code	Name	On Belgian Market	Brand name	Brand company	Generics
C10AA01	simvastatin	Yes	ZOCOR®	MSD	Yes
C10AA02	lovastatin	No	-	-	-
C10AA03	pravastatin	Yes	PRAVASINE®	Bristol-Meyers Squibb	Yes
C10AA04	fluvastatin	Yes	LESCOL®	Novartis	No
C10AA05	atorvastatin	Yes	LIPITOR®	Pfizer	Yes
C10AA06	cerivastatin	Withdrawn (2001)	-	-	-
C10AA07	rosuvastatin	Yes	CRESTOR®	Astra-Zeneca	Yes (since Jan 2018)
C10AA08	pitavastatin	No	-	-	-

However, those statins appear to have varying potency to lower low density lipoprotein cholesterol (LDL-C), and have been classified in a NICE guideline (2014 but updated in 2016) accordingly as low, intermediate and high intensity (see Table 4).[14] It should be appreciated, however, that other classifications for low, intermediate and high intensity exist.[15] It should also be appreciated that in individual patients, effect on LDL-C can be very variable.

Table 4 – Intensity of statins on Belgian Market

	% reduction in LDL-C				
Dose (mg/day)	5 mg	10 mg	20 mg	40 mg	80 mg
simvastatin	23%	27%	32%	37%	42%
pravastatin	15%	20%	24%	29%	33%
fluvastatin	10%	15%	21%	27%	33%
atorvastatin	31%	37%	43%	49%	55%
rosuvastatin	38%	43%	48%	53%	58%

Source: NICE Clinical Guideline 2014, updated 2016 [14] based on Law and Wald 2003.[16]
20%–30%: low intensity; 31%–40%: medium intensity; above 40%: high intensity.

3.3.2 Combination products containing a statin

Apart from the plain statins, there are several combination products that either combine a statin with another lipid lowering drug (ATC C10BA) or statins in other combinations (ATC C10BX, sometimes referred to as *'polypills'*). Some of these combinations are marketed in Belgium (see Table 5). Those are still under patent and only recently a first generic alternative has been added on the NIDHI lists but it is currently unavailable due to legal concerns. Other lipid lowering drugs, not containing statins, are not considered in this report.

Table 5 – Combination products containing statins, availability on Belgian Market and availability of generics

ATC code	Name	On Belgian Market	Brand name	Brand company	Generics
C10BA01	lovastatin and nicotinic acid	No	-	-	-
C10BA02	simvastatin and ezetimibe	Yes	INEGY®	MSD	Yes but unavailable*
C10BA03	pravastatin and fenofibrate	Yes	PRAVAFENIX®	SMB	No
C10BA04	simvastatin and fenofibrate	No	-	-	-
C10BA05	atorvastatin and ezetimibe	Yes	ATOZET®	MSD	No
C10BA06	rosuvastatin and ezetimibe	No	-	-	-
C10BX01	simvastatin and acetylsalicylic acid	No	-	-	-
C10BX02	pravastatin and acetylsalicylic acid	No	-	-	-
C10BX03	atorvastatin and amlodipine	No	-	-	-
C10BX04	simvastatin, acetylsalicylic acid and ramipril	No	-	-	-
C10BX05	rosuvastatin and acetylsalicylic acid	No	-	-	-
C10BX06	atorvastatin, acetylsalicylic acid and ramipril	Yes	TRINOMIA®	Therabel	No
C10BX07	rosuvastatin, amlodipine and lisinopril	No	-	-	-
C10BX08	atorvastatin and acetylsalicylic acid	No	-	-	-
C10BX09	rosuvastatin and amlodipine	No	-	-	-
C10BX10	rosuvastatin and valsartan	No	-	-	-
C10BX11	atorvastatin, amlodipine and perindopril	Yes	LIPERTANCE®	Servier	No
C10BX12	atorvastatin, acetylsalicylic acid and perindopril	No	-	-	-
C10BX13	rosuvastatin, perindopril and indapamide	No	-	-	-
C10BX14	rosuvastatin, amlodipine and perindopril	No	-	-	-
C10BX15	atorvastatin and perindopril	No	-	-	-

** Can be reimbursed without prior approval, but is currently unavailable on the Belgian market due to legal concerns. Expected in the middle of 2019*

3.4 Reimbursement rules for statins

3.4.1 Basic rules

The rules for the reimbursement of statins have changed over time. At first the aim was mainly to contain expenditures and the rules for prescription were rather strict at that moment in time. All statins were in the so-called chapter IV, i.e. the prior approval of the advisory physician of the sickness funds was required. Later, as prices decreased due to the arrival of cheaper generics and consequent price decreases in the brand product the rules were relaxed. In August 2010 the recommendations concerning statin prescription were changed by the *'Commission for the Reimbursement of Pharmaceuticals'* (CTG – CRM) to stimulate the prescription of the cheapest products from each class. Current recommendations can be found on the RIZIV – INAMI website on reimbursement of pharmaceutical (https://www.riziv.fgov.be/nl/themas/kost-terugbetaling/door-ziekenfonds/geneesmiddel-gezondheidsproduct/terugbetalen/specialiteiten/hoofdstukken/Paginas/indicatoren-statines.aspx#.WjfT1yiWw2x). To monitor whether individual physicians sufficiently follow the guidelines issued by the appropriate commission (CTG – CRM), indicators were developed (https://www.riziv.fgov.be/SiteCollectionDocuments/statines-indicatoren.pdf). If physicians strongly deviated from these indicators they could have been asked to explain the reason. These rules were mandatory while statins were in the system of a posteriori control (chapter II).

However, nowadays all statins are reimbursable without neither prior approval of the advisory physician of the sickness funds nor posterior control (the so called chapter I). The only exception until recently was Crestor® (rosuvastatin) where prior approval of the advisory physician was still necessary. However, since the availability of the generic alternatives and the ensuing drastic price reduction of Crestor® (from € 158.96 in 2017 for a packaging of 98 * 40mg to only € 24.58 in October 2018), this product is now also available without prior approval.

The combination products were more recently introduced: Inegy® (C10BA02) can be reimbursed since 2007 and Pravafenix® (C10BA02) since 2013. Atozet® (C10BA05) is even more recent. A generic alternative for Inegy® exists, is reimbursable, but is not yet on the market due to legal concerns. The combination products of the C10BA group on the Belgian market all need prior approval (except for the non-available generic alternative for Inegy®). The two C10BX ('polypill') products Trinomia® (C10BX06) and Lipertance® (C10BX11) are cheaper and can be prescribed without prior approval.

3.4.2 Indications and indicators

The abbreviated RIZIV – INAMI guidelines for the prescription of statins can be found in two documents and focus on primary prevention, secondary prevention and on statin use for primary prevention in patients with diabetes (https://www.riziv.fgov.be/SiteCollectionDocuments/statines-aanbevelingen-voorschrijven.pdf – http://www.riziv.fgov.be/SiteCollectionDocuments/statines-samenvatting-tabel.pdf).

For primary prevention, starting statin treatment in a patient should be based on a primary hypercholesterolemia with fasting total cholesterol ≥ 190 mg/dl or fasting LDL cholesterol ≥ 115 mg/dl, measured twice with an interval of 1 to 8 weeks while following an appropriate diet AND presenting a 10 year fatal cardiovascular risk higher than 5% using the SCORE tool (and taking into consideration additional *'risk qualifiers'*, such as physical inactivity, family history of premature CVD, triglyceride level, diabetes, obesity, social deprivation etc.). This table is calibrated for the Belgian population and estimates the 10 year cardiovascular mortality based on age, gender, smoking, systolic blood pressure and total cholesterol (http://lipidclub.be/resources/pdf/Scoretable.pdf).[17]

It is recommended to start treatment with simvastatin or pravastatin. Only when adequate cholesterol levels (total cholesterol<190 mg/dl or LDL-C<115 mg/dl) are not obtained after at least 3 months other statins, or a combination with other pharmaceuticals, should be considered.

For the primary prevention in patients with diabetes (type I diabetes with microalbuminuria or type II diabetes >40 years), the required cholesterol levels are lower (total cholesterol ≥ 175 mg/dl or LDL cholesterol ≥ 100 mg/dl

respectively). Also here, it is recommended to start with simvastatin or pravastatin, except when cholesterol levels are very high (>290 mg/dl or > 165 mg/dl respectively). Patients with specific additional risk factors, also called *'qualifiers for risk'* such as for example familial hypercholesterolemia or without a CVD event but at very high risk, are excluded from those guidelines and should be treated separately.

Prescribing physicians should keep relevant information on several parameters in their medical records and specific indicators were chosen to allow for automatically monitoring the correct use of these guidelines through the Farmanet system that monitors all prescriptions obtained in public pharmacies in Belgium for a given patient. A first indicator monitors the high risk status of the patient population, namely the presence of diabetes and/or cardiovascular disorders by assessing concurrent medication use: antidiabetic drugs, or all cardiovascular drugs excluding statins. Formulae were developed to identify outliers in prescription behaviour. A second indicator monitors the cost awareness of the prescriber while choosing a statin.

Those indications and indicators are not completely in line with the current international guidelines.[1, 18] However, since the development of these indications and indicators, all statins were moved to chapter I without any control (no prior and no posterior), so it is unclear how enforceable those indicators are nowadays, although they are still published on the RIZIV – INAMI website.

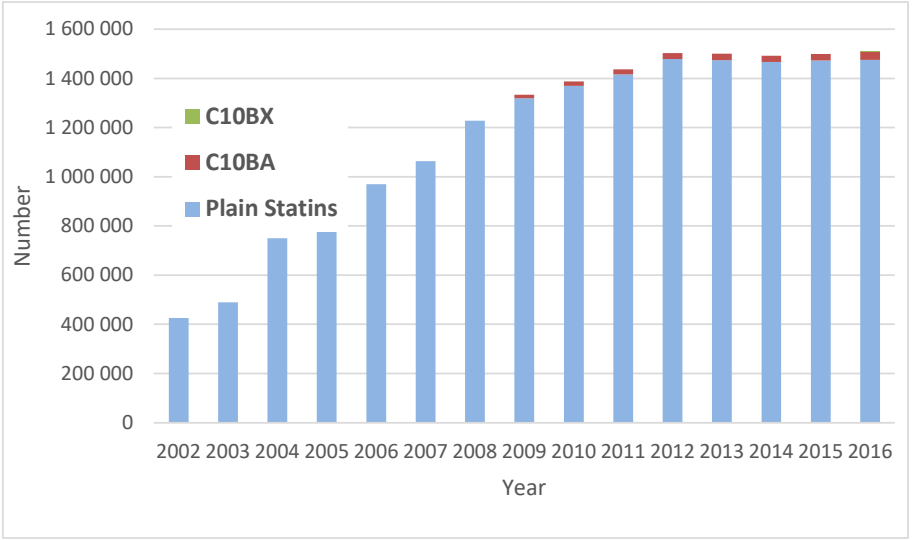
3.5 Number of statin users (global data)

We define a statin user as an individual who has bought at least one packaging of a statin during a given year.

The yearly number of statin users has been growing until 2012 and stabilized since around 1.5 million users each year. This number for corresponds to about 13% of the total population and 25% of the population aged 40 and over.

The total number of statin users shown in Figure 1 is an approximation since the NIHDI Top 25 only reports the exact number of users for the top three statins. For the users of other statins the numbers are an approximation based on the volumes purchased. Also the number of users of the combination products (ATC C10BA) was estimated. In 2016 the number of users of ATC C10BX was estimated at 1160 users (extrapolated from the permanent sample and not visible on the graph).

Figure 1 – Approximate number of statin users



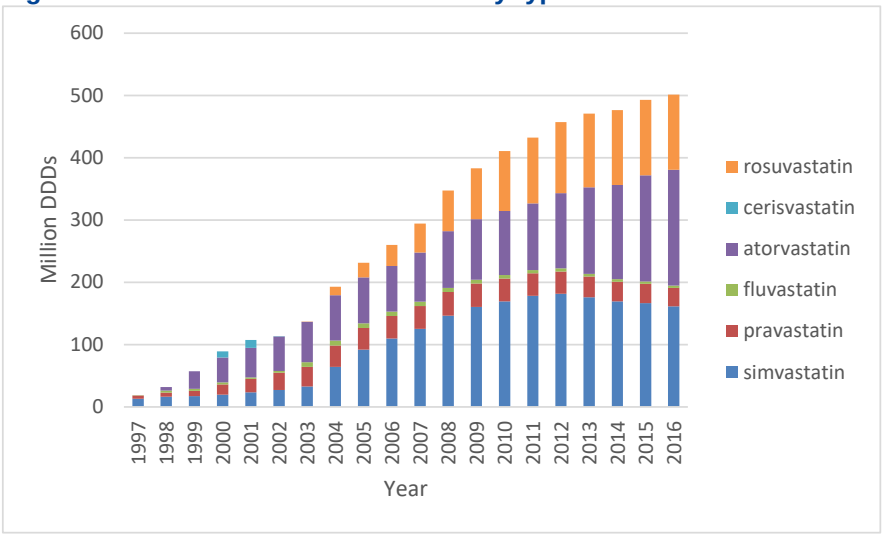
3.6 Volumes of prescribed statins (global data)

The assessments of volumes and reimbursement of prescribed statins are based on several sources: the Morse report 2015 with data until 2014 (http://www.riziv.fgov.be/SiteCollectionDocuments/morse-rapport-2014.pdf), the report from 2016 of the Christian Mutualities (CM – MC) on statin use in Belgium 2005-2015 (https://www.cm.be/binaries/Statines-bijlage_tcm375-177537.pdf), the overview of all prescriptions by year http://www.riziv.fgov.be/nl/statistieken/geneesmiddel/Paginas/geneesmiddelen-groep-voorschrijvers.aspx#.WoV8DiiWw2w and on the Top 25 of pharmaceutical expenditures in 2016 (http://www.inami.fgov.be/SiteCollectionDocuments/infospot-2017-03-nl.pdf).

3.6.1 Statins

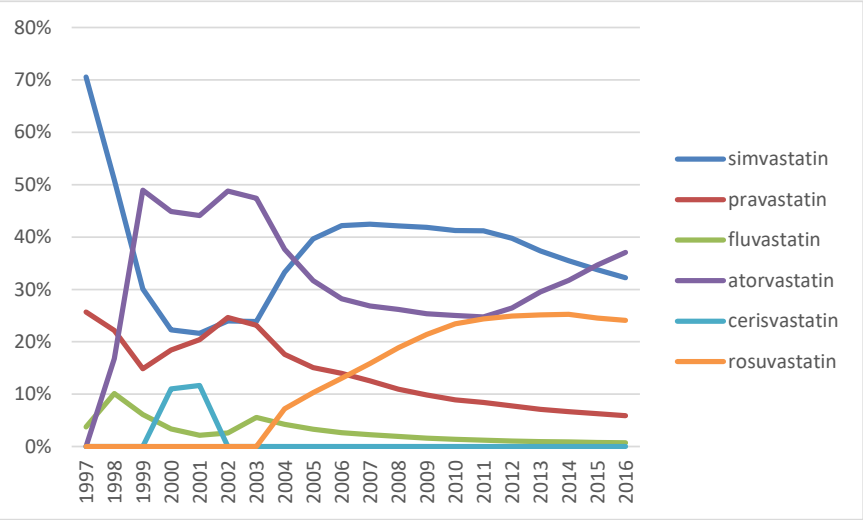
Drug consumption is commonly assessed using the defined daily dose (DDD), the assumed average maintenance dose per day for a drug used for its main indication in adults (https://www.whocc.no/ddd/definition_and_general_considera/). In recent years this yearly number of DDD's increased continuously and reached 500 million in 2016 (see Figure 2). The market share was historically at about 40% for simvastatine but has been decreasing since 2012 (see Figure 3). Also the market share of pravastatine has been gradually decreasing since 2003. The market share is increasing especially for atorvastatine and in 2015 the DDD volume of atorvastatin overtook that of simvastatine. The market share of fluvastatin is marginal.

Figure 2 – Evolution of DDD volumes by type of statin



Data sources: KCE report 141 and NIDHI, http://www.riziv.fgov.be/nl/statistieken/geneesmiddel/Paginas/default.aspx#.WoV6BSiWw2w

Figure 3 – DDD market share by type of statin

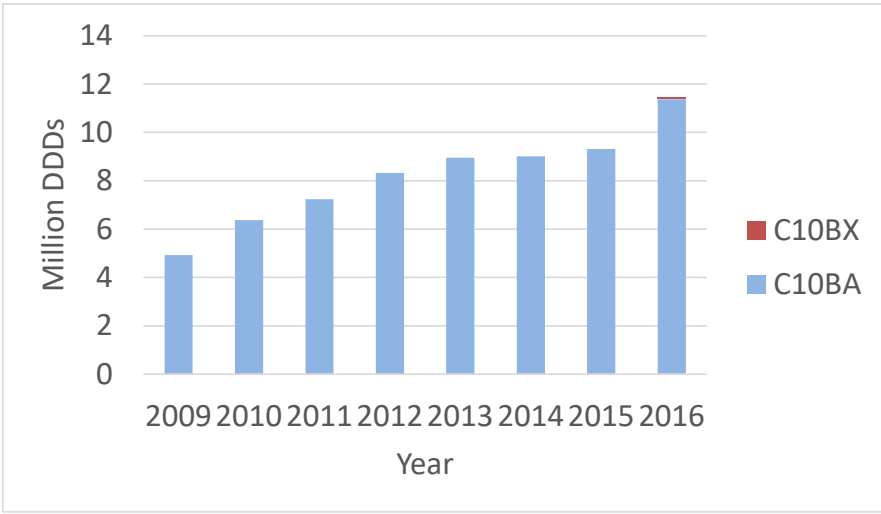


Data sources: KCE report 141 and NIDHI, http://www.riziv.fgov.be/nl/statistieken/geneesmiddel/Paginas/default.aspx#.WoV6BSiWw2w

3.6.2 Combination products containing a statin

Products that combine a statin with another pharmaceutical were introduced more recently and their use really started in 2008. The number of patients treated increased and reached approximately 29 000 in 2014, mainly for Inegy® for historical reasons since it was the first combination pharmaceutical to be introduced. The number of DDDs for products from ATC class C10BA that year was approximately 9 million. In 2016, this number of DDDs increased markedly to 11.3 million (see Figure 4). Products from ATC class C10BX (polypill) are not included in this table, since their volume is too low to be reported. Extrapolation from the permanent sample indicates that in 2016 approximately 0.08 million DDD were sold.

Figure 4 – Evolution of DDD volumes for combination products (ATC C10BA and C10BX)

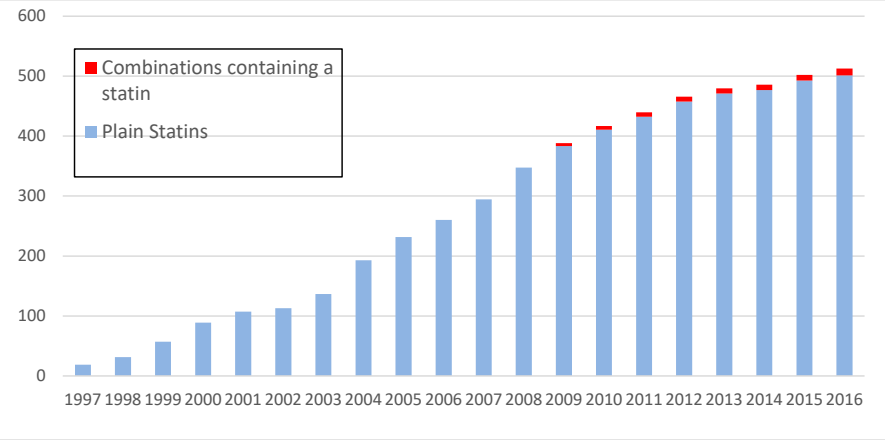


Source: RIZIV – INAMI http://www.riziv.fgov.be/nl/statistieken/geneesmiddel/Paginas/default.aspx#.WoV6BSiWw2w and extrapolation from EPS

3.6.3 All products containing a statin

The previous reported volumes indicate still growing volumes of statin use, despite the stabilisation of the number of yearly users. This indicates that the average number of DDD's per user is increasing. The bulk of the statins used are plain statins. However, the use of combination products containing a statin is rising in recent years. See Figure 5 for the relative importance of plain status vs. combination products.

Figure 5 – Evolution of DDD volumes for all products containing a statin (in millions)



3.7 Cost of statins (global data)

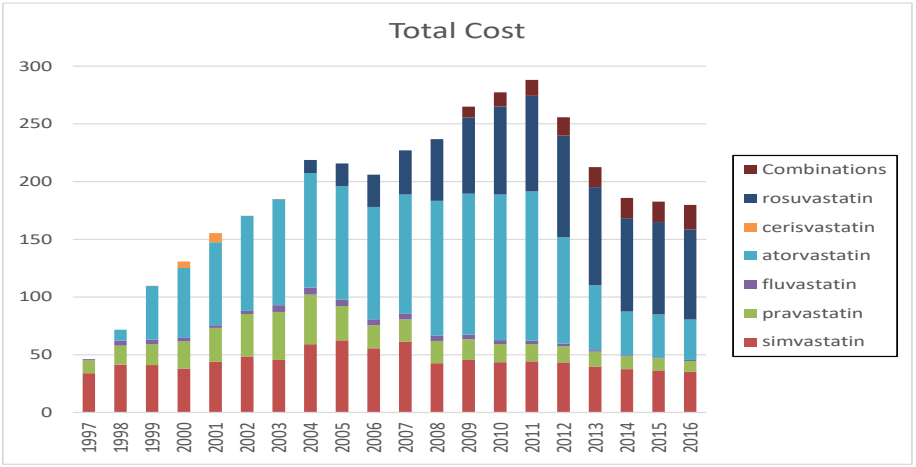
3.7.1 Total cost

Figure 6 shows the total yearly cost (RIZIV – INAMI reimbursement + patient contribution) for statins and combination products. The main cost for statins is for the plain statins but the contribution of the combination products, first available since 2008, is increasing.

The total cost (RIZIV – INAMI reimbursement + patient contribution) for statins and combination products sold in public pharmacies continued to increase over the years reaching almost € 290 million in 2011. Afterwards it declined to € 180 million in 2016. This decline is mainly due to the availability of generics for atorvastatin (after the patent for Lipitor® expired) and a resulting price decline since 2012. This decrease in total costs continued in further use due to the lower prices for statins. However, the number of DDD's continued to increase as shown previously.

The contribution of the combination products is increasing over the years, from 3.5 % of the total cost in 2009 to almost 12 % in 2016. The total cost of those combination products increased from € 9.4 million to over € 21 million in 2016.

Figure 6 – Evolution of the total cost (RIZIV – INAMI reimbursement plus patient contribution in public pharmacies) for statins and combination products (in million €)



Source: KCE report 141 and RIZIV – INAMI
http://www.riziv.fgov.be/nl/statistieken/geneesmiddel/Paginas/default.aspx#.WoV6BSiWw2w

3.7.2 Reimbursements

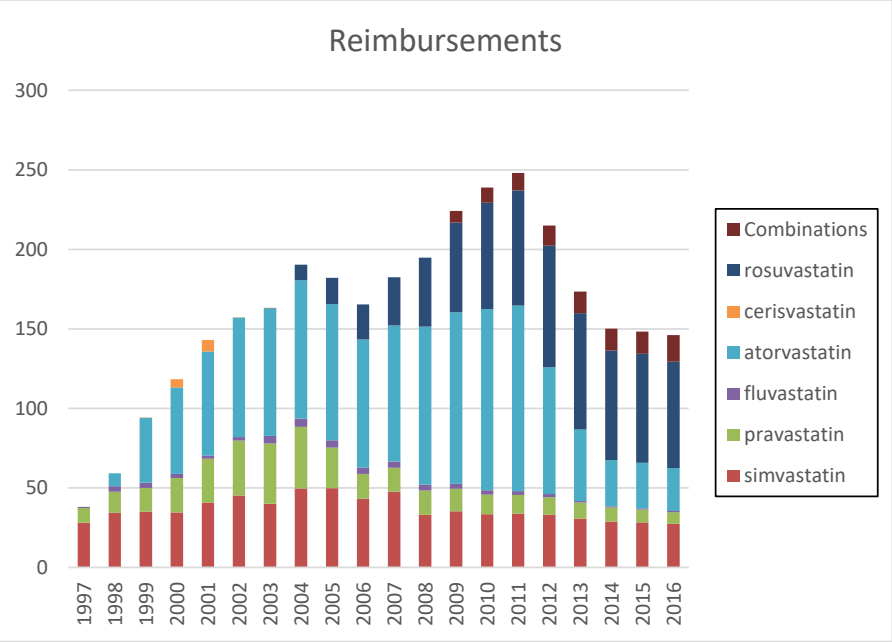
A major part of the total costs are reimbursed through social security (RIZIV – INAMI). The reimbursement costs basically follow the same pattern as the total costs but at a slightly lower level, as shown in Figure 7.

Also reimbursement costs increased up to 2011, reaching almost € 250 million and decreasing thereafter to almost € 150 million in 2016.

In 2016, three statins figured in the TOP 25 of reimbursements of pharmaceuticals report of NIHDI: rosuvastatin (2nd place: € 66.918.988), simvastatin (11th place: € 27.409.902) and atorvastatin (12th place: € 26.974.239). However, until 2018 no generic alternatives for rosuvastatin (Crestor®) were available and it is currently too early to estimate the effect of this introduction, but it can be anticipated that the total yearly cost and the reimbursement cost of statin use will further decrease.

Reimbursements for combination pharmaceuticals, up to 2014 mainly Inegy® (C10BA02), have been rising from € 9.4 million in 2009 to almost € 17 million in 2014. Although the total cost for these combination products is still relatively low compared with the plain lipid lowering drugs the arrival of future combination pharmaceuticals, or changing prescription behaviour, might change this cost element in the future. However, also here the growing contribution of combination products is obvious rising from 3.3 % in 2009 to 11.4 % in 2016 despite the required prior approval.

Figure 7 – Evolution of net expenditures of RIZIV – INAMI (public pharmacies) for statins and combination products (in million €)



3.7.3 Patient contribution

The average out of pocket contribution for the use of statins for the patients varies slightly over the years but is never higher than 20%.

3.8 Summary of the global data

It should be emphasised that the data based upon global data are about statin use in both primary and secondary prevention, as it is impossible to make the difference in those global data. We try to separate both indications using the individual data analysed in the next sections, and especially in section 1.1.

The number of users has increased over the years from around 400 000 in 2002 until approximately 1 500 000 in 2012. Since then the number has stabilized. However, as we show in the individual data this stabilisation does not mean that they are always the same users. It means that as many users begin as other users quit using statins.

Combination products started to be used in 2008. The number of its users is increasing but still marginal (slightly over 30 000 in 2016 or roughly 2% of statin users). It is unknown to what extend those combinations are also used in primary prevention.

The volumes of statins sold, expressed as DDD, increased significantly from around 100 million DDD in 2002 to around 500 million DDD in 2016. However, the relative contribution of each of the different statins varies over the years as is shown in section 3.6. In recent years the use of simvastatin and pravastatin is decreasing while especially the use of atorvastatin is increasing.

The volume of combination products containing a statin increased from less than 5 million DDD in 2009 to over 11 million DDD. Reimbursement cost increased likewise from € 7 to € 17 million. Again, it is unknown to what extend those combinations are also used in primary prevention.

The total yearly cost for statins has increased from € 170 million in 2002 and peaked in 2011 at over € 270 million. Both due to a stabilizing of the number of users and decreasing prices it came back down to around € 160 million in 2016.

The reimbursement cost for the social security followed a similar pattern: around € 160 million in 2002, almost € 240 million in 2011 and € 130 million in 2016.

The total cost for combination products containing a statin increased from € 9 million in 2009 to € 21 million. Reimbursement cost increased likewise from € 7 to € 17 million.

3.9 Statin users (individual data)

3.9.1 Users and New users

Table 6 shows the number of statin users remains stable since 2012. We see that, in terms of number of users, simvastatin comes first, followed by atorvastatin and rosuvastatin. Since 2012, the number of users of atorvastatin is increasing at the expense of the number of users of simvastatin. Pravastatin and fluvastatin represent less than 100 000 users per year. The number of users of associations is growing each year, but remains relatively low with 32 800 users in 2016.

The number of new users of statin is stable during the last years, with around 240 000 new users per year, which represents less than 20% of all statin users. About the same number quits using statins leading to a stable number of 1.5 million users each year.

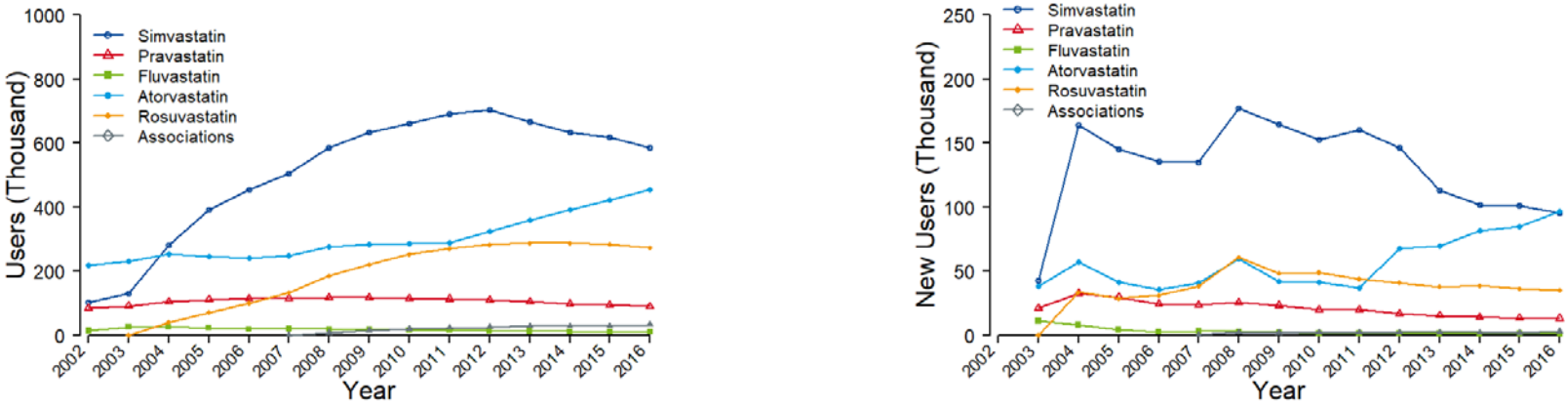
Table 6 – Users and new users per statin per year (numbers x 1000)

		2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
Simvastatin	Users	102,0	130,7	279,8	391,3	454,3	504,0	584,4	632,9	661,2	691,2	703,0	664,9	633,3	617,3	585,5
	New Users		42,8	164,7	145,5	136,0	135,9	178,0	165,7	154,3	161,8	148,3	114,7	103,6	103,5	97,7
	% New Users		32,7%	58,8%	37,2%	29,9%	27,0%	30,5%	26,2%	23,3%	23,4%	21,1%	17,2%	16,4%	16,8%	16,7%
Pravastatin	Users	83,5	90,6	104,1	111,1	113,7	115,6	116,6	116,8	114,2	112,9	109,3	103,6	98,0	93,8	88,9
	New Users		21,0	32,9	29,9	24,5	23,6	25,7	23,5	20,1	20,1	16,8	15,4	14,3	13,5	13,1
	% New Users		23,2%	31,6%	26,9%	21,6%	20,4%	22,0%	20,1%	17,6%	17,8%	15,4%	14,9%	14,6%	14,3%	14,7%
Fluvastatin	Users	14,5	25,2	26,2	22,3	19,1	19,2	18,3	17,0	15,8	14,7	13,1	12,0	10,8	10,5	9,7
	New Users		11,1	8,0	4,3	2,4	3,3	2,9	2,0	1,2	1,4	1,3	1,1	0,8	1,0	1,0
	% New Users		44,1%	30,4%	19,3%	12,8%	17,1%	15,6%	12,0%	7,5%	9,7%	9,6%	8,8%	7,4%	9,9%	10,1%
Atorvastatin	Users	217,7	230,1	252,6	245,4	240,6	249,4	275,6	282,3	286,1	287,5	323,0	359,0	391,5	421,4	453,3
	New Users		38,7	57,8	41,8	35,9	41,0	60,2	42,5	42,0	37,8	67,9	70,7	82,4	86,2	98,3
	% New Users		16,8%	22,9%	17,0%	14,9%	16,4%	21,8%	15,1%	14,7%	13,1%	21,0%	19,7%	21,0%	20,4%	21,7%
Rosuvastatin	Users		0,1	39,8	70,3	99,7	133,2	184,9	219,7	252,3	270,3	282,9	288,0	288,1	283,9	272,9
	New Users		0,1	33,5	28,6	31,2	38,3	60,9	48,8	49,3	44,5	41,7	38,5	39,2	36,9	36,1
	% New Users		100%	84,3%	40,7%	31,3%	28,7%	32,9%	22,2%	19,5%	16,5%	14,7%	13,4%	13,6%	13,0%	13,2%
Associations	Users						0,4	7,3	14,5	19,3	22,9	25,5	28,4	29,0	29,0	32,8
	New Users						0,3	2,1	1,9	2,1	2,0	2,0	2,2	2,3	2,0	3,0
	% New Users						94,4%	28,6%	13,1%	11,0%	8,7%	7,9%	7,6%	7,9%	6,7%	9,2%
Total	Users	417,6	476,7	702,5	840,4	927,4	1021,6	1187,2	1283,2	1349,0	1399,4	1456,8	1455,8	1450,7	1456,0	1443,1
	New Users		113,7	296,9	250,2	230,1	242,4	329,7	284,5	268,9	267,6	277,9	242,5	242,7	243,0	249,2
	% New Users		23,9%	42,3%	29,8%	24,8%	23,7%	27,8%	22,2%	19,9%	19,1%	19,1%	16,7%	16,7%	16,7%	17,3%

Analysing the evolution of the number of new users of simvastatin (Figure 8), we see a first peak in 2004 when the generic alternative became available. A second peak occurs in 2008, when a second price reduction occurred due to favouring the reimbursement of the cheapest products and so making them more attractive to patients. Since 2012, the number of new users of simvastatin is slightly decreasing. At the opposite, since 2012, the number of new users of atorvastatin is increasing, which corresponds to the time when the generic alternative became available. The number of new users of the other statins stays stable in time, even when generics became available for pravastatin (2005) or fluvastatin (2012). For rosuvastin, we can expect an increase in new users in 2018 with the newly available generic drug.

The same analyses have been done in different subgroups: subgroups of age (0-49, 50-59, 60-69, 70-79 and 80+, in Table 24, Figure 17, Table 25, Figure 18,Table 26, Figure 19, Table 27, Figure 20, Table 28 and Figure 21 in appendix), subgroups of gender (males and females, in Table 29, Figure 22, Table 30 and Figure 23 in appendix) and subgroups of region (Brussels-capital, Flemish and Walloon regions, in Table 35, Figure 24, Table 32, Figure 25, Table 33 and Figure 26 in Appendix). All subgroup analyses give similar results.

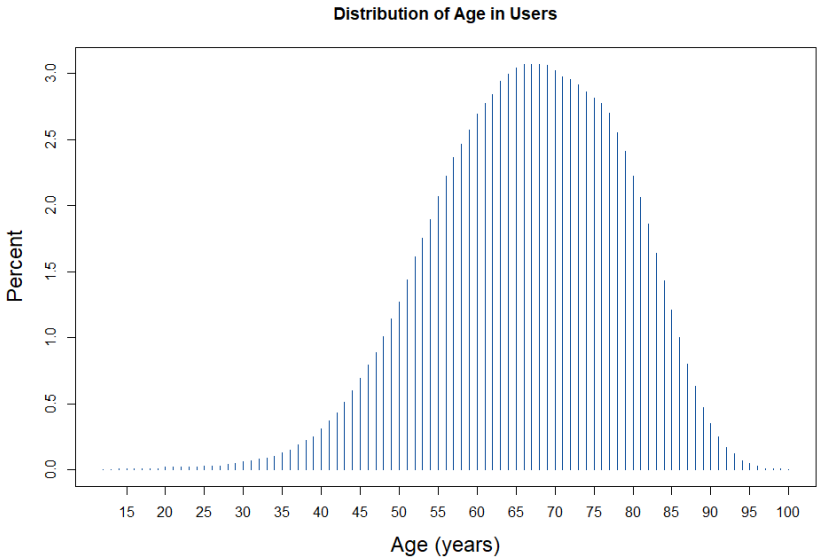
Figure 8 – Evolution of number of users (left) and new users (right) per statin and per year (in thousand)



3.9.2 Characteristics of users and new users of the last years of registration 2014-2015

The baseline characteristics of users and new users are shown in detail in Table 7. The mean age of users is 67.5 years (Figure 9). Comparing the age between users and new users in the years 2014 to 2015, we see that new users are younger, which means that the majority of patients start taking a statin between age 50 and 70 years (57.4%). There is no difference in gender in users or new users. When we analyse new users ≥75y, there are more women, and in new users of associations, there are a little more men.

Figure 9 – Distribution of age in users



In new users, we can analyse the frequency and duration of use: the mean time of consumption in new users is 490 days, with principally medium and high doses statin. Since we analyse subgroups of new users, users ≥75years are using more medium dose statins and users of associations only high dose statins. This last subgroup is the group in which there are most patients aged between 60 and 69 years, and users of antidiabetic drugs.

A generic statin is used in around 65% of new users and 60% in the subgroup ≥75years. However, nowadays the price difference between the brand product and the generic alternative is often minimal or even non-existent. The difference is in atorvastatin (29% in new users and 23% in the subgroup). Concerning the major statin used, no difference is seen. But in the subgroup of association it is principally simvastatin, which reflect the use of Inegy® being the main association drug.

Table 7 – Baseline characteristics of users, new users, new users>75y of statin, and new users of statin drugs in association in years 2014-2015 (numbers x 1000)

	Analysis of years 2014-2015			
	Users (n=2906.7)	New Users (n=485.7)	New Users ≥75y (n=89.4)	New Users of Associations (n=4.2)
Male gender (n, %)	2906.7 (52.0)	249.2 (51.3)	37.2 (41.6)	2.3 (55.2)
Age	67.5	62.4	80.8	63.3
Age [0;49] (n, %)	208.7 (7.2)	74.1 (15.3)	-	0.4 (9.4)
Age [50;59] (n, %)	529.9 (18.2)	114.8 (23.6)	-	0.7 (17.0)
Age [60;69] (n, %)	874.1 (30.1)	162.7 (33.5)	-	2.2 (52.8)
Age [70;79] (n, %)	778.7 (26.8)	86.4 (17.8)	41.7 (46.6)	0.6 (15.1)
Age [80; [(n, %)	515.3 (17.7)	47.7 (9.8)	47.7 (53.4)	0.2 (5.7)
Weak socio economic status (n, %)	511.5 (17.6)	76.9 (15.9)	24.6 (27.5)	0.6 (14.2)
Brussels-capital Region (n, %)	267.0 (9.2)	54.1 (11.1)	10.1 (11.3)	0.5 (11.3)
Flemish Region (n, %)	1799.5 (61.9)	281.7 (58.0)	54.0 (60.3)	2.3 (52.8)
Walloon Region (n, %)	840.2 (28.9)	149.9 (30.9)	25.4 (28.4)	1.5 (35.9)

Time of utilisation (days)	-	491.3	448.5	604.8
Time of utilisation (median [IQR], days)	-	486.7 [100-754]	439.9 [100-688]	645.0 [293-900]
Consumed Tablets	-	442.5	416.4	541.4
Consumed DDDs	-	510.4	460.0	554.3
Low statin dose (n, %)	196.1 (6.7)	28.5 (5.9)	6.6 (7.3)	-
Medium statin dose (n, %)	1459.9 (50.2)	255.1 (52.5)	49.1 (54.9)	-
High statin dose (n, %)	1250.7 (43.0)	202.1 (41.6)	33.7 (37.7)	4.2 (100)
Use of antidiabetic drug (n, %)	883.0 (30.4)	130.0 (26.8)	26.1 (29.1)	1.8 (42.9)
Use of anti-cardiovascular drug (n, %)	2489.7 (85.7)	383.2 (78.9)	84.2 (94.2)	3.7 (87.3)
Use of other lipid lowering drug (n, %)	450.1 (15.5)	64.4 (13.3)	15.1 (16.9)	4.2 (100)
First prescriber (GP)	2564.3 (88.2)	376.7 (77.6)	67.6 (75.6)	3.2 (75.5)
First statin used				
- Simvastatin Brand (n, %)	-	47.3 (9.7)	11.5 (12.9)	-
- Simvastatin Generic (n, %)	-	159.9 (32.9)	29.5 (33.0)	-
- Pravastatin Brand (n, %)	-	9.7 (2.0)	2.9 (3.2)	-
- Pravastatin Generic (n, %)	-	18.1 (3.7)	3.5 (3.9)	-
- Fluvastatin Brand (n, %)	-	1.7 (0.3)	0.5 (0.6)	-
- Fluvastatin Generic (n, %)	-	0.2 (0.04)	0.04 (0.04)	-
- Atorvastatin Brand (n, %)	-	35.5 (7.3)	8.6 (9.6)	-
- Atorvastatin Generic (n, %)	-	133.1 (27.4)	20.2 (22.6)	-
- Rosuvastatin (n, %)	-	76.2 (15.7)	12.0 (13.4)	-
- Associations (n, %)	-	4.2 (0.9)	0.6 (0.7)	4.2 (100)
First statin Generic (n, %)	-	311.2 (64.6)	53.3 (60.0)	-
Major statin used				
- Simvastatin (n, %)	1334.2 (45.9)	207.8 (42.8)	41.5 (46.4)	4.0 (95.3)
- Pravastatin (n, %)	210.4 (7.2)	28.3 (5.8)	6.4 (7.2)	0.1 (1.4)
- Fluvastatin (n, %)	24.4 (0.8)	2.1 (0.4)	0.6 (0.6)	0 (0)
- Atorvastatin (n, %)	797.3 (27.4)	170.7 (35.1)	29.1 (32.6)	0.1 (2.8)
- Rosuvastatin (n, %)	540.4 (18.6)	76.7 (15.8)	11.8 (13.2)	0.02 (0.5)

In new users, similar comparisons were made according to regions: the mean time of consumption in Brussels-capital is 457 days, in Flanders 513 days and in Wallonia 463 days. There are more people in a weak socio economic status in the Brussels-capital region. In this latter region, the statins are also less prescribed by a GP than in the other regions. The statin doses used are identical in the three regions: principally medium and high doses statins. All other parameters are similar in the three regions such as age, gender, consumed statins or concomitant drugs (see Table 8).

Table 8 – Baseline characteristics of statin new users in the Brussels-capital, Flemish and Walloon regions, in years 2014-2015 (numbers x 1000)

	Analysis of years 2014-2015		
	Brussels-Capital (n=54.1)	Flanders (n=281.7)	Wallonia (n=149.9)
Male gender (n, %)	26.4 (48.7)	146.6 (52.0)	76.2 (50.8)
Age	61.5	62.8	62.0
Age [0;49] (n, %)	10.3 (19.0)	40.1 (14.2)	23.7 (15.8)
Age [50;59] (n, %)	12.5 (23.1)	65.7 (23.3)	36.6 (24.4)
Age [60;69] (n, %)	16.7 (30.8)	95.3 (33.8)	50.7 (33.8)
Age [70;79] (n, %)	9.0 (16.6)	52.2 (18.5)	25.2 (16.8)
Age [80; [(n, %)	5.7 (10.5)	28.4 (10.1)	13.6 (9.1)
Weak socio economic status (n, %)	12.8 (23.9)	39.4 (14.0)	24.8 (16.6)
Time of utilisation (days)	457.0	512.7	463.3
Time of utilisation (median [IQR], days)	433.7 [99-723]	516.5 [100-772]	449.8 [99-729]
Consumed Tablets	393.2	472.2	404.5
Consumed DDDs	428.8	555.6	455.0
Low statin dose (n, %)	2.7 (4.9)	17.0 (6.0)	8.8 (5.9)
Medium statin dose (n, %)	30.6 (56.6)	146.5 (52.0)	78.0 (52.0)
High statin dose (n, %)	20.8 (38.5)	118.2 (42.0)	63.1 (42.1)
Use of antidiabetic drug (n, %)	17.6 (32.5)	63.4 (22.5)	49.1 (32.7)
Use of anti-cardiovascular drug (n, %)	42.9 (79.4)	215.7 (76.6)	124.5 (83.1)
Use of other lipid lowering drug (n, %)	8.2 (15.2)	30.8 (10.9)	25.3 (16.9)
First prescriber (GP)	38.6 (71.3)	221.9 (78.8)	116.2 (77.5)
First statin used			
- Simvastatin Brand (n, %)	5.4 (10.0)	22.9 (8.1)	18.9 (12.6)
- Simvastatin Generic (n, %)	19.5 (36.0)	95.8 (34.0)	44.5 (29.7)
- Pravastatin Brand (n, %)	0.8 (1.5)	5.6 (2.0)	3.3 (2.2)
- Pravastatin Generic (n, %)	1.8 (3.3)	10.8 (3.8)	5.5 (3.7)
- Fluvastatin Brand (n, %)	0.1 (0.2)	1.2 (0.4)	0.3 (0.2)

- Fluvastatin Generic (n, %)	-	0.1 (0.04)	0.04 (0.03)
- Atorvastatin Brand (n, %)	5.1 (9.4)	18.8 (6.7)	11.5 (7.7)
- Atorvastatin Generic (n, %)	12.6 (23.3)	83.1 (29.5)	37.3 (24.9)
- Rosuvastatin (n, %)	8.1 (15.0)	41.0 (14.6)	27.0 (18.0)
- Associations (n, %)	0.5 (0.9)	2.2 (0.8)	1.5 (1.0)
First statin Generic (n, %)	34.0 (63.4)	189.9 (67.9)	87.4 (58.9)
Major statin used			
- Simvastatin (n, %)	25.1 (46.4)	118.1 (41.9)	64.6 (43.1)
- Pravastatin (n, %)	2.6 (4.8)	16.9 (6.0)	8.8 (5.9)
- Fluvastatin (n, %)	0.2 (0.3)	1.5 (0.5)	0.5 (0.3)
- Atorvastatin (n, %)	18.0 (33.3)	103.5 (36.7)	49.2 (32.8)
- Rosuvastatin (n, %)	8.2 (15.2)	41.7 (14.8)	26.8 (17.9)

3.10 Primary vs. secondary prevention (individual data)

We tried to estimate the use for secondary prevention in new statin users by using a proxy variable based on the available data in the EPS. This is certainly no solid estimate but most likely an overestimate. This is due to the fact that surgery or hospitalisation for cardiovascular cause in a cardiovascular care unit B is not restricted to myocardial infarction, ischemic stroke or coronary artery diseases. Table 9 shows that the estimated number of new statin users in secondary prevention stays stable over time at around 12%. This proportion is similar to the one reported in the previous KCE report: 8.3% during the 2003-2006 period but based on a broader dataset for constructing a proxy variable.[3]

Table 9 – Estimated number of statin new users in secondary prevention (numbers x 1000)

	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
New Users	113.2	295.3	249.1	228.9	241	327.6	282.3	266	264.4	274.4	238.9	238.6	238.2	244.3
Secondary prevention	16,8 14,8%	40,5 13,6%	31,1 12,4%	28,2 12,2%	28,5 11,7%	34,9 10,6%	30,6 10,8%	31,1 11,6%	30,8 11,5%	30,4 10,9%	28,2 11,6%	29,0 12,0%	32,1 13,2%	32,3 13,0%

Comparing baseline characteristics of patients in primary and secondary prevention (Table 10) we observe that patients in secondary prevention are older (65% of patients ≥ 60years) and are consuming nearly two times more DDDs. Statins in secondary prevention are more prescribed by specialists (54%). The concomitant use of other CV or antidiabetic drugs is higher in secondary prevention, but the utilisation of generic statins is lower. Only the use of atorvastatin as major statin is higher in secondary prevention than in primary prevention (43% vs. 34%). The use of simvastatin is similar (~40%).

Table 10 – Primary and secondary prevention in new users of statin in years 2014-2015 (numbers x 1000)

	Analysis of years 2014-2015		
	Primary Prevention (n=424.6)	Secondary Prevention (n=61.1)	p-value
Male gender (n, %)	213.8 (50.4)	35.4 (57.9)	<0.001
Age	62.1	64.8	<0.001
Age [0;49] (n, %)	66.4 (15.6)	7.7 (12.6)	
Age [50;59] (n, %)	101.2 (23.8)	13.6 (22.2)	
Age [60;69] (n, %)	145.5 (34.3)	17.2 (28.2)	<0.001
Age [70;79] (n, %)	72.8 (17.2)	13.5 (22.1)	
Age [80; [(n, %)	38.6 (9.1)	9.1 (14.9)	
Weak socio economic status (n, %)	65.4 (15.4)	11.6 (19.0)	0.012
Brussels-capital Region (n, %)	46.8 (11.0)	7.3 (11.9)	
Flemish Region (n, %)	250.2 (58.9)	31.5 (51.6)	<0.001
Walloon Region (n, %)	127.6 (30.1)	22.3 (36.5)	
Time of utilisation (days)	487.4	518.0	<0.001
Time of utilisation (median [IQR], days)	479.6 [100-750]	524.5 [184-775]	-
Consumed Tablets	431.5	519.0	0.004
Consumed DDDs	473.7	765.7	<0.001
Low statin dose (n, %)	25.1.3 (5.9)	3.4 (5.5)	
Medium statin dose (n, %)	226.1 (53.3)	29.0 (47.4)	<0.001
High statin dose (n, %)	173.4 (40.8)	28.8 (47.1)	
Use of antidiabetic drug (n, %)	111.7 (26.3)	18.3 (30.0)	<0.001

Use of anti-cardiovascular drug (n, %)	327.9 (77.2)	55.3 (90.6)	<0.001
Use of other lipid lowering drug (n, %)	55.8 (13.1)	8.6 (14.0)	0.28
First prescriber (GP)	348.4 (82.1)	28.3 (46.3)	<0.001
First statin used			
- Simvastatin Brand (n, %)	37.7 (8.9)	9.6 (15.7)	
- Simvastatin Generic (n, %)	144.4 (34.0)	15.4 (25.2)	
- Pravastatin Brand (n, %)	8.8 (2.1)	0.9 (1.4)	
- Pravastatin Generic (n, %)	15.7 (3.7)	2.4 (4.0)	
- Fluvastatin Brand (n, %)	1.5 (0.4)	0.1 (0.2)	<0.001
- Fluvastatin Generic (n, %)	0.2 (0.04)	0.02 (0.03)	
- Atorvastatin Brand (n, %)	26.3 (6.2)	9.1 (15.0)	
- Atorvastatin Generic (n, %)	116.1 (27.3)	17.0 (27.8)	
- Rosuvastatin (n, %)	70.0 (16.5)	6.1 (10.0)	
- Associations (n, %)	6.5 (1.0)	0.7 (0.7)	
First statin Generic (n, %)	276.4 (65.1)	34.9 (57.1)	<0.001
Major statin used			
- Simvastatin (n, %)	183.2 (43.2)	24.6 (40.3)	
- Pravastatin (n, %)	24.8 (5.9)	3.5 (5.7)	
- Fluvastatin (n, %)	1.9 (0.4)	0.2 (0.3)	<0.001
- Atorvastatin (n, %)	144.4 (34.0)	26.4 (43.1)	
- Rosuvastatin (n, %)	70.3 (16.6)	6.4 (10.5)	

3.11 Adherence (individual data)

3.11.1 Regular and occasional users

Adherence is defined as a mean possession ratio (MPR) ≥ 80%. It has been estimated in new users for each year (see Table 11).

Individuals who purchased only one packaging cannot be classified as adherent or not. They represent well over 20% of new users in recent years. In 2016 this number increased markedly but this is an artefact. It can be anticipated that an important proportion of these will have purchased another packaging in 2017.

We observe that less than 50% of individuals are adherent to the statin treatment (regular users). Occasional users represent patients who are not regular users (both patients who purchase only one packaging and patients with MPR<80%). They represent more than half of the new users.

Among regular users, patients that stop the treatment for more than 3 months are defined as defaulters. The number of defaulters is decreasing with the year of beginning the treatment.

Among occasional users, some patients permanently stop taking statins and are defined as quitters. The number is increasing with time, because the later the year of quitting, the lower the number of years to take it again.

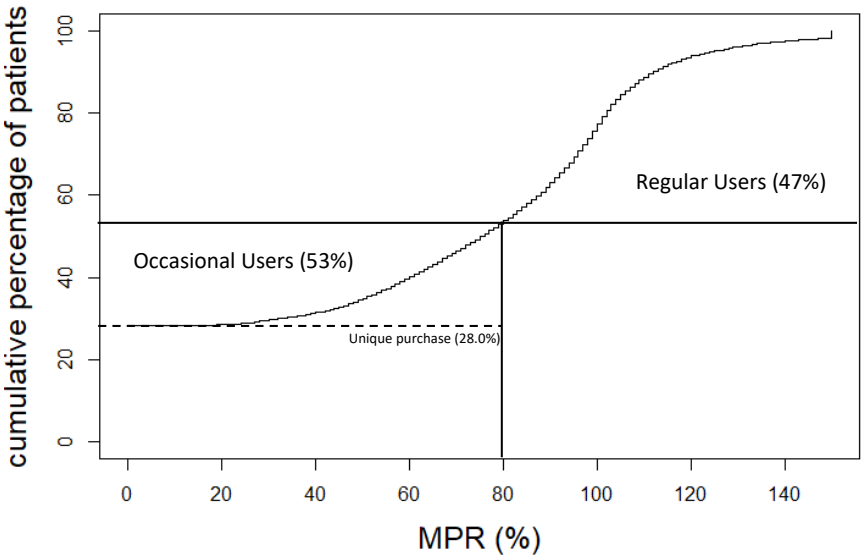
Table 11 – Adherence assessment of new users (numbers x 1000)

	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
New Users	113.2	295.3	249.1	228.9	241	327.6	282.3	266	264.4	274.4	238.9	238.6	238.2	244.3
Only one pack recorded	16.4 14,4%	40.1 13,5%	52.6 21,0%	52.5 22,8%	56.9 23,5%	65.7 19,9%	68.2 24,0%	65.9 24,5%	64.4 24,1%	72.7 26,2%	63.7 26,3%	66.9 27,6%	66.4 27,3%	120.7 48,4%
Regular users	54.7 48,1%	153.1 51,6%	107.8 43,1%	96 41,7%	99.7 41,1%	147.5 44,7%	114.8 40,4%	106.8 39,7%	110.7 41,4%	116.4 41,9%	100.8 41,6%	106.6 43,9%	120.3 49,5%	108 43,3%
Defaulters	28.8 52,8%	74.8 48,8%	52.3 48,5%	44.2 46,0%	43.6 43,8%	62.2 42,2%	44.8 39,0%	36.7 34,4%	35.1 31,7%	32.5 27,9%	23.4 23,2%	18.2 17,1%	10.3 8,6%	0.9 0,8%
Occasional users	59 51,9%	143.8 48,4%	142.4 56,9%	134.1 58,3%	142.7 58,9%	182.2 55,3%	169.6 59,6%	162.2 60,3%	156.9 58,6%	161.6 58,1%	141.7 58,4%	136 56,1%	122.8 50,5%	141.3 56,7%
Quitters	12,7 11,2%	36,1 12,2%	38,0 15,2%	32,3 14,0%	34,8 14,4%	49,5 15,0%	45,3 15,9%	44,4 16,5%	46,2 17,3%	51,2 18,4%	44,8 18,5%	47,3 19,5%	49,5 20,4%	63,3 25,4%

This adherence assessment has also been performed by region (see Table 35, Table 36, Table 37 in Appendix). All subgroups analyses show similar results.

Figure 10 shows the distribution of the mean possession ratio in patients with more than one packaging of statin purchase during the years 2014-2015. In those years regular users represent 47% of new users.

Figure 10 – Distribution of the mean possession ratio (MPR). MPR is defined for each new user in the years 2014-2015.



The baseline characteristics of these different categories of new users are presented in detail in Table 12. The mean age of the quitters is lower than the other subgroups. There is no difference in terms of socio-economic status and region between the different groups.

Table 12 – Baseline characteristics of different categories of new users in years 2014-2015 (numbers x 1000)

				Analysis of years 2014-2015		
	Regular users (n=226.9)	No defaulters (n=198.4)	Defaulters (n=28.5)	Occasional users (n=258.8)	No quitters (n=161.9)	Quitters (n=96.8)
Male gender (n, %)	121.0 (53.3)	105.5 (53.2)	15.5 (54.2)	128.2 (49.5)	79.1 (48.9)	49.1 (50.7)
Age	63.5	63.4	63.6	61.5	63.7	57.8
Age [0;49] (n, %)	26.0 (11.4)	22.9 (11.5)	3.1 (10.8)	48.1 (18.6)	22.8 (14.1)	25.4 (26.2)
Age [50;59] (n, %)	51.1 (22.5)	45.5 (22.9)	5.6 (19.6)	63.7 (24.6)	39.5 (24.4)	24.2 (24.9)
Age [60;69] (n, %)	88.2 (38.9)	76.0 (38.3)	12.1 (42.5)	74.5 (28.8)	43.9 (27.1)	30.6 (31.6)
Age [70;79] (n, %)	39.6 (17.4)	34.1 (17.2)	5.5 (19.2)	46.8 (18.1)	35.6 (22.0)	11.2 (11.5)
Age [80; [(n, %)	22.1 (9.7)	19.8 (10.0)	2.2 (7.8)	25.7 (9.9)	20.1 (12.4)	5.5 (5.7)
Weak socio economic status (n, %)	36.7 (16.2)	31.7 (16.0)	5.0 (17.5)	40.3 (15.6)	26.4 (16.3)	13.9 (14.4)
Brussels-capital Region (n, %)	22.7 (10.0)	19.6 (9.9)	3.1 (10.9)	31.4 (12.1)	19.7 (12.1)	11.7 (12.1)

Flemish Region (n, %)	137.9 (60.8)	121.1 (61.0)	16.8 (59.0)	143.8 (55.6)	90.0 (55.6)	53.8 (55.5)
Walloon Region (n, %)	66.3 (29.2)	57.7 (29.1)	8.6 (30.1)	83.6 (32.3)	52.3 (32.3)	31.3 (32.3)
Time of utilisation (days)	647.9	629.0	779.3	353.9	377.5	314.6
Time of utilisation (median [IQR], days)	652.6 [441-876]	625.5 [415-852]	787.4 [610-977]	99.8 [94-604]	303.4 [93-627]	99.1 [93-540]
Consumed Tablets	686.4	675.1	765.3	228.6	231.4	224.0
Consumed DDDs	799.6	787.9	880.5	256.9	266.1	241.6
Low statin dose (n, %)	12.7 (5.6)	10.9 (5.5)	1.8 (6.3)	15.8 (6.1)	10.7 (6.6)	5.1 (5.3)
Medium statin dose (n, %)	117.0 (51.6)	102.1 (51.5)	14.9 (52.3)	138.1 (53.4)	83.5 (51.5)	54.6 (56.4)
High statin dose (n, %)	97.2 (42.8)	85.3 (43.0)	11.8 (41.4)	105.0 (40.6)	67.8 (41.9)	37.1 (38.4)
Use of antidiabetic drug (n, %)	66.5 (29.3)	56.6 (28.5)	9.9 (34.5)	63.6 (24.9)	43.8 (27.0)	19.8 (20.4)
Use of anti-cardiovascular drug (n, %)	185.6 (81.8)	163.0 (82.2)	22.6 (79.3)	197.6 (76.4)	128.8 (79.5)	68.8 (71.1)
Use of other lipid lowering drug (n, %)	29.5 (13.0)	25.5 (12.8)	4.1 (14.3)	34.8 (13.5)	26.9 (16.6)	7.9 (8.1)
First prescriber (GP)	167.3 (73.8)	145.8 (73.5)	21.5 (75.4)	209.4 (80.9)	133.9 (82.7)	75.5 (78.0)
Secondary prevention (n, %)	37.6 (16.6)	33.8 (17.0)	3.7 (13.1)	23.5 (9.1)	12.6 (7.8)	11.0 (11.3)
First statin used						
- Simvastatin Brand (n, %)	22.6 (10.0)	19.6 (9.9)	3.0 (10.5)	24.7 (9.5)	15.5 (9.6)	9.2 (9.5)
- Simvastatin Generic (n, %)	71.0 (31.3)	61.8 (31.1)	9.2 (32.3)	88.9 (34.4)	54.3 (33.5)	34.5 (35.6)
- Pravastatin Brand (n, %)	4.3 (1.9)	3.6 (1.8)	0.7 (2.5)	5.3 (2.0)	3.7 (2.3)	1.6 (1.7)
- Pravastatin Generic (n, %)	8.0 (3.5)	7.0 (3.5)	1.1 (3.9)	10.1 (3.9)	6.7 (4.1)	3.3 (3.4)
- Fluvastatin Brand (n, %)	0.7 (0.3)	0.6 (0.3)	0.1 (0.4)	1.0 (0.4)	0.7 (0.4)	0.3 (0.3)
- Fluvastatin Generic (n, %)	0.1 (0.04)	0.1 (0.1)	0.02 (0.1)	0.1 (0.04)	-	0.1 (0.1)
- Atorvastatin Brand (n, %)	18.0 (7.9)	15.9 (8.0)	2.1 (7.4)	17.5 (6.8)	11.2 (6.9)	6.3 (6.5)
- Atorvastatin Generic (n, %)	67.7 (29.8)	60.3 (30.4)	7.4 (26.0)	65.4 (25.3)	36.6 (22.6)	28.8 (29.8)
- Rosuvastatin (n, %)	32.2 (14.2)	27.5 (13.9)	4.6 (16.1)	44.0 (17.0)	31.7 (19.6)	12.3 (12.7)
- Associations (n, %)	2.4 (1.1)	1.9 (1.0)	0.5 (1.8)	1.9 (0.7)	1.5 (0.9)	0.4 (0.4)
First statin Generic (n, %)	146.8 (65.4)	129.2 (65.7)	17.6 (62.8)	164.4 (64.0)	97.7 (60.9)	66.8 (69.2)
Major statin used						
- Simvastatin (n, %)	92.6 (40.8)	80.6 (40.6)	12.0 (42.1)	115.3 (44.5)	80.6 (40.6)	43.6 (45.1)
- Pravastatin (n, %)	12.8 (5.6)	10.8 (5.5)	1.9 (6.7)	15.6 (6.0)	10.8 (5.5)	5.1 (5.2)
- Fluvastatin (n, %)	1.0 (0.4)	0.9 (0.5)	0.1 (0.3)	1.1 (0.4)	0.9 (0.5)	0.3 (0.3)
- Atorvastatin (n, %)	87.7 (38.7)	78.2 (39.4)	9.5 (33.4)	83.0 (32.1)	78.2 (39.4)	35.3 (36.4)
- Rosuvastatin (n, %)	32.8 (14.5)	27.9 (14.0)	5.0 (17.4)	43.9 (17.0)	27.9 (14.0)	12.5 (12.9)

3.11.2 Factors associated with poor adherence

Table 13 compares characteristics of regular and occasional users in all patients and in the subgroup of primary prevention. Regular users are slightly older and obviously take more statins and for a longer time. No clear difference between the types of statin used was detected.

Table 13 – Regular and occasional new users of statin in years 2014-2015 (numbers x 1000)

	Analysis of years 2014-2015			Primary prevention (2014-2015)		
	Regular users (n=226.9)	Occasional users (n=258.8)	p-value	Regular users (n=189.4)	Occasional users (n=235.2)	p-value
Age	63.5	61.5	<0.001	63.1	61.3	<0.001
Time of utilisation (days)	647.9	353.9	<0.001	652.8	354.3	<0.001
Time of utilisation (median [IQR], days)	652.6 [441-876]	99.8 [94-604]	<0.001	658.8 [445;881]	99.8 [94;332]	<0.001
Consumed Tablets	686.4	228.6	<0.001	684.6	227.8	<0.001
Consumed DDDs	799.6	256.9	<0.001	750.6	250.8	<0.001
MPR (%)	112.2	70.8	<0.001	110.7	70.0	<0.001
First statin used						
- Simvastatin Brand (n, %)	22.6 (11.9%)	24.7 (10.5%)	0.018	16.2 (8.6%)	21.4 (9.1%)	0.98
- Simvastatin Generic (n, %)	71.0 (37.5%)	88.9 (37.8%)		62.2 (32.9%)	82.2 (35.0%)	
- Pravastatin Brand (n, %)	4.3 (2.3%)	5.3 (2.3%)	0.90	3.9 (2.0%)	4.9 (2.1%)	0.59
- Pravastatin Generic (n, %)	8.0 (4.2%)	10.1 (4.3%)		6.6 (3.5%)	9.1 (3.9%)	
- Fluvastatin Brand (n, %)	0.7 (0.4%)	1.0 (0.4%)	0.25	0.7 (0.3%)	0.9 (0.4%)	0.39
- Fluvastatin Generic (n, %)	0.1 (0.1%)	0.1 (0.03%)		0.1 (0.1%)	0.1 (0.03%)	
- Atorvastatin Brand (n, %)	18.0 (9.5%)	17.5 (7.4%)	<0.001	11.6 (6.1%)	14.7 (6.3%)	<0.001
- Atorvastatin Generic (n, %)	67.7 (35.7%)	65.4 (27.8%)		56.8 (30.0%)	59.3 (25.2%)	
- Rosuvastatin (n, %)	32.2 (17.0%)	44.0 (18.7%)	0.38	29.1 (15.4%)	40.9 (17.4%)	0.58
- Associations (n, %)	2.4 (1.3%)	1.9 (0.8%)	0.59	2.1 (1.1%)	1.7 (0.7%)	0.62
First statin Generic (n, %)	146.8 (77.5%)	164.4 (69.9%)	0.29	125.7 (66.0%)	150.6 (64.0%)	0.64

To look for variables associated with poor adherence, univariate and multivariate logistic regression was performed. We observe that variables independently associated with occasional use are age <50 years, female gender, living in Brussels-Capital region, the use of rosuvastatin and a GP as first prescriber. Variables associated with regular use (adherence) are age between 60 and 69 yeas, the concomitant use of other cardiovascular drugs or antidiabetic drugs, living in the Flanders region, the use of atorvastatin and to be using statins for secondary prevention (see Table 14 for details).

Table 14 – Factors associated with regular new users of statin in years 2014-2015 (numbers x 1000)

Analysis of years 2014-2015		Univariate Analysis		Multivariate Analysis	
	Regular users (n=226.9)	Univariate Analysis	P-value	Multivariate Analysis	P-value
Male gender (n, %)	121.0 (53.3%)	1.08 [1.05;1.11]	<0.001	1.07 [1.04;1.11]	<0.001
Age [0;49] (n, %)	26.0 (11.4%)	0.66 [0.61;0.71]	<0.001	0.67 [0.62;0.73]	<0.001
Age [50;59] (n, %)	51.1 (22.5%)	0.98 [0.92;1.04]	0.51	0.99 [0.93;1.06]	0.85
Age [60;69] (n, %)	88.2 (38.9%)	1.44 [1.37;1.52]	<0.001	1.49 [1.41;1.57]	<0.001
Age [70;79] (n, %)	39.6 (17.4%)	1.03 [0.97;1.09]	0.30	1.00 [0.95;1.06]	0.92
Age [80; [(n, %)	22.1 (9.7%)	1		1	
Weak socio economic status (n, %)	36.7 (16.2)	1.05 [0.96;1.13]	0.28		
Brussels-capital Region (n, %)	22.7 (10.0)	0.88 [0.82;0.94]	<0.001	0.88 [0.82;0.94]	<0.001
Flemish Region (n, %)	137.9 (60.8)	1.17 [1.12;1.23]	<0.001	1.20 [1.15;1.26]	<0.001
Walloon Region (n, %)	66.3 (29.2)	1		1	
Low statin dose (n, %)	12.7 (5.6%)	0.94 [0.86;1.02]	0.16		
Medium statin dose (n, %)	117.0 (51.6%)	0.99 [0.94;1.04]	0.63		
High statin dose (n, %)	97.2 (42.8%)	1			
Use of antidiabetic drug (n, %)	66.5 (29.3%)	1.27 [1.19;1.36]	<0.001	1.20 [1.12;1.29]	<0.001
Use of anti-cardiovascular drug (n, %)	185.6 (81.8%)	1.39 [1.29;1.51]	<0.001	1.19 [1.09;1.30]	<0.001
Use of other lipid lowering drug (n, %)	29.5 (13.0%)	0.96 [0.88;1.06]	0.42		
First prescriber (GP)	167.3 (73.8%)	0.81 [0.78;0.85]	<0.001	0.87 [0.84;0.91]	<0.001
Major statin used					
Simvastatin (n, %)	92.6 (40.8%)	1		1	
Pravastatin (n, %)	12.8 (5.6%)	0.94 [0.82;1.08]	0.37	0.95 [0.83;1.09]	0.43
Fluvastatin (n, %)	1.0 (0.4%)	1.11 [0.78;1.57]	0.58	1.06 [0.75;1.51]	0.73
Atorvastatin (n, %)	87.7 (38.7%)	1.21 [1.10;1.34]	<0.001	1.21 [1.10;1.35]	<0.001
Rosuvastatin (n, %)	32.8 (14.5%)	0.86 [0.77;0.96]	0.008	0.88 [0.79;0.99]	0.027
Secondary prevention (n, %)	37.6 (16.6%)	1.98 [1.80;2.18]	<0.001	1.73 [1.57;1.92]	<0.001

3.11.3 Adherence in primary prevention

We repeated this exercise for individuals using statins for primary prevention. Not surprisingly the results are very similar since this subgroup represent the major part of the statin users (see Table 15).

Table 15 – Factors associated with regular new users of statin in primary prevention in years 2014-2015 (numbers x 1000)

Primary prevention (2014-2015)		Univariate Analysis		Multivariate Analysis	
	Regular user (n=189.4)	Univariate Analysis	P-value	Multivariate Analysis	P-value
Male gender (n, %)	98.4 (52.0%)	1.06 [1.02;1.10]	<0.001	1.07 [1.03;1.11]	<0.001
Age [0;49] (n, %)	22.1 (11.7%)	0.68 [0.62;0.74]	<0.001	0.67 [0.62;0.74]	<0.001
Age [50;59] (n, %)	42.2 (22.3%)	0.97 [0.90;1.04]	0.35	0.97 [0.90;1.04]	0.43
Age [60;69] (n, %)	77.6 (41.0%)	1.55 [1.46;1.63]	<0.001	1.56 [1.48;1.65]	<0.001
Age [70;79] (n, %)	31.3 (16.5%)	1.02 [0.96;1.08]	0.60	1.00 [0.94;1.07]	0.90
Age [80; [(n, %)	16.2 (8.5%)	1		1	
Weak socio economic status (n, %)					
Brussels-capital Region (n, %)	18.9 (8.3)	0.90 [0.84;0.97]	0.004	0.90 [0.84;0.97]	0.006
Flemish Region (n, %)	117.2 (51.7)	1.17 [1.11;1.23]	<0.001	1.19 [1.13;1.25]	<0.001
Walloon Region (n, %)	53.3 (23.5)	1		1	
Low statin dose (n, %)	10.8 (5.7%)	0.95 [0.86;1.04]	0.26		
Medium statin dose (n, %)	99.6 (52.6%)	1.00 [0.94;1.05]	0.90		
High statin dose (n, %)	79.0 (41.7%)	1			
Use of antidiabetic drug (n, %)	55.3 (29.2%)	1.31 [1.21;1.41]	<0.001	1.24 [1.15;1.34]	<0.001
Use of anti-cardiovascular drug (n, %)	150.9 (79.7%)	1.29 [1.19;1.40]	<0.001	1.16 [1.06;1.27]	<0.001
Use of other lipid lowering drug (n, %)	24.4 (12.9%)	0.96 [0.87;1.06]	0.39		
First prescriber (GP)	151.3 (79.9%)	0.88 [0.84;0.92]	<0.001	0.88 [0.84;0.92]	<0.001
Major statin used					
Simvastatin (n, %)	77.9 (41.1%)	1		1	
Pravastatin (n, %)	10.7 (5.6%)	0.92 [0.80;1.06]	0.26	0.93 [0.81;1.07]	0.33
Fluvastatin (n, %)	0.9 (0.5%)	1.19 [0.82;1.73]	0.36	1.14 [0.79;1.63]	0.49
Atorvastatin (n, %)	70.3 (37.1%)	1.16 [1.04;1.29]	0.009	1.19 [1.07;1.32]	0.002
Rosuvastatin (n, %)	29.5 (15.6%)	0.88 [0.78;0.99]	0.029	0.88 [0.78;0.99]	0.029

3.11.4 Probability of stopping a statin for a period longer than 365 days in new users for primary prevention

Another analysis of adherence is to study the probability of stopping statins for a period longer than 365 days in new users of statins in the years 2014-2015 who use statins for primary prevention. The total numbers of new users for primary prevention is approximately 424 600 and the number of events is approximately 48 200 (11.3%) in the years 2014-2015.

A time to event Cox analysis shows that, both in uni- and multivariate analyses, the variables associated with stopping statin use longer than 365 days are a weak socio-economic status, a GP as a first prescriber and taking another lipid lowering drug. The latter might indicate that statins were insufficient to lower cholesterol and therapy was changed on purpose. We also observe in the multivariate analysis that age between 60 and 69 years or taking atorvastatin are variables in favour of continuing statin use in primary prevention. In the univariate analysis additionally the use of cardiovascular drugs favours continuing statin use but this is not observed in the multivariate analysis (for details see Table 16).

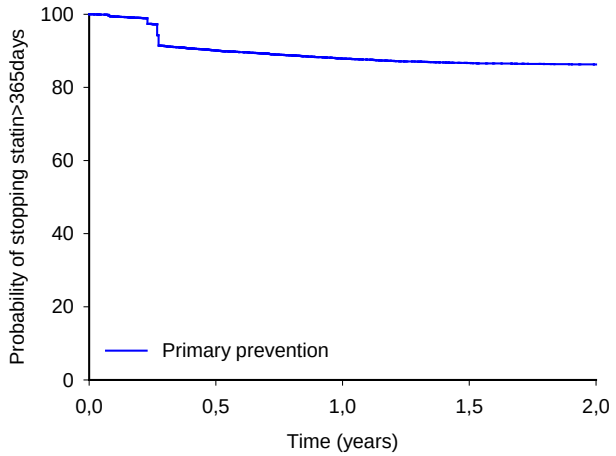
Table 16 – Factors associated with stopping statin use in new users (primary prevention) for longer than 365 days in the years 2014-2015 (numbers x 1000)

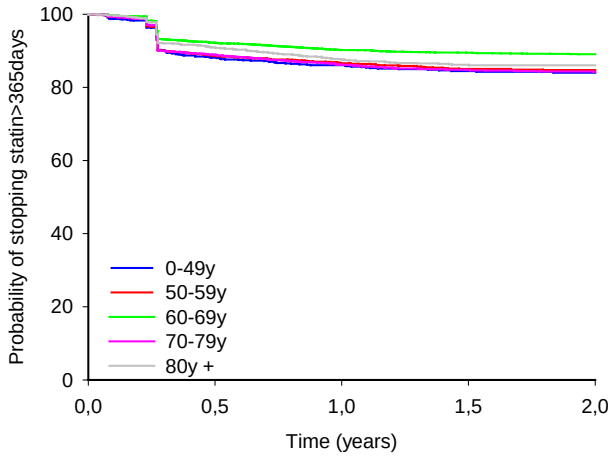
Analysis of years 2014-2015 – Primary prevention		Univariate analysis		Multivariate analysis	
	Stop statin >365 days Total n=48.2 (11.3% of total n)	HR [95%IC]	P-value	HR [95%IC]	P-value
Time to event (median [IQR], days)	99.1 [97;151]				
Consumed Tablets	157.0				
MPR (%)	26.0				
Male gender (n, %)	23.8 (49.3)	0.93 [0.84;1.03]	0.15		
Age [0;49] (n, %)	7.9 (16.4)	1.19 [0.98;1.44]	0.077	1.20 [0.98;1.46]	0.076
Age [50;59] (n, %)	12.7 (26.3)	1.13 [0.95;1.34]	0.18	1.13 [0.95;1.34]	0.18
Age [60;69] (n, %)	13.9 (28.8)	0.78 [0.67;0.92]	0.003	0.78 [0.67;0.92]	0.003
Age [70;79] (n, %)	9.5 (19.8)	1.16 [0.99;1.36]	0.074	1.18 [1.00;1.38]	0.049
Age [80; [(n, %)	4.2 (8.7)	1			
Weak socio economic status (n, %)	8.2 (17.1)	1.15 [1.02;1.31]	0.025	1.18 [1.03;1.34]	0.014
Brussels-capital Region (n, %)	5.8 (12.1)	1.09 [0.92;1.30]	0.30		
Flemish Region (n, %)	27.6 (57.2)	0.90 [0.80;1.00]	0.057		
Walloon Region (n, %)	14.8 (30.7)	1			
Low statin dose (n, %)	2.9 (5.9)	1.03 [0.83;1.26]	0.81		
Medium statin dose (n, %)	25.0 (51.9)	0.97 [0.88;1.08]	0.61		
High statin dose (n, %)	20.3 (42.2)	1			
Use of antidiabetic drug (n, %)	13.9 (28.9)	1.11 [0.99;1.23]	0.070		
Use of anti-cardiovascular drug (n, %)	36.6 (75.9)	0.88 [0.78;0.99]	0.037	0.90 [0.79;1.02]	0.096
Use of other lipid lowering drug (n, %)	7.6 (15.7)	1.25 [1.09;1.43]	0.001	1.23 [1.08;1.42]	0.003
First prescriber (GP)	40.7 (84.4)	1.19 [1.03;1.36]	0.015	1.20 [1.05;1.38]	0.009
Major statin used					
- Simvastatin (n, %)	21.3 (44.2)	1			

- Pravastatin (n, %)	2.9 (6.1)		1.03 [0.84;1.27]	0.78	1.02 [0.83;1.26]	0.85
- Fluvastatin (n, %)	0.2 (0.3)		0.72 [0.34;1.57]	0.41	0.75 [0.35;1.61]	0.45
- Atorvastatin (n, %)	14.6 (30.3)		0.81 [0.72;0.91]	<0.001	0.80 [0.71;0.90]	<0.001
- Rosuvastatin (n, %)	9.2 (19.1)		1.12 [0.98;1.27]	0.10	1.10 [0.96;1.25]	0.17

Figure 11 shows the probability of stopping statin use for a period longer than 365 days. The gap at the beginning of the graph represents all patients with only one purchase.

Figure 11 – Probability of stopping statin more than 365 days in primary and secondary prevention (left) and by age group (right)





3.11.5 Risk score assessment in regular versus occasional new users

The aim of this chapter is to assess adherence according to the risk score of the patients. For this purpose, we built a risk score based on mortality data, evaluated according to the presence of available cardiovascular risk factors: gender, presence of diabetes, and class of age (<48, 48-52, 53-57, 58-62, 63-67, ≥68) as defined in the SCORE risk assessment tool.

During the years 2014-2015, in primary prevention 12 460 individuals died (all-cause mortality). By logistic regression, the risk score was calculated by age category, gender and the use of anti-diabetic drugs as:

-4.8051-1.1265*Age[<48]-0.6938*Age[48-52]-0.6866*Age[53-57]-0.1085*Age[58-62]+0.7211*Age[63-67]+0.2970*AntiDiab+0.4594*Male

Performance analysis of the score shows a c-statistic of 0.59 [0.58;0.62].

Patients were then categorized into three risk groups according to tertiles of risk score: low, medium and high risk categories. In each category we evaluated the association of treatment adherence with risk of death. Results are summarized in Table 17. We observe that in individuals at low risk of death only 37% of the total risk-group is a regular user. This proportion increases to around 43% when they are at medium risk of death and at around 56% when they are at high risk.

Table 17 – Risk assessment of death according to cardiovascular risk factors (numbers x 1000).

	Average 2-year risk	Regular User 189.4 (44.6%)	Occasional User 235.2 (55.4%)	Total
Low risk	0.51%	57.3 (37.0%)	97.7 (63.0%)	155.0
Medium Risk	1.02%	66.1 (43.4%)	86.2 (56.6%)	152.3
High Risk	2.19%	66.0 (56.2%)	51.3 (43.8%)	117.3

Table 18 characterizes the number of patients (in thousand) according to the risk category. Thanks to this characterisation of use of these categories, we can identify groups of patients where the adherence is relatively good, and groups where adherence is clearly poor.

As expected, young patients and woman are in the low risk category. For patients under 48 years, in the low risk category, we can see that there are two times more occasional users than regular users. As women are diabetic in the middle age, they upgrade in the middle category of risk. In this category are also old woman patients, and diabetic young man. In the high risk category are patients between 63 and 68 years, and old diabetic men. In this category we have more regular users than occasional users.

Table 18 – Characteristics of patients at low, medium and high risk of death (numbers x 1000).

AGE	Regular User				Occasional User			
	WOMAN		MAN		WOMAN		MAN	
	No Diab	Diab	No Diab	Diab	No Diab	Diab	No Diab	Diab
<48	4.0	1.7	8.3	2.8	10.8	3.0	16.7	4.3
48-52	4.3	1.4	7.7	2.2	8.7	2.8	11.3	2.6
53-57	7.5	2.7	8.4	4.0	13.2	3.8	12.5	3.3
58-62	8.5	2.8	9.6	3.9	10.6	3.8	11.1	3.7
63-67	18.9	7.2	19.0	9.1	15.4	4.3	13.6	5.1
≥68	22.3	9.6	15.6	7.9	32.9	10.5	22.0	9.2

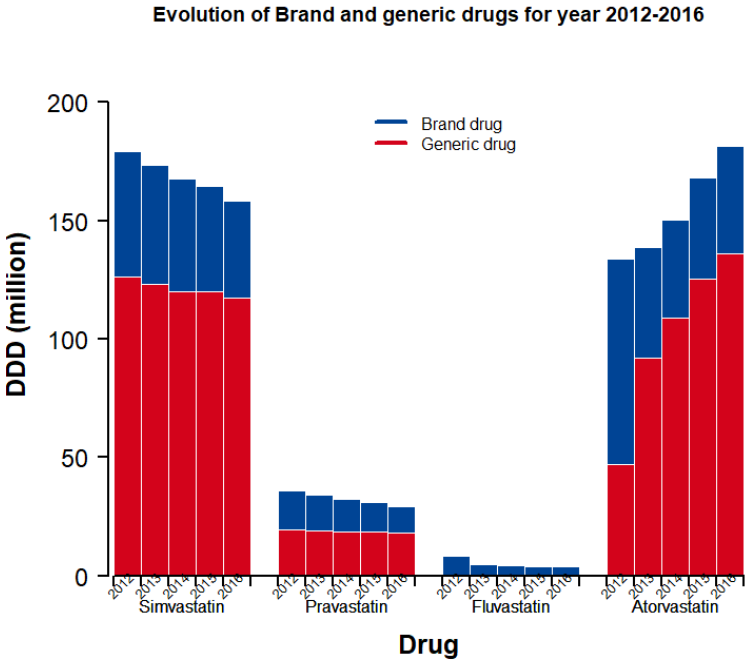
Low Risk Medium Risk High Risk

3.12 Expenses (individual data)

3.12.1 Brand drug or generic

In terms of drug consumption, 500 million DDD's were bought in 2016. But the market share of generic drugs has grown. As can be seen in Figure 12, the market share of generic drugs is stable since 2012 for simvastatin and pravastatin but increasing for atorvastatin. Rosuvastatin is not represented because the generic alternative is available only since January 2018. Currently there is no generic alternative for fluvastatin but these were available in the past (numbers to low to show on the graph).

Figure 12 – Evolution of the consumption of brand and generic statins for the years 2012-2016 (primary and secondary prevention)

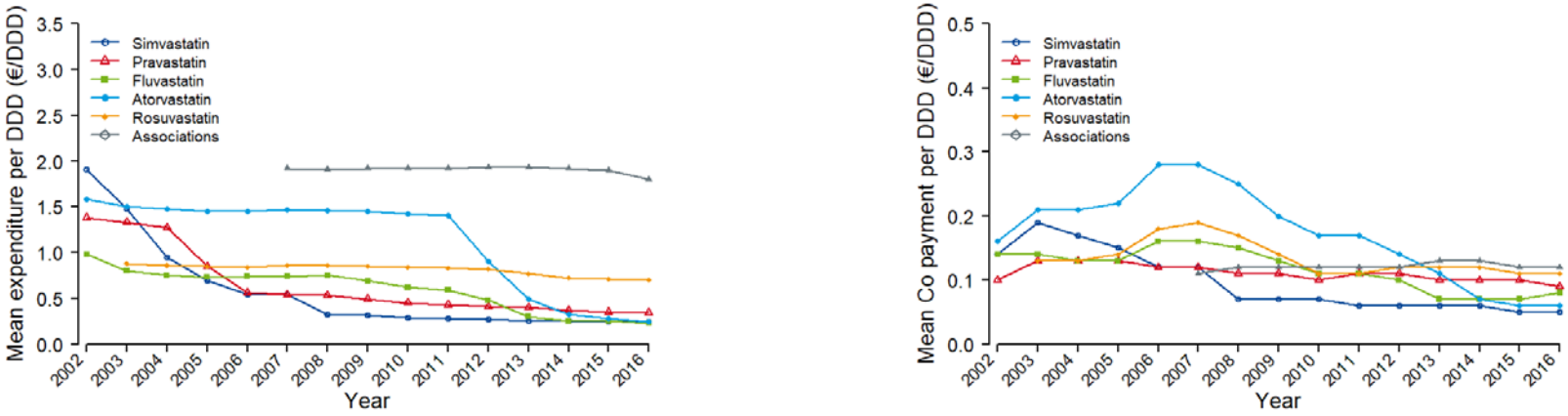


3.12.2 Evolution of mean expenditures per DDD over time

As we look for the evolution of the expenditures by DDD (Figure 13), the evolution of price follows the same pattern: at the moment generic alternative becomes available, the price decreases including the price for the brand product (in 2003 for simvastatin and in 2012 for atorvastatin). For simvastatin, the effect of a second price reduction in 2008 can also be seen. In 2016, only the price of associations is more than 1.5€/DDD, the second most expensive is rosuvastatin (0.70€/DDD), and then the other molecules (<0.35€/DDD). Since the introduction of a generic rosuvastatin, the price of this statin also dropped significantly.

When we look at the co-payment, the situation is different. Simvastatin is the cheapest statin since 2008. Since 2012, all molecules are <0.14€/DDD.

Figure 13 – Evolution of total (left) and patient co-payment (right) mean expenditure per DDD for years 2002-2016



In Table 38 in appendix, the reader finds a comparison of the average cost in 2016 vs. 2018 for each statin available in Belgium and an estimate of the cost of statin use for one year of utilisation if the patient is 100% adherent. For pharmaceutical products with an available generic alternative, one year of statin use costs the patient around 30€.

3.13 Summary of the individual data

The analyses of the current use of statin in Belgium population from EPS can be summarized as:

- The number of users of statins has been growing until 2012, but is stable since: about the same number quit using a statin as those who start, leading to a stable number of 1.5 million users each year. But the number of new users of simvastatin is decreasing, while the number of new users of atorvastatin is growing.
- The estimated number of patients in secondary prevention is around 12% and is stable over the years.
- Less than half of new users are regular users (adherent), and factors associated with low adherence are young age, GP as first prescriber and females.
- Patients with higher adherence are those with a higher 2-year risk of death (all causes).

The use of statins in Belgium has evolved during the past 15 years. We show the increasing number of users until 2012, and a stabilisation of it. But as we analyse the number of new users each year, it is interesting to see that the number of new users increases when the cost is decreasing. It has been seen in 2004, when the generic simvastatin became available, and a second time in 2008 when a second price reduction occurred, and in 2012 when the atorvastatin generic alternative came to market. From 2012, this resulted in an increase of atorvastatin users and a decrease of simvastatin users. Therefore, we can expect an increase in new users of rosuvastatin in 2018 with the newly available generic alternative.

We observe a mean age of users of 68 for all users and 62 years for new users. Patients are using mainly medium and high intensity statin doses. One third of patients are taking concomitant antidiabetic drugs and two-thirds are taking generic drugs. The mean time of use is 491 days for around 510 DDD. This means approximately 1 DDD/day. For secondary prevention, which represent 12% of patients, the majority are between 60 and 80 years old. The mean time of use is 518 days for 766 DDD. This results in 1.5 DDD/day.

The mean out-of-pocket cost of a statin for an individual patient is about € 30/year in 2016. Some packagings are cheaper such as low doses (*atorvastatin* 10mg or *simvastatin* 20mg), but some are more expensive such as high doses (*simvastatin* 80mg) or drugs with no available generic alternative in 2016, such as *rosuvastatin*, or associations of statins with other drugs. In comparison with the costs in 2018 (source: CBIP – BCFI), the mean out-of-pocket cost of a statin for an individual patient remains about € 25/year for big packagings. Even for rosuvastatin, with the available generic alternative, the costs is similar. We can notice that for *atorvastatin* 10mg and *rosuvastatin* 15mg, the mean out-of-pocket cost for an individual patient is < € 12/year.

In regular new users, the mean time of use is 648 days with a consumption of 800 DDD. This corresponds to 1.24 DDD/day.

The EPS shows that 28% of new users only had one purchase registered. This proportion was challenged by some of our external experts since they stated that in some cases (for instance side effects) patients are advised to take only 1 statin every three days. Then, one big packaging might be sufficient for almost a whole year, while our definition of a new user was *'a user who did not purchase a statin during the past 365 days'*. When we defined a single package user as *'an individual who did not purchase a statin since 2002, purchasing at least one packaging in a given year, and not purchasing a single packaging later'*, we can see that the proportion of individuals purchasing only one packaging over the whole period increases over the years (see Table 34 in appendix) from 4.2% in 2003 to 9.1% in 2006, to 12.1% in 2010 and 21.2% in 2014, 24.3% in 2015 and 42.8% in 2016. This observation is explained by the fact that a new user in 2003 has 13 more years to take another statin but that a new user in 2015 only has 1 more year to purchase another statin. The results in years 2014-2015 do not differ much from the initial definition of a new user; the proportion of regular users is lower than 50% (49.6%), and of the occasional users 51.4%.

In Belgium, it has been shown that 65% of the statin users are non-adherent.[19] In the UK, it was shown that 40% of patients who received a prescription of statins in primary prevention never got a second prescription.[20] This is explained by the fact that the patient doesn't see immediate benefit and also by the media reporting side effects such as muscular pain. For patients with more than one statin prescription, it has

been shown that 47% of patients in primary prevention discontinued statin treatment, and 28% of them never restarted.[21] In a Finnish register studying the adherence of new users of statins, and after exclusion of one-purchase only patients, it is reported that 55% of new users are adherent.[22] In the review of Lemstra et al. the adherence in observational studies and randomized trials was compared. It was shown that 49.0% of patients are adherent at 1 year of follow up in observational studies, as compared with 90.3% in randomized trials.[23] This underlines the important differences between observational studies in real life compared to randomized trials.

Factors associated with low adherence are young age, GP prescribers and female people, and being in primary prevention. Factors associated with good adherence are male gender, age group of 60 to 69 years, use of concomitant antidiabetic or cardiovascular drugs and use of atorvastatin.

These factors are also predictive in a second adherence analysis: when the adherence is assessed by the definition *'using a statin >365 days'*. In this analysis, gender is not a predictor of adherence, and the age group of 60-69 years is the most adherent group. These characteristics are also highlighted in the Finnish register.

It is difficult to predict the adherence to statin treatment. With variables as age, gender and diabetes, we calculated a risk of death (all-cause mortality). With an estimated 2-year risk of death we classified patients according to three levels of risk. The patients with the highest level of mortality risk are those with the highest levels of adherence. Adherent patients seem to have higher burden of disease, reflected by the fact that adherence is associated with prescription by a specialist and statins with a higher intensity dose.

4 CLINICAL EFFECTIVENESS AND HARMS

4.1 Introduction

Several parameters are important when balancing clinical benefits and harms of any intervention. Benefits relate to the risk reduction obtained by using the intervention. Those benefits are dependent upon the baseline risk of the individual to have the event that we try to prevent. Harms on the contrary are related to the number of people receiving the intervention and can also occur in individuals who would not have benefitted from the intervention.

This balance is dependent on the number needed to treat (NNT) to avoid one specific outcome. Benefits are best studied in randomized controlled trials (RCTs) while for harms, that are by definition unwanted but rare events those RCTs are insufficient since they are not powered to detect such rare events and reporting of those events in trials is often insufficient.

Whereas, additional large RCTs are unlikely to be conducted since all statins went out of patent, additional observational evidence is still needed, especially to evaluate the harms.

4.2 Methods

Numerous systematic reviews on the clinical efficacy of statins in primary prevention of cardiovascular events are available. Therefore we proceeded in two steps.

- The first step consisted in the identification of the most recent high-quality systematic review specific to the research question. The search strategy is presented in the appendix. The search was limited to systematic reviews published since 2016. Inclusion criteria are presented in Table 43 in appendix. The first selection was done on title and abstract. Among the systematic reviews retrieved through this first selection, we examined full texts in a backward approach, i.e. starting by the most recently published SR, until a SR with sufficient quality was

identified and retained. We critically appraised the quality of SR with the AMSTAR-2 tool.[24]

- The second step consisted in the identification of primary studies (RCT) published after the search date of the systematic review retained in the first step, if any. In case such more recent primary studies had been published, the decision to update the retained SR would be based on the criteria proposed in the Ottawa methods.[25] The inclusion-exclusion criteria are presented in Table 43. We planned to critically appraise the quality of the RCTs with the Cochrane risk of bias tool.[26]

Those systematic searches were conducted end of February 2018.

4.3 Results from the search strategy

Our search strategy for systematic reviews yielded 189 references (Cochrane SR: 12; Embase: 46; Ovid-Medline: 131). We retrieved an additional reference from the NICE website. After removal of duplicates (n=13) and exclusion on title and abstracts of 149 references not fulfilling the inclusion criteria, 28 SR were selected.[6, 7, 14, 27-51]

The most recent high-quality systematic review fulfilling the inclusion criteria was the one by Chou et al.[46] Reasons for excluding SR published in the same year or after the SR by Chou are presented in Table 44 in appendix. SR published before 2016 could not include the results of the HOPE-3 trial (n=12 705) published in 2016.[52]

After the systematic search, an new SR from Revue Prescrire was published in April 2018.[53] This review was more selective in its search strategy that the Chou SR and more focussed on primary prevention. It included only eight of the RCTs included in SR from Chou et al. However, in addition it included the original Allhat-LLT trial which was eliminated from the USPSTF report because it included 23% of patients for secondary prevention. Where relevant we will present additional information from this more recent review.

The search strategy of the SR by Chou et al. ended in June 2016. We retrieved 133 references of primary studies published since 2016, among which 8 were duplicates. None of the references for RCTs fulfilled the inclusion criteria, i.e. there were no new RCT's testing the efficacy of statins in primary prevention. However, secondary analyses and/or follow-up of some previous trials were retrieved (WOSCOPS trial,[54, 55] ALLHAT-LLT trial,[56, 57] HOPE-3 trial.[58])

4.4 Characteristics and quality appraisal of the selected systematic review.

Therefore, our analysis is based on the SR by Chou et al.[46] A full version of this SR has been published as a book, and we used that source for critical appraisal and data extraction.[2]

The quality appraisal of the SR by Chou et al. is presented in Table 45 in appendix. The SR was appraised high-quality. Although the authors did not report an official registration of the review protocol, the protocol was established in collaboration with the USPSTF and a publication bias seems unlikely. For point 6, no details were reported by the authors, therefore we considered duplicate data extraction had not been done. Another limitation was the exclusion of non–English-language articles. However, comparison with previous SR did not show that any relevant RCT had been missed.

The characteristics of the studies included are presented in Table 46 in appendix. As Chou et al. used the USPSTF Quality Rating Criteria, we re-assessed the quality of the included studies with the more common Cochrane risk of bias tool. The quality appraisal of each study has been integrated in a forest plot with the RevMan 5.3 software to easily visualize potential influence on outcomes. This is shown in Figure 28 in appendix. The other forest plots can be found in the original report.[2]

Nineteen randomized trials assessed the effects of statins on health outcomes in adults at increased cardiovascular risk but without prior CVD events (=primary prevention). There were obvious variations across trials.[2]

- **Inclusion criteria:** in six trials, presence of dyslipidemia was the main criterion for enrolment, although definitions for dyslipidemia varied, (see **Table 46 i**n appendix): AFCAPS/TexCAPS,[59] Bone,[60] KAPS,[61] MEGA,[62] Muldoon,[63] and WOSCOPS.[64] Three trials were restricted to patients with early-onset cerebrovascular disease: ACAPS,[65] CAIUS,[66] and METEOR.[67] One trial enrolled patients with mild to moderate aortic stenosis: ASTRONOMER.[68] Four trials were restricted to patients with diabetes: ASPEN,[69] Beishuizen,[70] CARDS,[71] and Heljic.[72] Two trials focused on patients with hypertension: ASCOT-LLA,[73] and HYRIM.[74] One trial enrolled patients with microalbuminuria: PREVEND-IT,[75] and one trial enrolled patients with elevated CRP levels (≥2.0 mg/dL) and non-elevated LDL-C levels (<130 mg/dL): JUPITER.[76]
- **Statins:** pravastatin (five trials), atorvastatin (four trials), rosuvastatin (four trials), lovastatin (two trials), simvastatin (two trials) and fluvastatin (one trial)[d]. The intensity of statin therapy was also variable, with a majority of trials testing a moderate intensity therapy (see **Table 46** in appendix).
- **Duration:** range 0.5 to 6 years (median: 4 years).
- **Gender:** three trials only enrolled men: HYRIM,[74] KAPS,[61] and WOSCOPS.[64] One trial enrolled only women: BONE.[60] In the other trials, the proportion of women ranged from 15% to 69%.
- **Patients with prior CVD events:** four studies included patients (<10%) with prior CVD events: ASCOT-LLA,[73] KAPS,[61] PREVEND-IT,[75] and WOSCOPS.[64]
- **Early termination:** two trials: CARDS,[71] and JUPITER,[76] with planned 5-year follow-up were stopped after 2 and 3 years due to observed cardiovascular benefits among patients randomized to statins. One other trial: ASCOT-LLA,[73] with planned 4-year follow-up was also stopped 2 years prior to anticipated study completion due to observed benefits in the statin group, although the median duration of follow-up for enrolled participants was 4 years.
- **Patient risk at baseline:** four studies included patients with an increased baseline risk but no prior CVD event. These were patients with either early cerebrovascular disease,[65-68] or with aortic stenosis.[68]

4.5 Evidence on effectiveness of statins in primary prevention

4.5.1 Preliminary remarks

Before considering the evidence for taking statins in primary prevention a few points should be emphasised.[53]

- The risk of CVD increases with increasing age, blood pressure cholesterol levels and weight.
- The risk of CVD is increased in men, smokers, persons with diabetes, a family history of early CVD and physical inactivity.
- The first step should always be to try and remediate conditions that can be changed.
- There is little evidence available that statin therapy reduces the risk of CVD events in patients younger than 40 or older than 75 years in primary prevention.
- While in some patients in primary prevention, daily statin therapy for about 5 years reduces the risk of fatal and non-fatal cardiovascular events only a few patients will eventually benefit from the medication but all would run the same risk of harms.
- Statins are relatively safe but adverse events, although rare and mainly temporarily, do occur.
- No trials have directly evaluated the potential benefits or harms of taking statin 10 years or more, although some follow-up on shorter

[d] Cerivastatin was initially used in one trial but later replaced with simvastatin

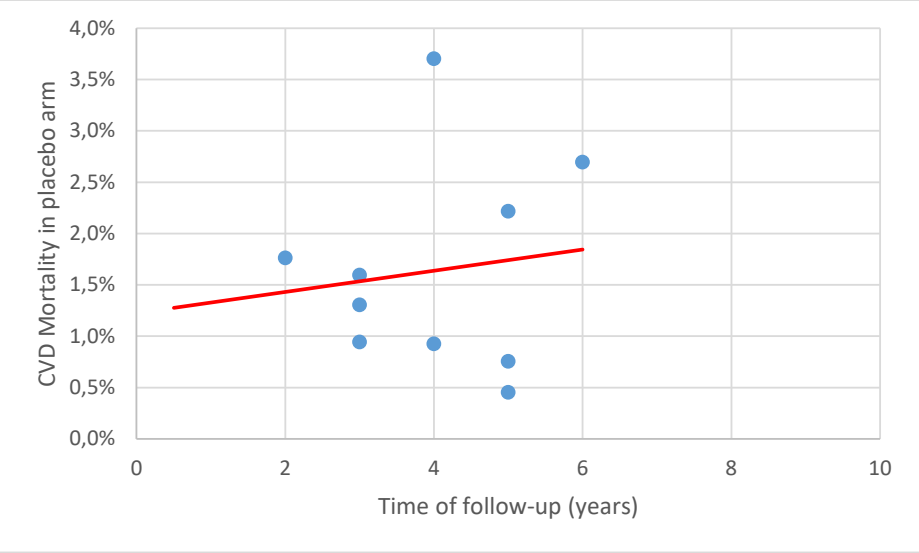
trials tried to evaluate this legacy benefit on a longer period (up to 20 years) after the trial was stopped.[54, 55]

4.5.2 *Baseline risk for CVD in the included patients and follow-up time*

Nineteen trials were included in this SR, although not all trials measured all outcomes and average follow-up varied from 0.5 to 6 years.

The stated goal of this review was to evaluate benefits and harms of statin therapy for the primary prevention of CVD in adults, i.e. adults without prior cardiovascular events. However, the baseline risk for CVD and the duration of follow-up differ substantially between the included studies. Since the commonly used risk indicator for CVD is SCORE, we compared the baseline risk for cardiovascular mortality. SCORE evaluates the 10-year risk for CVD mortality but none of the studies had a follow-up that long and not all studies specifically reported CVD mortality. Figure 14 shows that baseline CVD mortality risk was indeed relatively low in this short time frame, with the notable exception of the ASTRONOMER trial showing a CVD mortality risk in the placebo arm of 3.7% at 4 years of follow-up.[68] This is due to the fact that this trial was primarily meant to evaluate the effect of statins on the progression of existing moderate aortic stenosis, and therefore included patients at a higher risk. However this trial was small, and deleting it in our meta-analyses showed no significant effect on the overall estimates.

Figure 14 – Baseline risk for CVD mortality in the placebo arms vs. follow-up time



4.5.3 Overall results

Central point estimates from the Chou report are:

- All-cause mortality: 15 trials; RR 0.86 [95% CI 0.80 to 0.93], I^2=0%, ARD -0.40%, NNT 250
- CVD mortality: 10 trials; RR 0.72 [95% CI 0.59 to 0.88][e], I^2=38%, ARD -0.43% NNT 233.
- Fatal and non-fatal MI: 12 trials, RR 0.64 [95% CI 0.57 to 0.71], I^2=0%, ARD -0.81%, NNT 123.
- Fatal and non-fatal stroke: 13 trials, RR, 0.71 [95% CI 0.61 to 0.81], I^2=0%, ARD -0.38%, NNT 263.
- Revascularization: 7 trials, RR 0.63 [95% CI 0.54 to 0.72], I^2=8%, ARD -0.66%, NNT 152.
- Composite cardiovascular outcomes: 13 trials, RR 0.70 [95% CI 0.63 to 0.78], I^2 36%, ARD -1.39%, NNT 72.

4.5.4 Sensitivity analyses

Sensitivity analyses were performed by Chou et al.[2] and slightly modified by us.

For the sensitivity analyses we made a few adjustments to the original tables:

- Excluding trials stopped early: Chou et al. considered only two studies with early termination (CARDS and JUPITER,[71 76]) whereas ASCOT-LLA,[73] was also stopped prematurely. Therefore, we excluded those three studies.
- Limiting to only good quality trials. Six trials were rated good-quality by Chou.[52, 61, 64, 68, 71, 76]
- Excluding trials with patients with prior CV disease: Chou et al. considered only three studies in which there were patients with prior CVD events (ASCOT-LLA, KAPS and PREVEND-IT,[61, 73 75]), whereas such patients were also present in the WOSCOPS trial.[64] Therefore, we excluded those four studies.
- Excluding trials restricted to patients with diabetes. This was added by us and we excluded 4 trials.[69-72]
- Excluding trials restricted to patients presenting vascular disease. This was added by us. Four trials were restricted to patients with early-onset cerebrovascular disease or aortic stenosis and were excluded.[65-67,68]

Table 47 in appendix shows the details of this sensitivity analyses. However, excluding specific trials changed little in the point estimates reported in section 4.5.3 for the different effectiveness RR estimates, showing that those estimates are quite robust. Only for overall CVD mortality the range of RR estimates was larger, probably due to different definitions of this outcome.

In summary the sensitivity analysis shows that:

- The RR for all-cause mortality ranges from 0.85 to 0.89 (all statistically significant).
- The RR for CVD mortality ranges from 0.59 to 0.73 (all statistically significant).
- The RR for fatal and non-fatal MI ranges from 0.61 to 0.65 (all statistically significant).
- The RR for fatal and non-fatal stroke ranges from 0.68 to 0.77 (all statistically significant).

[e] Data slightly changed by us after recalculation, corrected forest plot can be found in Figure 29 in appendix.

- The RR for revascularization ranges from 0.62 to 0.66 (all statistically significant).
- The RR for composite cardiovascular outcomes: ranges from 0.69 to 0.74 (all statistically significant).

In addition we performed a separate analysis for the two trials that used exclusively a high intensity statin. [68,76] These result will be further discussed with the outcomes. However, these results should be interpreted with caution since the results for the high intensity treatment are mainly driven by one single trial (JUPITER),[76] while the much smaller ASTRONOMER trial deals with patients at a higher risk with moderate aortic stenosis at baseline.[68] The METEOR trial on progression of carotid intima media thickness only reported on all-cause mortality.[67]

4.5.5 All-cause mortality

Fourteen trials reported all-cause mortality. Pooling evidence from all trials resulted in a RR=0.86 [95% CI, 0.80 to 0.93]; I^2=0%; ARD, -0.40% [95% CI, -0.64 to -0.17]; I^2=4%) after 1 to 6 years.[2] Detailed results are presented in Figure 5 in appendix. The risk estimate was heavily influenced by the JUPITER and ASCOT-LLA studies, both of which were stopped early and together accounted for about 40% of the total sample. However, when we removed the 3 studies with early termination (ASCOT-LLA, CARDS and JUPITER from the meta-analysis,[71, 73, 76]) the point estimate was not significantly different (RR=0.82 [95%CI, 0.72, 0.92]; p=0.29 for subgroup differences). Results were similar in other sensitivity analyses: exclusion of studies restricted to diabetic patients; exclusion of studies having included a proportion of patients with prior CVD events; studies restricted to patients with early-onset cerebrovascular disease as shown in Table 47.

Considering the high intensity treatment JUPITER and METEOR trials separately the relative risk was lower: RR=0.80 [95% CI, 0.67 to 0.97]. For the other trials the combined relative risk was slightly higher: RR=0.88 [95% CI, 0.80 to 0.96].

4.5.6 Cardiovascular mortality

Cardiovascular mortality was reported in ten trials. However, in the SR there was a slight mistake in the numbers for CVD mortality due to a data entry error for the ASTRONOMER trial that had a small impact on the point estimate of the RR. The corrected forest plot can be found in Figure 29 in appendix. In pooled analyses, statin therapy was associated with decreased risk of cardiovascular mortality (RR, 0.72 after 2 to 6 years [95% CI, 0.59 to 0.88]) but statistical heterogeneity was present (I^2=38%). The pooled ARD was -0.43 percent (95% CI, -0.75 to -0.11; I^2=65%) and the pooled NNT was 233 (range, 8 to 1,000 in 8 trials; 2 trials found no benefit with statin therapy).[2]

None of the sensitivity analyses reduced dramatically the heterogeneity across studies. However, in our sensitivity analyses the estimated RR ranged from 0.59 to 0.73, a larger range than for other outcomes.

Considering the high intensity treatment JUPITER and ASTRONOMER trials separately the relative risk was much lower: RR=0.52 [95% CI, 0.40 to 0.68]. For the other trials together the relative risk increased RR=0.83 [95% CI, 0.71 to 0.96].

4.5.7 Fatal and non-fatal myocardial infarction

Twelve trials reported incidence of fatal and nonfatal myocardial infarction. In pooled analyses, statins were associated with decreased risk of MI (RR, 0.64 after 2 to 6 years [95% CI, 0.57 to 0.71]; I^2=0%; ARD, -0.81% [95% CI, -1.19 to -0.43]; I^2=70%).[2] Findings were similar in sensitivity analyses. Seven trials reported separate results for fatal and/or nonfatal MI. When analysed separately, estimates for fatal MI (RR, 0.70 [95% CI, 0.50 to 0.99]; I^2=0%; ARD, -0.16% [95% CI, -0.42 to 0.11]) and nonfatal MI (RR, 0.64 [95% CI, 0.46 to 0.91]; I^2=50%; ARD, -0.46% [95% CI, -0.90 to -0.02]) were similar.[2]

Considering the high intensity treatment JUPITER and ASTRONOMER trials separately the relative risk was much lower: RR=0.44 [95% CI, 0.29 to 0.57]. For the other trials together the relative risk increased slightly RR=0.65 [95% CI, 0.58 to 0.74].

4.5.8 Fatal and non-fatal stroke

Thirteen trials reported incidence of fatal and nonfatal stroke. Statins were associated with a decreased risk of fatal or nonfatal stroke (RR 0.71 after 6 months to 6 years [95% CI 0.61 to 0.81]; I^2=0%) and the pooled ARD was -0.38% (95% CI, -0.53 to -0.23; I^2=0%).[2] Findings were similar in sensitivity analyses.

There were too few studies reporting separately fatal and non-fatal stroke to achieve a sensible and precise stratification.[f]

Considering the high intensity treatment JUPITER and ASTRONOMER trials separately the relative risk was much lower: RR=0.53 [95% CI, 0.35 to 0.80]. For the other trials together the relative risk increased slightly RR=0.73 [95% CI, 0.63 to 0.85].

4.5.9 Revascularization

Revascularization was an outcome assessed in seven studies. Statins were associated with a decreased risk of revascularisation (RR 0.63 after 2 to 6 years [95% CI 0.54 to 0.72]; I^2=8%). Findings were similar in sensitivity analyses.

Considering the high intensity treatment JUPITER trial separately the relative risk was lower: RR=0.54 [95% CI, 0.40 to 0.72]. For the other trials together the relative risk increased slightly RR=0.66 [95% CI, 0.56 to 0.78].

4.5.10 Composite cardiovascular outcome

Composite cardiovascular outcomes were assessed in thirteen trials. Statins were associated with a decreased risk of those composite cardiovascular outcomes (RR 0.70 [95% CI 0.63 to 0.78], I^2 36%, ARD -1.39%, NNT 72. Findings were similar in sensitivity analyses.

Considering the high intensity treatment JUPITER trial separately the relative risk was lower: RR=0.59 [95% CI, 0.48 to 0.72]. For the other trials together the relative risk increased slightly RR=0.73 [95% CI, 0.66 to 0.80].

4.6 Evidence on harms from RCT's and observational research

4.6.1 Evidence on harms from RCTs in the selected systematic review on primary prevention

Chou et al. synthesized the evidence on harms from RCTs as follows. Citation:

'Seventeen trials reported harms of statin treatment versus placebo or no statin in adults without prior CVD events. Statin therapy was not associated with:

- *increased risk of withdrawal due to harms (9 trials; RR, 0.95 [95% CI, 0.75 to 1.21]; I2=86%; ARD, 0.02% [95% CI, -1.55 to 1.60]),*
- *serious harms (7 trials; RR, 0.99 [95% CI, 0.94 to 1.04]; I2=0%; ARD, 0.07% [95% CI, -0.29 to 0.42),*

[f] When stratified by fatal and nonfatal stroke, statins were associated with decreased risk of nonfatal (3 trials; RR, 0.57 [95% CI, 0.41 to 0.81]; I^2=0%; ARD, -0.32% [95% CI, -0.52 to -0.12]),[63, 71, 76] and fatal stroke (2 trials; RR, 0.38 [95% CI, 0.12 to 1.22]; I^2=0%; ARD, -0.11% [95% CI, -0.38 to 0.15]).[71, 76]

- *any cancer (10 trials; RR, 1.02 [95% CI, 0.90 to 1.16]; I2=43%; ARD, 0.11% [95% CI, -0.39 to 0.60]),*
- *new-onset diabetes (6 trials; RR, 1.05 [95% CI, 0.91 to 1.20]; I2=52%; ARD, 0.12% [95% CI, -0.31 to 0.54]),*
- *myalgia (7 trials; RR, 0.96 [95% CI, 0.79 to 1.16]; I^2=42%; ARD, 0.03% [95% CI, -0.53 to 0.60]), or elevated aminotransferases (11 trials; RR, 1.10 [95% CI, 0.90 to 1.35]; I^2=0%; ARD, 0.08% [95% CI, -0.04 to 0.19]).*

Evidence on the association between statins and renal or cognitive harms was sparse but did not clearly indicate increased risk. One trial (HOPE-3) found that statins were associated with increased risk of cataract surgery (3.8% vs. 3.1% after 6 years; RR, 1.25 [95% CI, 1.03 to 1.49]; ARD, 0.73% [95% CI, 0.10 to 1.36]), but this was not a pre-specified outcome, and none of the other trials reported risk of cataracts or cataract surgery. Few serious adverse events were reported.' (end of citation).

The review by Chou et al. found no evidence that statin treatment in adults without prior cardiovascular events is associated with increased risk of withdrawal due to adverse events, serious adverse events, cancer, or elevated liver enzymes versus placebo or no statin therapy. There was also globally no evidence of increased risk of diabetes, with the notable exception of the JUPITER trial (RR=1.25 [95%CI: 1.05 –1.49]). Several reasons may explain this absence of adverse events. Not all trials measured/reported adverse events. Most trials had a run-in period. Although this run-in period was in the majority of studies done with a placebo, it might have contributed to the selection of participants more compliant and possibly in better health.

The fact that no evidence on adverse events is found in RCTs is not surprising. RCTs are powered to provide evidence on efficacy not to provide evidence on harms.[2] However, and especially in primary prevention and depending on the cardiovascular risk, the benefits of the intervention are for few with over a hundred individuals needed to treat but the potential harms are for all those treated. Therefore, even a low proportion of people harmed can shift the benefit/harm balance. Therefore, we also searched for evidence on potential harms from RCTs on both primary and secondary prevention and also from observational research.

4.6.2 Evidence on harms from the previous KCE report

In a previous KCE report 141 from 2010,[3] we summarized the then available information on potential harms. Citation:

'*The publicity surrounding the removal of cerivastatin from the market in 2001 due to the increased risk of rhabdomyolysis has likely contributed to an increase in awareness of potential safety issues with statins. Although statins are generally well tolerated, there are well-described adverse events (AE), sometimes serious, associated with their use. The risk of a statin-associated adverse event (mild myalgia, myopathy, elevated hepatic transaminase and creatine kinase (CK) levels) has been reported to be increased by 40% relative to placebo.[77] The most common adverse effect, non-serious symptoms of myalgia,[g] has been reported by some 2% to 11% of patients.[78] Although this typically reversible effect is troublesome for patients, it may go unreported in many patients because of its self-limiting nature.[79] Although symptoms may subside after drug discontinuation,[3] symptoms frequently return on rechallenge (95% of patients have a return*

[g] *Myopathy is defined as any muscle symptom—pain, tenderness, or weakness—accompanied by a creatine kinase concentration greater than ten times the upper limit of normal for the particular laboratory40 (also called myositis). Rhabdomyolysis is severe myopathy involving muscle breakdown and myoglobin release into the circulation, which can cause a brown discolouration of urine and risk of renal failure. Rhabdomyolysis is usually diagnosed when creatine kinase concentration is greater than 40 times the upper limit of normal, or there is evidence of end organ damage (eg, acute renal failure or worsened renal function), or both, but differences in definition make comparisons between studies difficult. Myalgia refers to muscle pain with no rise in creatine kinase concentration to greater than ten times the upper limit of normal.*

of symptoms when restarting therapy at the same dose, 55% when restarting at a lower dose).[80] Statin-induced myositis can progress to clinically important myositis (CK ≥ 10 times the upper limit of normal) and to rhabdomyolysis,[h] which is the most serious AE associated with statins,[81, 82] and results in one statin-related death per 6.66 million statin prescriptions in the United States.[79] Elevated hepatic transaminases occur less frequently (0.5%-2.0% of patients) and there is no convincing evidence of an associated increased risk of serious hepatitis. Hepatic failure is also extremely rare.[i,83, 84]'

'A slight increased risk of the development of diabetes has also been reported.[85] Among thirteen statin trials including 91 140 participants, statin therapy was associated with a 9% increased risk for incident diabetes (OR=1.09; 95% CI: 1.02-1.17). Concerns regarding long-term complication of statin therapy on cancer incidence have not been confirmed.[86, 87] A suggested association of statin use with amyotrophic lateral sclerosis has not been confirmed.[88] Other potential unintended effects of statins, such as a protective effect on risk of Parkinson's disease, venous thromboembolism, rheumatoid arthritis, osteoporotic fracture, and dementia have also not been confirmed.[89]

The information on safety issues was however scarce, and there was no obvious difference between statins.' (end of citation).

4.6.3 Recent reviews on harms associated with statin use

Muscle symptoms are the most frequently cited side effect of using statins but they are difficult to quantify and are reported by 7% to 30% of patients taking statins.[53, 90] The symptoms are mainly minor and disappear upon abandoning statin use. However, the precise increased incidence attributable to statin use is difficult to quantify because these symptoms are also very frequently reported by patients not taking statins and can be caused by the so-called *'nocebo effect'*.[53]

Several reviews in recent years attempted to quantify the occurrence of side effects.

Review by Stroes et al. (EAS Consensus Panel Statement 2015)-

This review focuses on statin-associated muscle symptoms (SAMS) and its impact on statin therapy as one of the principal reasons for non-adherence and/or discontinuation.[90] The panel concludes that (citation): *'Statin-associated myopathy, with significant elevation of serum creatine kinase (CK), is a rare but serious side effect of statins, affecting 1 per 1000 to 1 per 10 000 people on standard statin doses. Statin-associated muscle symptoms cover a broader range of clinical presentations, usually with normal or minimally elevated CK levels, with a prevalence of 7–29% in registries and observational studies. Preclinical studies show that statins decrease mitochondrial function, attenuate energy production, and alter muscle protein degradation, thereby providing a potential link between statins and muscle symptoms; controlled mechanistic and genetic studies in humans are necessary to further understanding.'*

'The Panel proposes to identify statin-associated myopathy by symptoms typical of statin myalgia (i.e. muscle pain or aching) and their temporal association with discontinuation and response to repetitive statin re-

h *Severe myopathy leads to the release of muscle components such as creatine kinase into the bloodstream, which can accumulate in the kidney and lead to renal failure, sometimes resulting in death.*

i *The question is whether the effect on transaminases indicates hepatotoxicity or rather some sort of hepatic reaction to reduction of lipid levels. Other cholesterol-lowering agents, including fibrates, resins (which are not systemically absorbed), niacin, and ezetimibe, all increase liver enzymes, which suggests these changes could be a hepatic response to lipid lowering rather than hepatotoxicity.*

challenge. In people with SAMS, the Panel recommends the use of a maximally tolerated statin dose combined with non-statin lipid-lowering therapies to attain recommended low-density lipoprotein cholesterol targets. The Panel recommends a structured work-up to identify individuals with clinically relevant SAMS generally to at least three different statins, so that they can be offered therapeutic regimens to satisfactorily address their cardiovascular risk. Further research into the underlying pathophysiological mechanisms may offer future therapeutic potential.' (end of citation).

Review by Collins et al. (2016)

In a recent review based upon evidence from RCTs, Collins et al. stated that myopathy (defined as muscle pain or weakness combined with large increases in creatine kinase blood concentrations) and new-onset diabetes mellitus have been reliably shown to be caused by statin therapy, along with a probable increase in strokes due to bleeding (i.e. haemorrhagic strokes).[91] According to Collins et al., treatment of 10 000 patients for 5 years with a standard statin regimen (such as atorvastatin 40 mg daily) would be expected to cause absolute excesses of adverse events in 100 – 200 patients:

Estimated harms / 10 000 statin users for 5 year:[91]

- **50 – 100 cases of muscle pain and weakness**
- **about 5 cases of myopathy**
- **50–100 new cases of diabetes**
- **5–10 haemorrhagic strokes**

This analysis further concludes that the harmful effects of statin therapy can usually be reversed without any residual effects by stopping it. However, precise estimates of the number of harms are uncertain since studies contradict each other and definitions are not always similar.

Muscle pain might be underestimated as many of the trials did not ask about commonly reported statin effects, such as muscle pain and weakness, and only recorded myopathy, for which an increase in creatine kinase levels was required.[92]

In meta-analyses of the available results from the randomized trials, standard statin dose regimens were associated with a proportional increase of about 10% in reported diabetes,[85] and more intensive statin regimens (as used in JUPITER) with about a 10% further increase.[93] This excess of diabetes diagnoses appeared soon after the start of statin therapy, chiefly among patients who had risk factors for diabetes (e.g. elevated body-mass index or HbA1c, or impaired fasting glucose), and did not appear to get larger as treatment continued.[91]

Evidence on effects of statin intensity on harms was sparse; the only trial to find statin therapy associated with an increased risk of diabetes used high-intensity statin therapy.

AHA – ACC Guideline on the management of Blood Cholesterol (2018)

A very recent (November 2018) guideline on the management of blood cholesterol is not only based on evidence from RCTs but also on observational evidence (see Table 19).[94]

Rather than quantifying the statin-associated side effects they list them as rare, infrequent, unclear or unfounded.

Table 19 – Statin-Associated Side Effects (from Grundy et al.)

Statin-Associated Side Effects	Frequency	Predisposing Factors	Quality of Evidence
Statin-associated muscle symptoms (SAMS)			
Myalgias (CK Normal)	Infrequent (1% to 5%) in RCTs; frequent (5% to 10%) in observational studies and clinical setting	Age, female sex, low body mass index, high-risk medications (CYP3A4 inhibitors, OATP1B1 inhibitors), comorbidities (HIV, renal, liver, thyroid, pre-existing myopathy), Asian ancestry, excess alcohol, high levels of physical activity, and trauma	RCTs cohorts/observational
Myositis/myopathy (CK > ULN) with concerning symptoms or objective weakness	Rare		RCTs cohorts/observational
Rhabdomyolysis (CK >10× ULN + renal injury)	Rare		RCTs cohorts/observational
Statin-associated autoimmune myopathy (HMGCR antibodies, incomplete resolution)	Rare		Case reports
New-onset diabetes mellitus	Depends on population; more frequent if diabetes mellitus risk factors are present, such as body mass index ≥30, fasting blood sugar ≥100 mg/dL; metabolic syndrome, or A1c ≥6%	Diabetes mellitus risk factors/metabolic syndrome High-intensity statin therapy	RCTs/meta-analyses
Liver			
Transaminase elevation 3× ULN	Infrequent		RCTs/ cohorts/observational Case reports
Hepatic failure	Rare		
Central nervous system			
Memory/cognition	Rare/unclear		Case reports; no increase in memory/cognition problems in 3 large-scale RCTs
Cancer	No definite association		RCTs/meta-analyses
Other			
Renal function	Unclear/unfounded		

Cataracts	Unclear
Tendon rupture	Unclear/unfounded
Hemorrhagic stroke	Unclear
Interstitial lung disease	Unclear/unfounded
Low testosterone	Unclear/unfounded

CK indicates creatine kinase; HIV, human immunodeficiency virus; HMGCR, 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase; SAMS, statin-associated muscle symptoms; SAAM, statin-associated autoimmune myopathy; SASE, statin associated side effects; and ULN, upper limit of normal.

Review by Mach et al. (2018)

In this review a literature search was performed from 2000-2017 upon which a panel critically appraised the data and agreed by consensus.[95] They conclude that (citation):*'… statin therapy is associated with a modest increase in the risk of new-onset diabetes mellitus (about one per thousand patient-years), generally defined by laboratory findings (glycated haemoglobin ≥6.5); this risk is significantly higher in the metabolic syndrome or pre-diabetes. Statin treatment does not adversely affect cognitive function, even at very low levels of low-density lipoprotein cholesterol and is not associated with clinically significant deterioration of renal function, or development of cataract. Transient increases in liver enzymes occur in 0.5–2% of patients taking statins but are not clinically relevant; idiosyncratic liver injury due to statins is very rare and causality difficult to prove. The evidence base does not support an increased risk of haemorrhagic stroke in individuals without cerebrovascular disease; a small increase in risk was suggested by the Stroke Prevention by Aggressive Reduction of Cholesterol Levels study in subjects with prior stroke but has not been confirmed in the substantive evidence base of RCTs, cohort studies and case–control studies.'* (end of citation).

This consensus panel concludes that (citation): *'Long-term statin treatment is remarkably safe with a low risk of clinically relevant adverse effects as defined above; statin-associated muscle symptoms were discussed in a previous Consensus Statement. Importantly, the established cardiovascular benefits of statin therapy far outweigh the risk of adverse effects.'* (end of citation).

4.7 Conclusions

4.7.1 Conclusions on effectiveness

In the systematic review including 19 individual studies, statin use in primary prevention is associated with a (statistically significant) reduced risk of overall (RR=0.86) and cardiovascular mortality (RR=0.72), fatal and non-fatal myocardial infarction (RR=0.64), fatal and non-fatal stroke (RR=0.71), subsequent revascularization (RR=0.63) and composite CVD outcomes (RR=0.70) compared with placebo.[2]

In spite of the presence of risk of bias in some of the included studies, inclusion of secondary prevention patients in some trials, and early termination of three trials, the sensitivity analyses show that these results are robust. Therefore, the evidence was rated good quality for all-outcomes, except for the evidence on cardiovascular mortality, which was downgraded in the systematic review to moderate quality because of significant heterogeneity among studies.

A further sensitivity analysis performed by us, showed that the relative risks were lower (i.e. better) for the high intensity treatment. However, this concerned mainly one single trial, the JUPITER trial with rosuvastatin published in 2008.

4.7.2 Conclusions on harms

The diverging results are caused by different study designs, different statistical measures (cumulative incidences, incidence/person-year, etc.) and especially by the different definitions and assessment methods used. In general the incidence of harms appears to be higher in observational evidence than in RCTs.

Mild myalgia with normal CK value ranges from 50-100/10 000 in 5 years in RCTs,[91] 70 – 290/10 000 persons in observational studies and registries,[90] to 100-500/10 000 in RCTs and 500-1000/10 000 in observational studies and clinical settings.[94]

Severe myopathy, myositis with CK elevation and rhadomyolisis are considered *'rare'* by a consensus panel,[94], 5/10 000 over five years in RCTs by Collins et al.,[91] and 1-10/10 000 by Stroes et al.[90]

Numbers for diabetes type 2 are equally divergent: 50-100/10 000 over five years in RCTs,[91] *'depends on population'*,[94] and 10/10 000 in Mach et al.[95]

Estimates for haemorrhagic stroke are: 5-10/10 000 over five years in RCTs,[91] *'unclear'*,[94] and *'no evidence for increased risk in individuals without cerebrovascular disease*'.[95]

From those divergent estimates on the harms of statins it can be concluded that:

- **Statins are relatively safe but estimates on harms are uncertain and diverging,**
- **there is a lack of uniform definitions for the harms,**
- **estimates on harms are ill measured in RCTs where the prime focus is on efficacy and effectiveness,**
- **observational studies on large cohorts are better equipped to detect rare events but are prone to bias.**

5 COST-EFFECTIVENESS

5.1 Introduction

Over the years many cost-effectiveness studies have been performed, but obviously these are quickly outdated due to the many price reductions over the years. Those studies are mainly based on assumptions that can influence the outcomes. In this chapter we will describe economic reviews but also some recent specific cost-effectiveness studies.

5.2 Methods

The aim of this literature review is to provide an overview of economic evaluations estimating the cost-effectiveness of treatment with statins in patients with no history of cardiovascular events (our working definition of primary prevention).

5.2.1 Search strategy

The search for the economic literature on the use of statins in primary prevention of cardiovascular events was performed in two steps.

First, we performed a systematic literature review of economic reviews from 2008 to March 2018. Both electronic and manual searches were performed to retrieve systematic reviews of cost-effectiveness studies.

- Electronic search: the following databases were searched in March 2018: Ovid(Medline), Embase and CRD (Centre for Review and Dissemination) HTA (Health Technology Assessments). A combination of MeSH and text word terms related to statins, cardiovascular disease and primary prevention were combined with those related to full economic evaluations and systematic reviews (see Table 50 to Table 52 in appendix).

- Manual search: the websites of the HTA institutes listed on the International Network of Agencies for Health Technology Assessment (INAHTA) were also consulted. We looked also at some non-INAHTA members (e.g National Institute for Health and Care Excellence). The list of HTA institutes is provided in Appendix (Table 48 and Table 49).

An overview of the search strategy, flow charts and results is provided in appendix (Table 50 to Table 53 and Figure 30). After the selection process, two reviews of full economic evaluations of statins in prevention of cardiovascular events were selected. The first report is a previous KCE report published in 2007[j] in which a literature search for statins in primary prevention was performed until February 2007.[97] The second is a guideline from The National Institute for Health and Care Excellence (NICE),[14] where a systematic review of economic evaluation was performed for studies published up to November 2013.

Secondly, we systematically searched for additional primary economic evaluations published from January 2013[k] to 2018. This part is a systematic review of the published full economic evaluations of statins therapy in adult patients with no history of cardiovascular events i.e. our working definition of primary prevention. A similar search strategy was applied as before, but with the difference of not including a filter for systematic reviews and also searching CRD's NHS EED (National Health Service Economic Evaluation Database). More details of the search strategy and selection process, including flow charts and an overview of included studies are documented in the appendix (Table 54 to Table 57 and Figure 31). The reference lists of relevant review papers and full economic evaluations were manually searched for additional relevant articles. Non-selected reviews were also used to identify primary studies. Also the reference lists of included primary articles were checked for relevant publications that may have been missed.

5.2.2 Selection criteria

Reviews and primary studies were similarly assessed for eligibility using inclusion and exclusion criteria. All retrieved references were assessed using pre-defined selection criteria, in terms of population, intervention, comparator, and design (see Table 58 in appendix). For reviews, the design was restricted to systematic reviews of economic evaluations. The reviews were evaluated checking the following:

- whether there is a description of the search strategy,
- a search strategy using an economic filter,
- detailed information about inclusion/exclusion criteria and considering as far as possible statins therapy,
- presence of a flow chart with reasons of exclusion and presence of the list of included studies.

Reviews with a search strategy restricted to publication in a specific part of the world (e.g. with only U.S. studies included) or without a clear conclusion about the cost-effectiveness of statins were excluded. For primary studies, the design was restricted to full economic evaluations, i.e. studies comparing at least two alternative treatments in terms of costs and outcomes. Cost-minimization analyses (CMA), cost-utility analyses (CUA, with results expressed as incremental cost per quality-adjusted life year (QALY) gained), cost-effectiveness analyses (CEA, with results expressed as incremental cost per life year (LY) gained) and cost-benefit analyses (CBA, with a monetary valuation of health outcomes) were eligible. Other studies such as cost comparisons (not considering health outcomes) or cost-outcome descriptions (not considering an alternative treatment) were excluded.

The selection of relevant articles was performed by a single reviewer in a two-step procedure: initial assessment of the title, abstract, and keywords, followed by a full-text assessment of the selected references. In case of

j This report was identified through a publication in 2009 as Neyt M, De Laet C, Van Brabandt H, Franco O, Ramaekers D. Cost-effectiveness of statins in the primary prevention of cardiovascular disease: a systematic review and economic analysis for Belgium. Acta Cardiologica. 2009;64(1):1-10.[96]

k Since the last publication of economic review (NICE clinical guideline CG181 published in 2014).

doubt, a second reviewer was consulted. When no abstract was available and the citation was unclear or ambiguous, consideration of the citation was directly made on the basis of a full-text assessment. If no full-text was available, the study was not taken into account. Letters, news, conference proceedings and editorials were excluded. Studies published in a language other than English, Dutch or French were excluded.[l]

5.3 Results of the economic search strategy

5.3.1 Results of the search strategy of reviews

In March 2018, a search was performed to identify reviews of economic evaluations regarding the use of statins in primary prevention of cardiovascular events. The electronic searches returned 347 economic systematic reviews in total (191 in Medline(OVID), 126 in Embase and 30 in CRD HTA). After exclusion of duplicates, references published in other language than English, Dutch or French and exclusion on title and abstract, 18 references remained. Three others papers were added from websites of HTA institutes, reference lists and hand searching (for details see Figure 30 in appendix). Of the remaining 21 references, two references were finally retained based on full-text evaluation (list of excluded studies can be found in Table 60 in appendix).[14, 97] Both studies are reviews of full economic evaluations of statins in the prevention of cardiovascular events.

5.3.2 Results of the search strategy of primary studies

Also in March 2018, a search was performed to identify full economic evaluations regarding the use of statins in primary prevention of cardiovascular events since the last review published in 2014, the NICE clinical guideline CG181 2014.[14] The electronic searches returned 1822 full economic evaluations in total (808 in Medline(OVID), 986 in Embase and 28 in CRD EED). After exclusion of duplicates, references published in other language than English, Dutch or French and exclusion on title and abstract, 24 references remained (for details see Figure 31 in appendix). Ten references were finally included based on full-text evaluation,[99-108] (the list of excluded studies can be found in Table 66 in appendix).

5.4 Overview of reviews of economic evaluations

In this section, we describe only results that fit our scope and any other results, not relevant for this project, were not included (details of the selection of the studies already included in these reviews can be found in Table 61 – Table 64 in appendix).

5.4.1 Description of the selected reviews

KCE report 52B (2007)

In this previous KCE report,[97] a systematic review of the published economic evaluations of interventions for the primary prevention of CVD was performed in 2007. They searched for full economic evaluations that compare two or more options and consider both costs and health benefits between 2001 and 2007. Cost-effectiveness and cost-utility analysis expressing results as costs per life-year gained (LYG) or costs per quality-adjusted life years (QALYs) gained were taken into account. The studies had to be conducted in people in developed countries and only articles in English, French or Dutch were considered. Interventions considered for primary prevention were broader than our narrow scope and included lifestyle interventions (smoking cessation, increased physical activity, healthy diet) and other drug treatments such as aspirin, antihypertensive, and lipid-lowering drugs. This systematic review included nineteen articles and eleven fit our scope (nine articles compared statin with no treatment, one article compared aspirin plus statin versus aspirin and one article compared statin therapy with other interventions). Reasons for exclusion of

[l] Only one study was excluded based on language in this review (Cosin Sales et al. 2014[98] and results are in line with what we found. The inclusion of this study will not have changed the conclusion of this chapter.

the eight other studies are explained in Table 62 in appendix. An overview of the main results of each of the studies is described in Table 67 in appendix. For more detailed information, we refer the reader to the full report where all articles have been summarized.

NICE clinical guideline CG181 (2014)

NICE clinical guideline CG181 is an update and replaces the previous NICE clinical guideline 67 published in 2008.[14] Chapter 11 of this report is dedicated to the cost-effectiveness of statin therapy for adults without established cardiovascular disease (primary prevention) and those with established cardiovascular disease (secondary prevention). A systematic review was performed on November 11th 2013 in the NHS Economic Evaluation Database (NHS EED), the Health Technology Assessment database (HTA) and the Health Economic Evaluations Database (HEED) with no date restrictions. An additional search was made in MEDLINE and Embase using a specific economic filter, looking for relevant references from 2010 up to the date of the search.[m] Studies published in languages other than English were not reviewed and only full economic evaluations and comparative costing studies were considered. Literature reviews, abstracts, posters, letters, editorials, comment articles, and unpublished studies were excluded. This systematic review covers primary and secondary prevention and includes also adults with type 1 diabetes mellitus, type 2 diabetes mellitus and with chronic kidney disease (CKD). People with familial hypercholesterolaemia were not included. This systematic review included six economic evaluations that compared statins with either placebo or another statins. Among them, four studies concerned primary prevention and one article did not fit our inclusion criteria (see Table 63 in appendix for reason for exclusion). The main results of these three studies are summarised in Table 69 in appendix.[109-111] No relevant economic evaluations were identified that compared statins with either placebo or statins in people with type 1 diabetes or type 2 diabetes but one focuses on people with CKD. For further information, we refer the reader to the evidence tables in the original report (Table 70, 71 and 73 - page 423-431) included in the appendix of the NICE clinical guideline CG181. An intervention was considered to be cost-effective if the intervention dominated other relevant strategies or the intervention costs less than £20 000 per QALY gained compared with the next best strategy.

5.4.2 Main results of the studies selected in these reviews of economic evaluations

5.4.2.1 Statin versus no treatment

Based on the results of the nine studies comparing statin with no treatment (see Table 67 in appendix), the authors of the KCE report concluded in 2007 that the reported (citation): '*… cost effectiveness of statin treatment varies tremendously. Next to methodological considerations, the main determinants for cost effectiveness are the level of CHD risk, gender and age. Treatment is cost effective only at high levels of risk and expensive for low levels. Most of the times, results are more favourable (i.e. lower ICERs) for men than for women.*[97]' (end of citation). However, it should be emphasised that at the time of this review the cost of statins in most studies was much higher than nowadays, thanks to the wide availability of generic alternatives.

The review performed in the NICE clinical guideline showed that based on the two studies comparing statin with no treatment (see Table 69 in appendix),[109, 110] the cost-effectiveness of statin treatment varies. The cost-utility analysis of Ward et al. from 2007 found that (citation): *'statins (as a combined single class) were cost effective compared to no treatment for the primary prevention of CVD in men aged 65 at 1.5% annual[n] risk of CHD[o]*

[m] 11 November 2013

[n] It should be emphasized that an annual risk cannot be compared with the usual risk estimates that estimate a 10 year risk. So actually, this risk is relatively high.

[o] 1.5% annual risk of CHD correspond to 2.4% annual CVD risk.

(ICER: £ 11 200 per QALY gained).[14]' (end of citation). The other study by McConnachie et al. from 2013 found that (citation): *'5-year treatment with low-intensity statins was dominant (less costly and more effective) compared to no treatment over a 15-year period for the primary prevention of CVD in men aged 45–64*.[14]'(end of citation). Besides other methodological considerations, this difference in conclusion can mainly be explained by the difference in the prices of statin taken into account in these two studies. Indeed, in the study of Ward et al. from 2007, the annual statin costs was estimated to £ 317 while in the study of McConnachie et al. from 2013, the annual statin costs, due to the appearance of more generic alternatives decreased and was estimated to be only £ 36.[p]

5.4.2.2 Aspirin plus statin versus aspirin

Based on one of the selected studies (Pignone et al. 2006,[112] see Table 67 in appendix), the KCE report highlighted that (citation): *'the addition of a statin to aspirin therapy produced more QALYs gained than aspirin alone but at a higher cost. The cost per additional QALY gained was approximately $ 56 200 for 10 years of combination therapy. The cost-effectiveness ratios for aspirin alone and in combination with statin therapy improved as risk for CHD increased. When the 10-year risk was 10% or 15%, the addition of a statin to aspirin therapy had a cost of $ 33 600 and $ 42 500, respectively*.[97]' (end of citation).

5.4.2.3 Statin versus other risk-lowering interventions

Based on one of the selected studies (Franco et al. 2007,[113] see Table 67 in appendix), that compared four risk-lowering interventions (smoking cessation, antihypertensives, aspirin, and statins) for the primary prevention of cardiovascular events, the authors of the KCE report highlighted that (citation): *'compared to no treatment, smoking cessation therapy, is the most cost-effective treatment, representing savings in all situations. Statin therapy is the least cost-effective treatment (ranging from € 73 971 to € 190 276 per YLS). Aspirin was the second most cost-effective intervention (ranging from € 2263 to € 16 949 per YLS) followed by antihypertensive treatment (ranging from € 28 187 to € 79 843 per YLS).' 'Statins have very high ICERs compared to aspirin treatment. However, as they have higher effectiveness, they are never dominated by the other treatments.*[113]' (end of citation). Based on these results, the authors concluded that (citation): *'…for cost-effective population prevention of CHD, the first line of intervention should be smoking cessation therapy for smokers and aspirin for moderate and high levels of risk. Statin therapy is an expensive option and should not represent a first choice in the primary prevention of cardiovascular events.[113]'* (end of citation). Again, we should emphasize that average cost of statin use was much higher in 2007 than nowadays. Moreover, the evidence on aspirin treatment for CVD prevention has been challenged since.

5.4.2.4 People with chronic kidney disease (CKD)

Based on one cost-utility analysis (Erickson et al. 2013,[111] see Table 69 in appendix), included in the review of NICE, authors highlighted that for men aged 65 years with moderate hypertension and mild-to-moderate CKD (citation), *'statins reduced the combined rate of MI and stroke, yielded 0.10 QALYs, and increased costs by $ 1800 ($ 18 000 per QALY gained). For patients with lower baseline cardiovascular risks, health and economic benefits were smaller; for 65-year-old women, statins yielded 0.06 QALYs and increased costs by $ 1900 ($ 33 400 per QALY gained). Results were sensitive to rates of rhabdomyolysis and drug costs. Statins are less cost-effective when obtained at average retail prices particularly in patients at lower CVD risk*.[q,111]' (end of citation).

[p] Converted by NICE.

[q] *NICE clinical guideline CG181 concluded that statins were 'cost effective compared to placebo for the prevention of CVD in men aged 65 with CKD (ICER: £11,730 per QALY gained) but were not cost effective for women aged 65 with CKD (ICER: £21,760 per QALY gained).[q,14]'*

5.4.3 Main results of the models developed in these reviews of economic evaluations

KCE report 52B (2007)[97]

In this report a cost-utility analysis was performed based on the original model of Franco et al. from 2007,[113] judged as the most transferable to the Belgian context, and using Belgian costs. In 2007, the annual cost of the cheapest statin available in the Belgian market was € 87.08.[r] The main results of this analysis are presented in Table 68 in appendix.

The model showed that when other interventions than only statins compared to no treatment are taken into account, statin is not the first strategy to consider in primary prevention. Indeed, smoking cessation interventions (for smokers) should first be considered, followed by low-dose aspirin treatment. Statin was only considered as borderline cost-effective (€ 29 350/LYG) for non-smoking high-risk patients aged 60 years old. The authors added that this borderline ICER was calculated under the assumption the cheapest statin was prescribed (less than € 90 per year in 2007), which was not the case in daily practice. They therefore concluded that statin treatment was not cost-effective (citation): *'for primary prevention of CVD/CHD in the moderate or high risk population with current prescribing practices. For the very high risk population (Framingham >30%) no results are shown.*[97]*'* (end of citation, see Table 68 in appendix).

NICE clinical guideline CG181 (2014)[14]

In the NICE clinical guideline CG181, two health economic models were developed. The first Markov model was dedicated to secondary prevention and will not be presented here. The second Markov model included the same structure for secondary prevention but added an initial primary prevention phase. Different analyses were done comparing cost-effectiveness of different statin classes at set cardiovascular risk.[s] In 2014, the annual cost of atorvastatin 20mg was £ 16.44.[t]

The level of risk was measured by QRISK2 tool for the general population in primary prevention and by UKPDS tool for persons with diabetes. The main results of this analysis are shown in Table 70 in appendix.

Primary prevention in persons without diabetes

The main results of the model for primary prevention without diabetes showed that for people aged 60 years old at start and with a risk of 10% using the QRISK2 score (see Table 70 in appendix):

- low-intensity statins are dominated by medium-intensity statins and high-intensity statins (20 mg only),
- medium-intensity treatment is cost-effective or dominant compared to no treatment or low-intensity treatment at all risk levels,
- high-intensity statins are cost-effective compared to no treatment at a willingness to pay (WTP) threshold of £ 20 000/QALY.

The analysis also shows that with a WTP threshold of £ 20 000/QALY and for a risk threshold of 10%, high-intensity statin 20mg is cost-effective (or even in some cases dominant) for all age group and gender (men and women between 40-70 years old). Table 70 shows the risk thresholds from which atorvastatin 20mg is considered as cost-effective at a WTP threshold of £ 20 000. Concerning atorvastatin 80mg and a risk threshold of 10%, this statin is also considered as cost-effective compared to a medium-intensity

[r] Actually, the annual cost of the cheapest statin in the Belgian market is € 46.48, see Table 87 in appendix.

[s] After a comparison of the cost-effectiveness of 19 statin options, the low-intensity statins group was represented by Simvastatin 10mg, the medium-intensity statins group was represented by Simvastatin 20mg and 2 statins (Atorvastatin 20 mg and Atorvastatin 80 mg) were considered for the high-intensity statins group.

[t] It should be noted that the annual cost of statin was lower in NICE 2014 than in KCE report 2007 and it is still cheaper in 2018. In 2018, the annual cost of the cheapest statin in the Belgian market is € 46.48 (see Table 87 in appendix).

statin at a WTP threshold of € 20 000/QALY except for men and women aged 70 years old.

Primary prevention in persons with type 2 diabetes

The following conclusions were made for persons without CVD and with type 2 diabetes (see Table 70 in appendix) aged 60 years old at start and with a UKPDS score of 10%:

- low-intensity statins are dominated by medium-intensity statins and high-intensity statins (20 and 80 mg),
- medium-intensity statins are dominated by high-intensity statins (Atorvastatin 20 mg only),
- high-intensity statin (atorvastatin 80mg) is cost-effective compared to medium-intensity statins at a WTP threshold of € 20 000/QALY (ICER of € 3 445/QALY for men and € 3 416/QALY for women),
- high-intensity statin (atorvastatin 20mg) is cost-effective compared to no treatment at a WTP threshold of € 20 000/QALY (ICER of € 1822/QALY for men and about € 1712/QALY for women).

The analysis also shows that with a WTP threshold of € 20 000/QALY and for people aged 60 years old, a high-intensity statin 20mg is cost-effective compared to medium-intensity statins from UKPDS scores of 4% for men and 3% for women aged 60 years old.

In comparison with published studies, the results of NICE clinical guideline (citation): *'are largely consistent with previous published cost-effectiveness analyses, but support the use of higher-intensity statins than some previous studies have done due to the recent decrease in statin costs, notably of atorvastatin.[14]'* (end of citation).

5.4.4 Recommendations from these reviews of economic evaluations

KCE report 52B 2007[97]

This systematic review concluded (citation): *'that it is necessary to incorporate not only baseline risk of CHD but also age and gender into the discussion, just as guidelines also take into account the combination of these factors and estimate the global cardiovascular risk.[97]'* (end of citation).

Based on this report, the following key points were formulated for primary prevention of CVD (citation):

- ***'Smoking cessation is the most recommended intervention for smokers and is even cost-saving.***
- ***In low risk individuals (Framingham < 10%), there are no arguments to initiate pharmaceutical treatment, since it is uncertain that benefits outweigh possible harms.[97]'***
- ***Recommendation on low-dose aspirin,[u]***
- ***'Available simulations highly depend on the cost of treatment. Taken into consideration the recent lowering of statin prices, cost-effectiveness measures will be rendered more favourable.***
- ***Statin therapy in primary prevention of CVD for men at levels of 10-year Framingham CHD risk above 20%[v] and at ages above 60 years, becomes borderline cost-effective compared to low-dose aspirin (€ 30 000 per life-year gained) only if there is a widespread prescription of the cheapest alternative (< € 90 per year).***

[u] The KCE report recommended that "low-dose aspirin is a more cost-effective preventive intervention than statins at all risk levels" but recent evidence does not support any more aspirin for primary prevention of CVD.[18]

[v] High risk is defined as 20-30% 10-year absolute risk of CHD (Framingham).

- ***In women of all ages and in men above the age of 70 no solid evidence about clinical effectiveness of statin use in primary prevention were available. Economic evaluations for those populations were based on extrapolations of effectiveness in other subgroups. More research should be performed first to the benefits and harms of treatment in these populations.[97]'*** **(end of citation).**

It should be noted that these recommendations are partially out-dated. Although the cheapest alternative (simvastatin) already had a low price in 2007, the recommendation on aspirin is not valid anymore since evidence has evolved.

NICE clinical guideline CG181 2014[14]

Based on this report, the following recommendations were formulated:

- **<u>For primary prevention of CVD (citation)</u>:**
  - **'*Before offering statin treatment for primary prevention, discuss the benefits of lifestyle modification and optimise the management of all other modifiable CVD risk factors if possible. [new 2014]***
  - ***Recognise that people may need support to change their lifestyle. To help them do this, refer them to programmes such as exercise referral schemes. (See Behaviour change: individual approaches [NICE public health guidance 49].) [new 2014]***
  - ***Offer people the opportunity to have their risk of CVD assessed again after they have tried to change their lifestyle. [new 2014]***
  - ***If lifestyle modification is ineffective or inappropriate offer statin treatment after risk assessment. [new 2014]***
  - ***Offer atorvastatin 20 mg for the primary prevention of CVD to people who have a 10% or greater 10-year risk of developing CVD. Estimate the level of risk using the QRISK2 assessment tool. [new 2014]***
  - ***For people 85 years or older consider atorvastatin 20 mg as statins may be of benefit in reducing the risk of non-fatal myocardial infarction. Be aware of factors* that may make treatment inappropriate (see recommendation 48). [new 2014]' (end of citation).**
- **<u>For primary prevention of CVD - People with Type 1 Diabetes (citation):</u>**
  - **'*Consider statin treatment for the primary prevention of CVD in all adults with type 1 diabetes. [new 2014]***
  - ***Offer statin treatment for the primary prevention of CVD to adults with type 1 diabetes who are older than 40 years or have had diabetes for more than 10 years or have established nephropathy or have other CVD risk factors. [new 2014]***
  - ***Start t*reatment for adults with type 1 diabetes with atorvastatin 20 mg. [new 2014]' (end of citation).**
- **<u>For primary prevention of CVD - People with Type 2 diabetes (citation):</u>**
  - ***'Offer atorvastatin 20 mg for the primary prevention of CVD to people with type 2 diabetes who have a 10% or greater 10-year risk of developing CVD. Estimate the level of risk using the QRISK2 assessment tool. [new 2014]'* (end of citation).**
- **<u>For primary prevention of CVD - People with CKD (citation):</u>**
  - ***'Offer atorvastatin 20 mg for the primary or secondary prevention of CVD to people with CKD"***

- ***Increase the dose if a greater than 40% reduction in non-HDL cholesterol is not achieved (see recommendation 64) and eGFR is 30 ml/min/1.73 m^2 or more.***
- ***Agree the use of higher doses with a renal specialist if eGFR is less than 30 ml/min/1.73 m^2. [new 2014]'*** **(end of citation).**

5.4.5 Summary of results

Before offering statin therapy, reviews and guidelines recommend:[14, 97]

- discussing the benefits of lifestyle modification and change in CVD risk factors for all people,[14, 97]
- recommend smoking cessation for smokers,[97]
- offering the opportunity to assess patients' risk of CVD for all people, especially before and after if they have tried to change their lifestyle,[14]
- considering statin therapy only if lifestyle modification is ineffective or inappropriate.[14]

According to risk level and population, recommendations in starting statin therapy are quite similar:

- for people at low risk level (10-year Framingham CHD < 10%), not to initiate pharmaceutical treatment due to uncertainty that benefits outweigh possible harms, in KCE 2007,[97]
- at intermediate and high risk level (QRISK2 10-year risk of developing CVD ≥ 10%), treating all people with atorvastatin 20 mg, in NICE 2014,[14]
- at high risk level (10-year Framingham CHD ≥ 20%), treating all men aged above 60 years old with statin therapy can be considered (borderline cost-effective compared to low-dose aspirin), in KCE 2007,[97]
- treating patients with type 1 diabetes aged 40 years or older or have had diabetes for more than 10 years or have established nephropathy or have other CVD risk factors with atorvastatin 20mg, in NICE,[14]
- treating patients with type 2 diabetes at intermediate or high risk level (QRISK2 10-year risk of developing CVD ≥ 10%) with atorvastatin 20mg, in NICE,[14]
- treating all persons with CKD in primary prevention with atorvastatin 20 mg, in NICE.[14]

The KCE report from 2007 stated that other interventions such as aspirin should be considered in primary prevention but recent evidence does not support aspirin for primary prevention. Indeed, the European Guidelines on cardiovascular events prevention in clinical practice recommend not using antiplatelet therapy (e.g. with aspirin) for people without CVD and also for diabetic patients due to the increased risk of major bleeding.[18]

It should be noted that even while the prices of statins changed in recent years, these results are still partially valid. In the KCE model, authors used the annual cost of the cheapest statin available on the Belgian market in 2007(i.e. € 87.08 for pravastatin 20 mg) and it costs € 20 less in 2018 (€ 66.93, see Table 87 in appendix). This difference should be moderated because the average price for pravastatin 20mg for the different packaging and trademark used in practice is higher (i.e. € 99.82 on average prices in 2016; see Table 38 in appendix). Similarly, the prices of statins used in NICE model (£ 16.44 for atorvastatin 20 mg) are cheaper than the cheapest atorvastatin 20 mg available on the actual Belgian market (€ 88.38; see Table 87 in appendix).

5.5 Overview of selected primary studies

As described in section 5.3.2, ten primary studies were selected.[99-108] Six of them assessed the impact of statins therapy to determine which CVD risk and age thresholds can be considered as cost-effective.[102, 103, 105-108] Two other studies concerned specific population i.e. patients with diabetes or chronic kidney disease.[99, 104] The two latest studies were related to so-called *'polypills'*, combining a statin and an antihypertensive agent.[100, 101]

5.5.1 Comparison of various CVD risk and age thresholds

Baseline population

Six studies that assessed the cost-effectiveness of various CVD risk thresholds and age have been selected.[102, 103, 105-108] A description of the studies' baseline populations can be found in Table 71 in appendix. One study by Odden et al.[106] assessed the cost-effectiveness of statin in the elderly (from 75 years old) while others studies focused on adults from 40/45 years old to 65/75 years old.[102, 103, 105, 107, 108] Two studies were European studies.[107, 108] while other studies were from the US.[102, 103, 105, 106]

Instruments used to determine the 10-years CVD risk differed: three studies were based on the ACC/AHA ASCVD Risk Calculator,[w,102, 105, 106] one study was based on the European SCORE Risk,[108] one study was based on the FINRISK risk function,[107] and one study was based on both the ACC/AHA ASCVD Risk Calculator and the Framingham Risk Score.[103] See Table 71 in appendix for details.

All studies assessed the impact of various risk thresholds except the study of Odden et al.,[106] that assessed different Low-Density Lipoprotein Cholesterol levels (LDL-C), and the study of Shiffman et al.[102] that focused only on people with an intermediate risk.

It should also be noted that the baseline population focused on non-diabetic patients in only three studies,[102, 103, 108] while other studies included both patients with and without diabetes, and the presence of diabetes was assessed in the risk score calculation.

Study characteristics

Main studies' characteristics are described in Table 72 in appendix. Among them, three studies seemed to have a potential conflict of interest and funding was not clear.[102, 106, 107]

All studies used a Markov model,[102, 103, 106, 107] except Pandaya et al.[105] that used a microsimulation model and Romanens et al.[108] that used a non-conventional calculation based on unrealistic assumptions. Costs and QALYs were discounted at 3% in all studies, except in the study of Romanens et al.[108] Most studies had a 10-year time horizon,[x,103, 106-108] except the study of Pandaya et al.[105] that used a lifetime horizon and the study of Shiffman et al.[102] that used a 5-year time horizon.[y] When assessed, sensitivity analyses showed that longer periods were in favour of statin therapies at lower risk thresholds.[107, 108]

It should be noted that the study of Romanens et al.[108] was neither performed alongside a clinical trial nor trough modelling techniques and that authors only assumed that all events occurred at year 5 (on a 10-year period). Patients were then assumed to remain in their health state for the next five years (i.e. without events, with a non-fatal cardiovascular events or dead). This study also did not apply discounting of costs and outcomes.

Intervention and comparators

Three studies assessed no treatment in the comparators,[102, 107, 108] while other studies[103, 105, 106] used current levels of statin use (usually without specific risk assessment / algorithm) rather than no treatment as comparator. Various guidelines, risk thresholds and LDL-C levels were also tested (see Table 73 in appendix). Shiffman et al.[102] and Heller et al.[103] are both studies that made a distinction between high-intensity statins and moderate-intensity statins. As shown in section 4.5, high-intensity statins seem to be more effective (lower RR) than moderate/low-intensity statin. Shiffman et al.[102] also investigated the cost-effectiveness of using low density lipoprotein particle number (LDL-P) to target intermediate risk patients to benefit from initiating or intensifying statin therapy.

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w From http://tools.acc.org/ascvd-risk-estimator-plus/#!/calculate/estimate/

x This was justified by the fact that uncertainty was too high after 10 years.

y 5-year time horizon was considered to better align with the payer perspective of the analysis.

Outcome data

As shown in Table 74 in appendix, the study of Aarnio et al.[107] did not take into account the impact of statin on stroke. This study of Aarnio et al. and the study of Romanens et al.,[108] also did not assessed the impact of statin on adverse events. As it was shown in the sensitivity analysis of Pandaya et al.,[105] an increase of the risk of statin-induced diabetes resulted in net harms and therefore results were less in favour of statin therapy.

The impact of real world adherence levels was assessed in three studies.[102, 105, 107] As was shown in the study of Aarnio et al.,[107] it is important to include adherence in models. Poor adherence leads to a decrease of the effectiveness of statins therapy and therefore interventions become less cost-effective (even when treatment costs were reduced due to the non-adherence.

To estimate the effectiveness of statins, studies used a global risk ratio or assumed a decrease of LDL-C level from statins and applied risk reduction for each mmol/L LDL reduced (see Table 75 in appendix). When performed, sensitivity analyses showed that an increase of effectiveness of statin therapy was in favour of statin therapies at lower risk thresholds.[106]

The disutility for taking a statin pill every day was included in two studies,[102, 105] and in the sensitivity analyses in two other studies.[103, 106] These studies highlighted the importance of including patient's preferences of taking a daily pill and resulted in a significant deterioration of the cost-effectiveness of statins treatment.[102, 103, 105]

Cost data

In Belgium, the annual cost for the cheapest big box statin vary between € 46.48 (Atorvastatin 10) and € 220.13 (Simvastatin 80) (prices on 01/01/2018). A description of the actual annual cost of each type of statin according to small or big boxes can be found in Table 87 in appendix. The monitoring cost of statin can be estimated to €51.09.[z] Further explanation on the estimation of monitoring costs can be found in Table 88 in appendix. Therefore, total annual costs for Belgium can vary between € 97.57 and € 271.22. We compared each study with the annual cost of the most comparable statin in addition to the estimated monitoring cost. In term of annual total costs, we observed that Belgium has higher costs than the studies of Heller et al.,[103] Odden et al.[106] and Shiffman et al..[102] Shiffman et al.[102] seems to underestimate the annual costs because they did not consider cost of monitoring (see Table 76 in appendix). In the other studies, the annual total cost is quite similar or higher than in Belgium. Even if the annual statin cost of Aarnio et al.[107] is similar to Belgium, the cost of monitoring is three times more expensive (€ 147.9 vs € 51.09), which give an annual total cost higher than in Belgium. In the study of Romanens et al.,[108] the annual total cost is four times higher than in Belgium. In the study of Pandaya et al.[105] the scenario on generic price only is more transferable to the Belgian situation than the base case scenario.

Results and discussions

Results are summarized in Table 20. A difference can be highlighted according to the fact whether adherence was considered or not.

When adherence was not considered, results went in favour of statin strategies, even at low risk thresholds:

- Heller et al.[103] concluded that compared to statin decisions not based on specific guidelines, the follow-up of guidelines[aa] is a dominant strategy (more QALYs and less costs). A universal coverage (all men aged 45 to 74 years old and women aged 55 to 74) would yet improve results (dominate all other strategies). They nevertheless highlighted that such conclusion is only valid for a population at low risk of harms from statin use and unburdened by daily pill use. They also showed that results highly depend on the disutily associated with pill burden. Heller et al.[103] concluded that individual patients' preference for taking a daily pill is an important factor to take into account in assessing whether statin

[z] It included €29.24 fee for a GP consultation or specialist consultation and €21.85 costs for blood sample taking.

[aa] American College of Cardiology/American Heart Association (ACC/AHA) guideline or Adult treatment panel III (ATPIII) guideline

use and its potential side effects result in net benefit. They suggested that physicians should assess each patient's individual preference for daily pill use in making a share-decision in starting a long-term treatment, particularly for patients at lower risk.

- Odden et al.[106] concluded in favour of statin treatment in primary prevention for the elderly (from 75 years old, all considered with a 10-year risk score >7.5%). Odden et al.[106] used a low total annual cost in primary prevention and could underestimate the ICER. Authors highlighted that even a small increase in geriatric specific side effects (e.g. on functional limitation or mild cognitive impairment) could offset the cardiovascular benefit. Moreover, poor evidence about clinical effectiveness of statin use in primary prevention in the elderly (>75 years) is available,[114] see chapter 4.
- Romanens et al.[108] concluded that SCORE thresholds lower than 5% (e.g., 1.1–2.5%) could be considered for patients aged between 40 and 65 years. Nevertheless it should be noted that the quality of this study was limited (a lot of unrealistic assumptions, adverse events not taking into acount, related to the fact that no model or trial was done).

When adherence was considered, discrepancies between studies can be shown and conclusions are not straightforward:

- Shiffman et al.[102] showed that for intermediate risk patients aged between 40 and 75 years (ASCVD 10-year CVD Risk between 5% and 7.5%), high-intensity satins is the preferred care strategy (more QALYs and less costs) compared to no statin, moderate-intensity statin, or deciding between moderate- or high-intensity statin based on LDL-P levels. They also insisted on the importance of discussion between physician and patients about taking statin treatment (high- or moderate-intensity) or not. Conflict of interest were nevertheless highlighted for this study and costs were under-estimated (no annual cost of monitoring were reported).
- Pandaya et al.[105] showed that statins decision based on risk assessment can be considered as cost-effective for people aged 45 to 75 years from a 10-year ASCVD risk of 4% or more (based on generic prices and for a willingness to pay (WTP) threshold of $50 000/QALY) compared to no risk assessment to make the decision. With a lower WTP, e.g. $20 000/QALY, statins (generic prices) decision based on risk assessment can be considered as cost-effective from a 10-year ASCVD risk of 7.5%. It should be highlighted that in this study, the comparator is no ASCVD risk–based treatment strategies and lifetime horizon was used (more in favour of statins therapy at lower risk threshold). The optimal risk threshold was sensitive to patient preferences for taking a pill daily, changes to statin price, and the risk of statin-induced diabetes. The study showed that if no disutility was assumed for taken a pill every day, the optimal ASCVD threshold is yet reduced (4% instead of 7.5% at a WTP threshold of $50 000/QALY). Sensitivity analysis showed also that treating all adults with statins was not an optimal strategy.
- Aarnio et al.[107] concluded that in the real world adherence scenario, statins seemed to be cost-effective in the older patients (from 55 to 65 years old) from a 10-year CHD risk as high as 20% and did not seem cost-effective in the youngest age groups (45 to 50 years old). Even in the full adherence scenario, results are not considered cost-effective at a threshold of €20 000/QALY for 55-year-old men and 60-year-old women with a 10-year CHD risk of 10% or less. It should also be noted that in this study, CHD risk threshold was assessed according to the FINRISK risk function. Authors specified that a 10-year CHD risk of 10% with the FINRISK risk function correspond to around 19% with the ASCVD risk estimator from the ACC/AHA guideline and around 21% with the QRISK2-tool. At this risk threshold and with real-world adherence scenario, statin was not considered as cost-effective for all age group (based on the UK WTP threshold of £30 000/QALY). It should be highlighted that in this study adverse events were not taking into account.

Table 20 – Statins therapy: Results

	ICER	Sensitivity analysis	Conclusion
Aarnio 2015[107]	**Women, real-world adherence** **Risk* / Age** | **5%** | **10%** | **15%** | **20%** **65** | >30 000/QALY | >30 000/QALY | 20 000-30 000/QALY | <20 000/QALY **60** | >30 000/QALY | >30 000/QALY | 20 000-30 000/QALY | <20 000/QALY **55** | >30 000/QALY | >30 000/QALY | >30 000/QALY | 20 000-30 000/QALY **50** | >30 000/QALY | >30 000/QALY | >30 000/QALY | 20 000-30 000/QALY **45** | >30 000/QALY | >30 000/QALY | >30 000/QALY | >30 000/QALY ** The risk was estimated by FINRISK risk function for 10-year CHD risk.* **Men, real-world adherence** **Risk* / Age** | **5%** | **10%** | **15%** | **20%** **65** | >30 000/QALY | >30 000/QALY | 20 000-30 000/QALY | <20 000/QALY **60** | >30 000/QALY | >30 000/QALY | 20 000-30 000/QALY | <20 000/QALY **55** | >30 000/QALY | >30 000/QALY | 20 000-30 000/QALY | <20 000/QALY **50** | >30 000/QALY | >30 000/QALY | >30 000/QALY | 20 000-30 000/QALY **45** | >30 000/QALY | >30 000/QALY | >30 000/QALY | 20 000-30 000/QALY ** The risk was estimated by FINRISK risk function for 10-year CHD risk.*	**Sensitivity analysis** Results were sensitives to: • Statins and monitoring costs: <20 000/QALY if no monitoring cost considered (even for 45-year old women wih a 10-year CHD risk of 5%, i.e. with the highest ICER) • Selected time horizon: results improved with longer time horizon. • Patients adherence. Nevertheless even in the full adherence scenario, results are not considered cost-effective at a threshold of €20 000/QALY for 55-year-old men and 60-year-old women with a 10-year CHD risk of 10% or less.	*"At an assumed WTP threshold of €20 000 per QALY gained, statin treatment in the real world adherence scenario seemed to be cost-effective among the older patient groups when the patients' 10-year CHD risk was as high as 20% and did not seem cost-effective in the youngest age groups even at this highest tested risk level." "Even though generic statins are now low-cost drugs, treatment adherence seems to have a major impact on the cost-effectiveness of statin treatment in primary prevention."* NB: Authors estimated that a **10-year CHD risk of 10%** (CVD risk of 17%) for women aged 50-years old according to the **FINRISK risk function** correspond to a **10-year CVD risk of around 19%** with the **ASCVD risk estimator** from the ACC/AHA guideline and around **21% with the QRISK2-tool**.

<table>
<tr><th></th><th>ICER</th><th>Sensitivity analysis</th><th>Conclusion</th></tr>
<tr><td>Odden 2015[106]</td><td>
Base case results
<table>
<tr><th></th><th>DALYs</th><th>Incre-mental DALYs</th><th>Total costs (millions)</th><th>Incre-mental costs (million)</th><th>ICER</th></tr>
<tr><td>Status Quo</td><td>179 779 000</td><td>-</td><td>$4 351 900</td><td>-</td><td>-</td></tr>
<tr><td>Secondary Prevention</td><td>180 048 000</td><td>269 000</td><td>$4 346 200</td><td>-$5 700</td><td>Cost Saving</td></tr>
<tr><td>Primary prevention</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>LDL-C ≥ 4.91 mmol/L (190 mg/dL)</td><td>180 065 000</td><td>17 000</td><td>$4 346 000</td><td>-$200</td><td>Cost Saving</td></tr>
<tr><td>LDL-C ≥ 4.14 mmol/L (160 mg/dL)</td><td>180 098 000</td><td>33 000</td><td>$4 345 900</td><td>-$100</td><td>Cost Saving</td></tr>
<tr><td>Diabetics</td><td>180 103 000</td><td></td><td>$4 346 200</td><td></td><td>Dominated</td></tr>
<tr><td>LDL-C ≥ 3.36 mmol/L (130 mg/dL)</td><td>180 156 000</td><td>58 000</td><td>$4 346 200</td><td>$300</td><td>$5 300/DALY</td></tr>
<tr><td>Treat All (with a risk > 7.5%)</td><td>180 245 000</td><td>89 000</td><td>$4 348 500</td><td>$2 300</td><td>$25 200/DALY</td></tr>
</table>
</td><td>
Sensitivity analysis
Results are sensitive to:
• The effectiveness of statin in this population age: with a lower effectiveness (Beta coefficient of 0.001) , only treating patients with LDL-C ≥ 4.91 mmol/L (190 mg/dL) remain cost-effective (<$50 000/DALYs)
• Statin cost: with an annual cost of $365, only treating patients with LDL-C ≥ 4.91 mmol/L (190 mg/dL) remain cost-effective (<$50 000/DALYs)
The probabilities to be cost-effective at a threshold of $50 000/DALY was 99% (for patients >190 mg/dL), 94% (for patients >160 mg/dL), 83% (for patients >130 mg/dL) and 81% (for all patients with a risk > 7.5%).
</td><td>
“At effectiveness similar to trial findings, statins are projected to be cost-effective for primary prevention in adults age 75–94 years; however, even a small increase in geriatric specific side effects could offset the cardiovascular benefit. Improved data on the potential benefits and harms of statins are needed to inform decision-making."
</td></tr>
<tr><td>Pandaya 2015[105]</td><td>
Results of the base case analysis
<table>
<tr><th>ACC/AHA ASCVD Risk Threshold, % (10-years CVD risk)</th><th>Statin eligible, %</th><th>QALYs</th><th>Costs</th><th>ICER</th></tr>
<tr><td>No ASCVD threshold</td><td>8</td><td>17.276</td><td>21 310</td><td>-</td></tr>
<tr><td>≥30.0</td><td>34</td><td>17.287</td><td>21 649</td><td>Extended dominance</td></tr>
<tr><td>≥20.0</td><td>36</td><td>17.299</td><td>21 898</td><td>Extended dominance</td></tr>
<tr><td>≥15.0</td><td>39</td><td>17.309</td><td>22 109</td><td>$24 000/QALY</td></tr>
</table>
</td><td>
Sensitivity analysis
Results were sensitive to:
• the annual statin cost (see the column beside)
• The disutility of taking a pill daily: if no disutility is considered, the optimal ASCVD threshold becomes 3.0% (instead of 7.5%) at a WTP threshold of $50 000/QALY.
</td><td>
“In this microsimulation model of US adults aged 45 to 75 years, the current 10-year ASCVD risk threshold (≥7.5% risk threshold) used in the ACC/AHA cholesterol treatment guidelines has an acceptable cost-effectiveness profile (ICER, $37 000/QALY)”.
</td></tr>
</table>

ICER				Sensitivity analysis	Conclusion
≥10.0	44	17.32	22 455	$30 000/QALY	
≥7.5	48	17.327	22 696	$37 000/QALY	
≥5.0	57	17.333	23 039	$57 000/QALY	
≥4.0	61	17.335	23 200	$81 000/QALY	
≥3.0	67	17.336	23 406	$140 000/QALY	
≥2.0	75	17.337	23 656	$830 000/QALY	
≥1.0	87	17.336	23 952	Dominated	
Treat all adults with statins	100	17.334	24 225	Dominated	

Results with a generic annual statin cost of $68

ACC/AHA ASCVD Risk Threshold, % (10-years CVD risk)	Adults statin eligible, %	QALYs	Costs	ICER
No ASCVD threshold	8	17.276	20 695	-
≥30.0	34	17.287	20 808	Extended dominance
≥20.0	36	17.299	20 878	Extended dominance
≥15.0	39	17.309	20 942	$7 400/QALY
≥10.0	44	17.32	21 073	$12 000/QALY
≥7.5	48	17.327	21 169	$15 000/QALY
≥5.0	57	17.333	21 330	$27 000/QALY
≥4.0	61	17.335	21 406	$38 000/QALY
≥3.0	67	17.336	21 514	$72 000/QALY
≥2.0	75	17.337	21 651	$460 000/QALY
≥1.0	87	17.336	21 819	Dominated
Treat all adults with statins	100	17.334	21 986	Dominated

- The odds ratio of statin induced diabetes: with an odds ratio of 1.17 (upper bound) instead of 1.09, the optimal ASCVD threshold becomes around 10-15% (instead of 7.5%) at a willingness-to-pay threshold of $50 000/QALY.

Conclusion were not changed with the following scenario:

- An acute CVD mortality reduced by 20%
- Statin effectiveness based on proportional LDL reductions

The probability that ASCVD thresholds of 7.5% or lower were optimal at a WTP threshold of $50 000/QALY was 86%. The probability that ASCVD thresholds of 3% or lower were optimal at a WTP threshold of $50 000/QALY was around 0%.

	ICER	Sensitivity analysis	Conclusion

Optimal ASCVD treatment threshold as a function of statin price for a willingness to pay threshold of $50 000/QALY

Annual statin cost	$0	$50	$68	$100	$150	$250	$267	$500	$750 - $2000
Optimal 10-years CVD risk threshold (%)	3.0	4.0	4.0	4.0	5.0	7.5	7.5	10.0	None

Shiffman 2016[102]

Base case results per 100 000 patients

Intervention	Cost ($1000)	QALYs	ICER
HST all[bb]	258 460	460 516	Dominant
HST Test+[cc]	298 547	460 119	Dominant
MST all[dd]	303 215	460 004	-
MST Test+[ee]	336 633	460 162	Dominant
No Statin	339 879	460 118	-

Deterministic analysis: "HST" dominate other strategies in all situation except on the parameter "utility of being disease free while taking a statin pill daily" (if 0.991 instead of 0.998 => MST Test + results in fewer QALYs than "no statin")

Probabilistic analysis

- "HST all" dominated "MST all" in 100% of the iteration of the simulations.
- "HST test +" dominated "MST all" in 99.9% of the iteration of the simulations.
- "MST test +" dominated "No statin" in 80% of the iterations (but in 100% if the utility of being

"HST is the preferred care strategy in intermediate risk patients. However, the HST strategy also caused more diabetes than did any of the other strategies."

"For patient-clinician discussions that would otherwise lead to the MST strategy, we found the test-and-HST strategy reduced costs by $4.67 MM and resulted in 134 fewer CVD events and 115 additional QALYs. For patient-clinician discussions that would otherwise lead to no statin therapy, we found that the test-and-MST strategy reduced costs by $3.25 MM, resulted

bb HST all: High-intensity statin for all patients

cc HST Test +: High-intensity statin therapy for patients in the top decile of LDL-P levels and moderate-intensity statin therapy for others

dd MST all: Moderate-intensity statin therapy for all patients

ee MST Test+: Moderate-intensity statin therapy for patients in the top decile of LDL-P levels

<table>
<tr><th></th><th>ICER</th><th>Sensitivity analysis</th><th>Conclusion</th></tr>
<tr><td></td><td></td><td>disease-free while taking statin pill remained unchanged).</td><td>in 97 fewer CVD events and 44 additional QALYs. »</td></tr>
<tr><td>Heller 2017[103]</td><td>Compared to “status quo”<table><tr><th></th><th>ATP III</th><th>ACC/AHA</th><th>Universal</th></tr><tr><td>Total cost, $×109</td><td>-10,7</td><td>-14,6</td><td>-26.0</td></tr><tr><td>QALYs gained</td><td>+253 000</td><td>+436 000</td><td>+705 000</td></tr></table></td><td>Sensitivity analysis: Without pill burden:
ATP III: all of the simulations were cost-saving (100%)
ACC/AHA: all except one of the simulations were cost-saving
Universal: all except one of the simulations were cost-saving
Sensitivity analysis: With pill burden:
ATP III: all of the simulations were cost-saving
ACC/AHA: a small number of simulations were no longer cost-saving
Universal: a small number of simulations were no longer cost-saving</td><td>“In populations at low risk of harms from statin use and unburdened by chronic pill use, broader use of statins would both avert substantive cardiovascular morbidity and prove cost-saving, even when baseline cardiovascular risk is low.”</td></tr>
<tr><td>Romanens 2017[108]</td><td>For a 10-year period with an RR assumed at 70<table><tr><th></th><th colspan="3">CVD Risk (score)</th></tr><tr><th></th><th>2,50%</th><th>5%</th><th>10%</th></tr><tr><td>Incremental QALYs (for 1000 people)</td><td>71,3</td><td>142,5</td><td>213,8</td></tr><tr><td>Incremental Costs (for 1000 people)</td><td>CHF 2 712 500</td><td>CHF 725 000</td><td>CHF -1 262 500</td></tr><tr><td>ICER</td><td>CHF 38 070/QALY</td><td>CHF 5 088/QALY</td><td>Dominant</td></tr></table></td><td>Not performed</td><td>“Future guidelines should consider SCORE thresholds lower than 5% (e.g., 1.1–2.5%) for the initiation of statins in primary care for those aged 40–65 years”</td></tr>
</table>

ICER	Sensitivity analysis	Conclusion

For a 10-year period with an RR assumed at 78%

	CVD Risk (score)		
	2,50%	**5%**	**10%**
Incremental QALYs (for 1000 people)	52.3	104.5	156.8
Incremental Costs (for 1000 people)	CHF 3 242 500	CHF 1 785 000	CHF 327 500
ICER	CHF 62 057/QALY	CHF 17 081/QALY	CHF 2 089/QALY

Note: CHD = Coronary heart disease; CVD: Cardiovascular disease; QALY: Quality-adjusted life year; DALY: Disability Adjusted Life Years; WTP: W*illingness to pay; ICER: incremental cost-effectiveness ratio; RR: Risk ratio; ASCVD: Atherosclerotic Cardiovascular Disease; ACC/AHA: American College of Cardiology and American Heart Association; SCORE: Systematic COronary Risk Evaluation*

5.5.2 Patient with diabetes or chronic kidney disease

Baseline population and studies' characteristics

One study by De Vries et al. assessed statin (simvastatin 40mg) compared to no treatment for type 2 diabetes patients aged < 45 years old, 45-55 years old and 55-65 years old.[99]

Another study by Mihaylova et al. assessed statin (simvastatin 20mg) plus ezetimibe 10mg compared to no treatment for patients with chronic kidney diseases aged from 40 years old. [104] Characteristics are described in Table 77 and Table 78 in appendix.

Outcomes and costs data

Both studies assessed the impact on major adverse events and took patient adherence into account (see Table 79 in appendix).[99, 104] Effectiveness data are described in Table 80 in appendix. Based on findings in the chapter on the clinical effectiveness, estimates reported in De Vries et al.[99] are realistic. However, there is no evidence on risk ratios of simvastatin plus ezetimibe in primary prevention.

The annual cost of simvastatin (40 mg) in the study by De Vries et al. was lower than in Belgium (€ 7.3 compared to € 74.39),[99] but including cost of monitoring, annual total cost is comparable to Belgium.

Annual cost of simvastatin (20mg) and ezetimibe (10mg) in the study of Mihaylova et al.[104] is more comparable (£ 434.35 compared to € 592.23, see Table 81 in appendix) and will be higher when the generic alternative will become available in mid-2019 in Belgium (£ 434.35 compared to €182.95).

Results and discussion

De Vries et al.[99] concluded that, by taking into account real world adherence, statin was cost-effective compared to no treatment for type 2 diabetes patients aged 55 years and more regardless risk level at a WTP threshold of € 20 000/QALY. For type 2 diabetes patients aged between 45 and 55 years at diagnosis, statin treatment was only cost-effective from a 10-year CHD threshold of ≥ 6%. For type 2 diabetes patients aged less than 45 years

old, statin was not cost-effective except if the CHD risk was high or very high. Because annual statin costs in this study was much lower than in Belgium, the ICER in Belgium is expected to be higher but univariate sensitivity analysis showed that even with an annual statin cost of € 100 instead of € 7.3, statins remained cost-effective at a threshold of € 20 000/QALY (without stratification by age and risk level), with an ICER of € 5547/QALY (instead of € 2245/QALY in the base case).

The study of Mihaylova et al.[104] concluded that high-intensity statins were more cost-effective than simvastatin and ezetimibe for patients with CKD. This was nevertheless based on high combination costs compared to current costs in Belgium but will be more comparable in mid-2019 (availability of generic in Belgium). The ICER of high-intensity statins compared to no treatment ranged between £ 12 700 and £ 36 300 according to the 5-year CVD risks (<10%; 10-20%; ≥20%) and the annual statin cost (UK £18.25 – £401.5).

Table 21 – Results for patients with diabetes or chronic kidney disease

<table>
<tr><th></th><th>ICER</th><th>Sensitivity analysis</th><th>Conclusion</th></tr>
<tr><td>De Vries 2014[99]</td><td>
Base case: €2 245/QALY

Stratified by age and risk:
<table>
<tr><th>Age group</th><th>Level of risk*</th><th>QALYs 1.000 patients</th><th>Costs per 1.000 patients (€)</th><th>ICER</th></tr>
<tr><td rowspan="5"><45</td><td>Very low-risk</td><td>-8</td><td>€814 012</td><td>ICER not calculated (negative QALYs)</td></tr>
<tr><td>Low-risk</td><td>-3</td><td>€789 256</td><td>ICER not calculated (negative QALYs)</td></tr>
<tr><td>Medium</td><td>11</td><td>€738 926</td><td>€66 537/QALY</td></tr>
<tr><td>High-risk</td><td>43</td><td>€689 576</td><td>€16 085/QALY</td></tr>
<tr><td>Very high-risk</td><td>77</td><td>€634 993</td><td>€8 223/QALY</td></tr>
<tr><td rowspan="3">45-55</td><td>Very low-risk</td><td>9</td><td>€758 216</td><td>€88 440/QALY</td></tr>
<tr><td>Low-risk</td><td>49</td><td>€674 895</td><td>€13 828/QALY</td></tr>
<tr><td>Medium</td><td>75</td><td>€623 327</td><td>€8 345/QALY</td></tr>
</table>
</td><td>
Tornado diagram shows that the efficacy of the statins, the baseline risk for CHD and stroke, and the adherence rates have a large effect on the outcome of the cost-effectiveness.

One-way sensitivity analyses:

Statin costs: with an annual cost of €7.3 (basecase), the ICER is €2245/QALY; with an annual cost of €100, the ICER is €5547/QALY.
Reduction of the time horizon from 10 to 5 years: €12.424 per QALY
Full adherence: €1.534/QALY
Changing the assumptions on the adherence rate after year 3 does have a low effect on cost-effectiveness

</td><td>“With the adherence rates seen in practice, it can be concluded that treating all patients younger than 45 years with type 2 diabetes at diagnosis with statins for primary prevention is not cost-effective. For patients aged between 45 and 55 years at diagnosis, statin treatment is cost-effective except when the 10-year risk for CHD is as low as 6%. For the other patients, statin treatment is expected to be cost-effective”</td></tr>
</table>

	High-risk	96	€559 641	€5 810/QALY
	Very high-risk	145	€486 131	€3 353/QALY
55-65	**Very low-risk**	43	€638 881	€14 824/QALY
	Low-risk	61	€618 594	€10 119/QALY
	Medium	193	€432 890	€2 245/QALY
	High-risk	197	€382 633	€1 939/QALY
	Very high-risk	453	€276 148	€609/QALY

** The United Kingdom Prospective Diabetes Study (UKPDS) risk engine was used to estimate the patients' 10-year risks for CHD and stroke.*

Definition of risk category:

- For <45 years old

	10-year risk for CHD	10-year risk for fatal CHD	10-year risk for stroke	10-year risk for fatal stroke
Very low-risk	3%	1%	1%	0%
Low-risk	6%	1%	1%	0%
Medium	9%	3%	1%	0%
High-risk	13%	4%	2%	0%
Very high-risk	16%	6%	3%	1%

The acceptability curve (threshold of €20.000 per QALY)

- 100% probability that statin treatment is cost-effective for the average 60-year-old patient
- <15% probability that it is cost-effective for the average 40-year-old patient

- For 45-55 years old

	10-year risk for CHD	10-year risk for fatal CHD	10-year risk for stroke	10-year risk for fatal stroke
Very low-risk	6%	2%	1%	0%
Low-risk	10%	4%	2%	0%
Medium	15%	6%	3%	0.5%
High-risk	20%	7%	4%	0.5%
Very high-risk	26%	10%	5%	1%

- For 55-65 years old

	10-year risk for CHD	10-year risk for fatal CHD	10-year risk for stroke	10-year risk for fatal stroke
Very low-risk	6%	3%	3%	1%
Low-risk	10%	4%	3%	1%
Medium	21%	11%	6%	1%
High-risk	27%	13%	7%	1%
Very high-risk	35%	24%	9%	2%

Mihaylova 2016[104]

In the base-case cost-effectiveness analysis, the use of simvastatin plus ezetimibe for about 5 years in SHARP is projected to result in net costs of £30 500 to £39 600 per QALY across risk groups and £13 000 to £43 300 per QALY across CKD stages

Base-case scenario (Simvastatin + Ezetimibe)

		QALY gained	Additions cost (£) of treating end-stage renal disease	Net cost per QALY
By 5-year risk of CVD at start of treatment*	**<10%**	0.06	£1 090	£39 600/QALY
	10%-<20%	0.08	£1 400	£30 500/QALY
	>=20%	0.05	£810	£33 300/QALY
By CKD stage at start of treatment	**3**	0.13	£440	£13 000/QALY
	4	0.11	£1 370	£22 400/QALY
	5	0.04	£840	£43 300/QALY
	On dialysis	0.05	£1 100	£42 700/QALY

**The cardiovascular risk was determined using a Cox proportional hazards model based on the following variables: Gender, Ethnicity, Smoking status, diabetes status, Type of renal disease, and Systolic blood pressure, Albumin, Hemoglobin, Total cholesterol, HDL-cholesterol, and Urinary ACR levels.*

- The cost-effectiveness of simvastatin plus ezetimibe was very sensitive to drug price
- Full adherence with simvastatin plus ezetimibe would result in only a slight reduction in ICER (larger treatment benefits and additional treatment costs).

"Simvastatin plus ezetimibe prevented atherosclerotic events in SHARP, but other less costly statin regimens are likely to be more cost-effective for reducing cardiovascular risk in CKD "

Comparison between base-case scenario and High-intensity statin regimens

		Simvastatin + Ezetimibe	High-Intensity statins[ff]	
			UK £219-£401.5 (£0.60-£1.10/day)	UK £18.25-£36.5 (£0.05-£0.10/day)
By 5-year risk of CVD at start of treatment	<10%	£39 600	£30 900-£36 300	£17 300-£18 100
	10%-<20%	£30 500	£24 800-£28 400	£15 800-£16 300
	>=20%	£33 300	£25 300-£30 200	£12 700-£13 400
By CKD stage at start of treatment	3	£13 000	£9 100-£11 500	£3 100-£3 400
	4	£22 400	£18 000-£20 800	£11 100-£11 500
	5	£43 300	£33 400-£39 500	£17 900-£18 800
	On dialysis	£42 700	£34 000-£39 400	£20 100-£20 900

Note: CHD = Coronary heart disease; CVD: Cardiovascular disease; CKD: Chronic kidney disease; QALY: Quality-adjusted life year; CE: cost-effectiveness; SHARP: Study of Heart and Renal Protection.

[ff] Projected net costs per QALY of 5-year LDL Lowering

5.5.3 *'Polypills' compared to plain statins, antihypertensive guidelines and current practice*

Baseline population and study characteristics

Two studies on *'polypills'* have been selected.[100, 101] Description of the studies' populations and characteristics can be found in Table 82 and Table 83 in appendix.

In the two studies, people at the beginning of the modelling were aged 40 years or older. Their baseline characteristics nevertheless differed because the baseline population were persons already on treatment in the study of Jowett et al.[101] while only persons not on medication were considered in the study of Ferket et al.,[100] which impacted the way the effectiveness was assessed. The time horizon also differed (10 years vs. lifetime). The impact of different timeframes was nevertheless not tested in the sensitivity analysis of these studies.

The cardiovascular risk was assessed by the Framingham equation in the study of Jowett et al.[101] and the QRISK score in the study of Ferket et al.[100]

Intervention and comparators

The type of polypill investigated differed (see Table 83 in appendix). In both studies,[100, 101] polypill use was compared to specific guidelines and current practice. In the study of Jowett et al.,[101] the current practice corresponded to the treatment already taken by the patients (as stated above, people without treatment were excluded) and the strategy *'optimal guidelines'* considered that additional drugs were added up to reach the target systolic blood pressure of 140mmHg.

In the study of Ferket et al.,[100] current practice corresponded to no primary prevention program and different guideline strategies were considered (statin and/or antihypertensive drugs from different CVD risk threshold at 10 years, i.e. 10% and 20%).

In the Belgian market, only two of those combination pharmaceuticals for the primary prevention of CVD exist.[gg] Their compositions are not the same as those included in the studies. Therefore, transferability of these studies to the Belgian context is limited.

Outcomes and costs data

Both studies took into account population adherence. Additionally, the study of Ferket et al. considered the adverse effect of statin on diabetes while no adverse events were considered in the study of Jowett et al.[101] (see Table 84 in appendix).

It should also be noted that the characteristics of the baseline population influenced the effectiveness assessment because in the study of Jowett et al., no risk reduction due to statin was for example applied if the patient was already using a statin as usual care (see Table 85 in appendix).

(Over)optimistic assumptions were also made in both studies concerning the polypills, i.e. the effects of the separate drugs were assumed additive, which remains unproven. Moreover, in terms of QALYs, the disutility for taking a pill every day, an important parameter influencing conclusions, was only taken into account in the study of Ferket et al. (see Table 85 in appendix).

Concerning the annual cost for a polypill, Jowett et al.[101] based their estimations on the annual cost of Trinomia® (i.e. £ 171, see Table 86 in appendix). In Belgium, the lowest annual cost of Trinomia®[hh] (based on one pill per day) is lower, i.e. € 140.97 (see Table 87 in appendix). The total annual cost including costs of monitoring is lower in Belgium (i.e. € 191.06 versus £ 230.25, also based on one pill per day).

[gg] Association 1: acetylsalicylic acid, atorvastatin and ramipril; Association 2: atorvastatin, perindopril and amlodipine.

[hh] The composition of the polypill Trinomia® available in Belgium is different from the polypills used in the article (acetylsalicylic acid (100 mg), atorvastatin (20 mg), ramipril (5 mg)).

In the study of Ferket et al.,[100] the annual cost of the polypill is higher than in Belgium (£ 382.64 in the study of Ferket et al. versus € 177.62 in Belgium[ii]) as well as the total annual cost (see Table 86 in appendix).

Results and discussion

Results differed between studies and are shown in Table 22. The study of Jowett et al.[101] was more positive than Ferket et al.[100] concerning a polypill and concluded that a polypill may be considered as a cost-effective strategy in most people aged 50 and over with high cardiovascular risk on treatment. It should be emphasized that this conclusion is only applicable to the baseline population, i.e. high-risk patients that are already under treatment. Moreover, in this study, the effects of the separate drugs was assumed additive, no disutility for taking a pill every day was considered, and adverse events were not taken into account.

In the study of Ferket et al.[100], the base-case analysis showed that using old guidelines, i.e.:

- statin from a 10-year total CVD risk of 20%,
- and antihypertensive medication for patients with systolic blood pressure (SBP) ≥ 140 mm Hg and a 10-year CVD risk of 20% or with SBP ≥ 150 mm Hg regardless of risk,

was the most cost-effective strategy (at threshold of £ 20 000/30 000/QALY). Nevertheless, they also highlighted that with an annual cost of the polypills inferior to £ 240, polypills from 60 years old (regardless of risk) was the optimal strategy under the additive effect assumption). Finally, they also showed that the disutility for taking a pill every day has an important impact on results and that usual care could become the optimal strategy in scenarios with a higher disutility.

In conclusion, polypills seems to be considered as cost-effective at UK threshold of £ 20 000/30 000 only if the prices are low (e.g. <£ 240), if the assumption of an additive effect of drugs would be confirmed and if the fact that taken a polypill every day has limited impact on the quality of life. However, an additive effect (or even a multiplicative effect) has never been proven. Therefore additional studies are needed to accept such an assumption before concluding on the cost-effectiveness of polypills.

[ii] The composition of the polypill Trinomia® used in Belgium is different than the polypills used in the article (acetylsalicylic acid (100 mg), atorvastatin (20 mg), ramipril (10 mg)).

Table 22 – Polypill results

<table>
<tr><th></th><th>ICER</th><th>Sensitivity analysis</th><th>Conclusion</th></tr>
<tr><td>Jowett 2017[101]</td><td>
For men:
<table>
<tr><th></th><th></th><th>ICER (£/QALY) (Efficiency frontier)</th><th>Probability cost-effective at £20 000/QALY</th><th>ICER Polypill vs current practice</th></tr>
<tr><td rowspan="3">40-49</td><td>Current practice</td><td>-</td><td>0%</td><td></td></tr>
<tr><td>Optimal care</td><td>604</td><td>41%</td><td></td></tr>
<tr><td>Polypill</td><td>18 057</td><td>59%</td><td>9 166</td></tr>
<tr><td rowspan="3">50-59</td><td>Current practice</td><td>-</td><td>0%</td><td></td></tr>
<tr><td>Optimal care</td><td>182</td><td>0%</td><td></td></tr>
<tr><td>Polypill</td><td>6 466</td><td>100%</td><td>2 897</td></tr>
<tr><td rowspan="3">60-69</td><td>Optimal care</td><td>-</td><td>0%</td><td></td></tr>
<tr><td>Current practice</td><td>Dominated</td><td>0%</td><td></td></tr>
<tr><td>Polypill</td><td>4 791</td><td>100%</td><td>698</td></tr>
<tr><td rowspan="3">70-74</td><td>Optimal care</td><td>-</td><td>9%</td><td></td></tr>
<tr><td>Current practice</td><td>Dominated</td><td>0%</td><td></td></tr>
<tr><td>Polypill</td><td>5 068</td><td>91%</td><td>33</td></tr>
<tr><td rowspan="3">75+</td><td>Optimal care</td><td>-</td><td>69%</td><td></td></tr>
<tr><td>Current practice</td><td>Dominated</td><td>31%</td><td></td></tr>
<tr><td>Polypill</td><td>Dominated</td><td>0%</td><td>Dominant</td></tr>
</table>
For women:
<table>
<tr><th></th><th></th><th>ICER (£/QALY) (Efficiency frontier)</th><th>Probability cost-effective at £20 000/QALY</th><th>ICER Polypill vs current practice</th></tr>
<tr><td rowspan="3">40-49</td><td>Current practice</td><td>-</td><td>0%</td><td></td></tr>
<tr><td>Optimal care</td><td>2 994</td><td>94%</td><td></td></tr>
<tr><td>Polypill</td><td>33 585</td><td>6%</td><td>21 798</td></tr>
<tr><td rowspan="3">50-59</td><td>Current practice</td><td>-</td><td>0%</td><td></td></tr>
<tr><td>Optimal care</td><td>950</td><td>46%</td><td></td></tr>
<tr><td>Polypill</td><td>18 811</td><td>54%</td><td>9 696</td></tr>
<tr><td rowspan="3">60-69</td><td>Current practice</td><td>-</td><td>0%</td><td></td></tr>
<tr><td>Optimal care</td><td>1 304</td><td>2%</td><td></td></tr>
<tr><td>Polypill</td><td>10 730</td><td>98%</td><td>5 667</td></tr>
<tr><td rowspan="3">70-74</td><td>Current practice</td><td>-</td><td>0%</td><td></td></tr>
<tr><td>Optimal care</td><td>2 105</td><td>0%</td><td></td></tr>
<tr><td>Polypill</td><td>4 245</td><td>100%</td><td>2 797</td></tr>
</table>
</td><td>
See Probability cost-effective at £20 000/QALY.

“Polypill had a high probability (over 90%) of being cost-effective at a £20 000 (€22 500/QALY) threshold for men except for the youngest and oldest sub-groups. There was much more uncertainty in the results for women, with only the 60-69 and 70-74 sub-groups having a high probability of the polypill being the most cost-effective option.”

“Result was highly sensitive to cost of a polypill, take up of this treatment and potential effectiveness in reducing CV risk.”
</td><td>
“A polypill strategy may be a cost effective means to improve primary prevention in most people aged 50 and over with high cardiovascular risk on treatment, as long as the cost of a polypill is sufficiently low.”
</td></tr>
</table>

	75+	**Current practice**	-	0%	
		Optimal care	1 606	63%	
		Polypill	4 131	37%	1 870

Ferket 2017[100]

	ICER	% cost-effective Threshold of £20 000	% cost-effective Threshold of £30 000
Current practice	-	36%	28.40%
Cardiovascular risk assessment scenarios			
Old guidelines	£11 797/QALY	29%	24.60%
Current guidelines	Extended dominance	22.60%	19%
Alternative guidelines	Dominated	9%	10.20%
Polypill scenarios			
60+	£39 945/QALYs	2.80%	12.40%
55+	Dominated	0.40%	3.20%
50+	Dominated	0.20%	1.60%
45+	Dominated	0%	0.40%
40+	Dominated	0%	0.20%

Sensitive Analysis

Results were sensitive to:

- The disutility of daily pill use: Current practice or alternaive guidelines scenario could become the optimal option according to the assumptions and the threshold (£20/30 000)
- The risk of developping diabetes
- The prices of polypill, statin and anti-hypertensive drugs:
  - Polypill starting at age 60 becomes the optimal strategy with an annual polypill price below £240 (and cost-saving below £60.
  - Current practice becomes the optimal strategy with an annual price of statin above £100.

A periodic risk assessment with the prescription of preventive (statin and/or SBP) drugs from a 10-year risk of 20% was most cost-effective option.

"Periodic risk assessment with lower risk thresholds to initiate preventive drugs is unlikely to be cost-effective. A population approach with the polypill would become cost-effective if drug prices were reduced."

5.5.4 Summary of results

This review of additional primary studies (see section 5.5) confirmed the previous results found in the previous economic systematic reviews: outcomes of cost-effectiveness analyses of statin therapy are sensitive to the patient risk level, age and gender, to the statin price, and the presence of conflict of interests. The update with more recent primary studies additionally showed that results were also sensitive to the adverse events (if taken into account), patient preferences for taking a pill daily, and above all, patient adherence. Based on a scenario of full adherence and generic prices, results went in favour of statin strategies, even at low risk threshold:

- treating all men aged 45 to 74 years old and women aged 55 to 74 in the study of Heller et al.[103],
- treating all people aged 75 years old and more in the study of Odden et al.[106],
- treating all people with a SCORE thresholds of 1.1–2.5% in the study of Romanens et al.[108]

It should nevertheless be noted that the quality of these studies can be questioned: poor evidence from the literature on the use of statins in patients over 75 in primary prevention, lower annual costs used and potential conflict of interests concerning the study of Odden et al.[106] and analysis based on unrealistic assumptions in the study of Romanens et al.[108], as described in section 5.5.1.

By taking into account real world adherence, ICERs were less favourable and discrepancies were found between studies concerning the optimal risk threshold:

- treating with high-intensity statins from an ASCVD 10-year CVD Risk ≥ 5% (intermediate risk) for people aged 40 to 75 years old in the study of Shiffman et al.,[102]
- treating patients from an ASCVD 10-year CVD Risk ≥ 4% (with a WTP threshold of €50 000/QALY) or ≥ 7.5% (with a WTP threshold of €20 000/QALY) in the generic scenario of Pandaya et al.,[105]
- treating patients aged ≥ 55 years old for men and ≥ 60 years old for women if the 10-year CHD risk is ≥ 20% in the study of Aarnio et al.[107] (estimated by the FINRISK risk function, while a 10% CHD FINRISK risk already correspond to a 10-year CVD risk of around 19% with the ASCVD risk estimator according to the authors),
- treating patients with type 2 diabetes aged between 45 and 55 years if the 10-year risk for CHD is ≥ 6% and treating all patients with type 2 diabetes aged ≥ 55 years old regardless risk level in the study of De Vries et al.,[99]
- treating patients with CKD is more cost-effective with high-intensity statins than simvastatin and ezetimibe in the study of Mihaylova et al..[104]

Again, some parameters likely to reduce the ICERs, in favour of statins have been highlighted in these studies (see previous section and Table 23) and four studies seemed to have potential conflicts of interests (Aarnio et al. ,[107]Shiffman et al. ,[102]De Vries et al.[99] and Mihaylova et al.[104]). Statin price is a key driver of cost-effectiveness results and prices were lower in most of these studies,[99, 102, 104] compared to Belgium and therefore, even if adherence was taken into account, the ICER rates were better than what we could observe currently in Belgium. In term of total annual costs, Aarnio et al.[107] and the generic scenario of Pandaya et al.[105] are the most transferable studies. Results from Mihaylova et al.[104] will be more transferable in mid-2019 when generic alternatives for Inegy® will be available on the Belgian market.

One study shows differences in cost-effectiveness of statin in primary prevention between high- and moderate-intensity statin but costs were under-estimated in this study.[102] Further research is needed to conclude on the cost-effectiveness of statin in function of its intensity (the difference in effectiveness is only based on one trial, see section 4.5).

Concerning polypills, because the effects of statins and antihypertensives drugs were assumed additive in these models (overoptimistic assumption), no conclusion can be drawn and additional evidence is needed.

Table 23 – Presence of parameters that are likely to reduce the ICER in favour of statins

	Aarnio 2015[107]	Odden 2015[106]	Pandaya 2015[105]	Shiffman 2016[102]	Heller 2017[103]	Romanens 2017[108]	De Vries 2014[99]	Mihaylova 2016[104]	Jowett 2017[101]	Ferket 2017[100]
Conflict of interest	X	x		x			x	x		
Unrealistic model / course of the disease						x				
"No treatment" not in the comparators		x	x		x					
Lifetime horizon			x							x
Adherence not taken into account		x			x	x				
Adverse events (AE) not considered	x					x			x	
Effectiveness parameters not in line (overoptimistic) with the evidence found in the clinical chapter		x		x					x	x
Disutility for taking a statin pill every day not included	x	x				x		x	x	
Lower annual total cost than in Belgium		x		x	x		x	x		

5.6 Conclusions for the cost-effectiveness of statins in primary prevention of cardiovascular events

Even if no optimal risk threshold can be recommended based on these studies, the following conclusions can be made:

- before considering statin therapy in primary prevention, other interventions should be considered (e.g. lifestyle modification, stopping smoking, change in CVD risk factors…) and the patient should be informed on the importance of these life style modification,
- it seems important to assess the CVD risk before deciding to start statin therapy,
- for the decision to start statin therapy, information should be given to the patient on the necessity to be adherent to the treatment and the patient's acceptance to take a pill every day should also be assessed,
- even if no optimal risk threshold can be recommended, there is an agreement that statins are cost-effective in primary prevention for high risk patients, but more uncertainties remained on the cost-effectiveness of statin in primary prevention for intermediate and low risk patients,
- diabetic patients and patients with CKD are considered as higher risk patients and therefore, statins are likely to be more cost-effective for this specific population,
- based on one RCT only, cost-effectiveness seems to be different in primary prevention between high- and moderate-intensity statin therapy but further evidence is needed to confirm this,
- there is little and inconclusive evidence about the clinical effectiveness of statin use in primary prevention in patients aged over 75 and therefore no conclusion on the cost-effectiveness of statins for this group of patients can be made.

6 SUMMARY AND DISCUSSION

6.1 Scope of this Health Technology Assessment

Cardiovascular disease (CVD) remains a leading cause of morbidity and mortality, and despite improvements in CVD outcomes,[1] preventing CVD events remains important.

Taking statins is only an option for the prevention of CVD after prior interventions to tackle an unhealthy lifestyle (e.g. poor quality diet, physical inactivity, smoking) and obtain better blood pressure levels and adequate diabetes control have been undertaken. When these interventions give no satisfactory results, reducing increased levels of risk factors for CVD such as increased lipid levels through the use of statins becomes an option.[1] Statins can reduce the risk of CVD-associated morbidity and mortality through their effects on lipid levels,[2] and possibly other mechanisms (pleiotropic effect).

The aim of this Health Technology Assessment (HTA) report is to assess the potential of statins in the primary prevention of CVD events, which, in this report, is defined as the absence of a prior CVD event. Technically this term is incorrect, since a real primary prevention would be the prevention of the development of precursors for CVD events, such as atherosclerosis.

However, while some of the risks are modifiable through a healthier lifestyle or a timely blood pressure control, some of the other risk factors (age and gender) are not. **Therefore, we use in this report the term *'primary prevention'* as the prevention of a first CVD event.**

6.2 Historical and current use of statins in Belgium

6.2.1 History of the marketing of statins in Belgium

The first statin introduced was simvastatin, marketed since the middle of the nineteen nineties. Very quickly other statins were developed and marketed in Belgium during the remainder of the previous century. One statin (cerivastatin) was withdrawn from the market in 2001 because of safety concerns.

Because of their high price, the reimbursement of statins was initially restricted to selected patients at high risk. Since 2003, and due to patent expirations, generic alternatives became increasingly available leading to a sharp decline of prices of those statins that went out of patent. As a consequence, the necessity for a strict control of the reimbursement of statins diminished and reimbursement rules were softened over the years. This led to a marked increase in the volumes sold.

There are currently five statins on the Belgian market, each coming in different dosages, with varying intensity i.e. their potential to reduce LDL-C.

More recently, combination products came to the market that combine a statin with another pharmaceutical in one tablet.

6.2.2 Global statin use in Belgium

A detailed description of statin use, both in terms of number of users as in volumes, and the cost of it for the reimbursement authorities and for the individual user can be found in great detail in chapter 3.

It should be emphasised that those numbers are about statin use in both primary and secondary prevention, as it is impossible to make the difference in these global data from RIZIV – INAMI.

The number of users has increased over the years from around 400 000 in 2002 until approximately 1 500 000 in 2012 (about 13% of the Belgian population, and 40% of the population aged 40 and over). Since then the number has stabilized. However, as we show in the individual data this stabilisation does not mean that these are always the same users. Stabilisation just means that as many users begin as other users quit using statins.

Combination products started to be used in 2008. The number of its users is increasing but still marginal (slightly over 30 000 in 2016). It is unclear to what extend those combination products are also used in primary prevention.

The volumes of statins sold, expressed as defined daily dose (DDD) increased significantly from around 100 million DDD in 2002 to around 500 million DDD in 2016. However, the relative contribution of each of the different statins varies over the years as is shown in section 3.6.1. In recent years the use of simvastatin and pravastatin is decreasing while especially the use of atorvastatin is increasing.

The total yearly cost for statins has increased from € 170 million in 2002 and peaked in 2011 at over € 270 million. Both due to the stabilizing of the number of users and decreasing prices it came back down to around € 160 million in 2016.

The reimbursement cost for the social security followed a similar pattern: around € 160 million in 2002, almost € 240 million in 2011 and € 130 million in 2016.

The volume of combination products containing a statin increased from less than 5 million DDD in 2009 to over 11 million DDD in 2016. The total cost for combination products containing a statin increased from € 9 million in 2009 to € 21 million. Reimbursement cost increased likewise from € 7 to € 17 million. Again, it is unknown to what extend those combination products are also used in primary prevention.

6.2.3 Individual statin use in Belgium

For the analysis of the use of statin by individuals in Belgium we used the permanent sample (EPS). This is a sample of 1/40 of the inhabitants in the compulsory health care insurance system (1/20 in individuals aged 65 and above) and for this population the most important data on health care consumption are permanently coupled. To test whether this sample gives an accurate impression of the global statin use we extrapolated the number of statin users and volumes of statin use to the total population. These numbers correspond well to the global numbers obtained from RIZIV – INAMI as is shown in section 3.2.2.

In the analysis of statin use since 2002, we observe that the number of new users increases according to changes in statin prices and reimbursement rules. It has been seen in 2004, when the generic simvastatin became available, and a second time in 2008 when a second price reduction occurred, and again in 2012 when the atorvastatin generic alternative came to the Belgian market. In 2012, this resulted in an increase of atorvastatin users and a decrease of simvastatin users. Therefore, we can expect an increase in new users of rosuvastatin in 2018 with the newly available generic alternative and the important price reduction.

We observe a mean age of 68 year for all users and 62 year for new users. Patients are using mainly medium- and high-intensity statin doses. One third of patients are taking concomitant antidiabetic drugs and two-thirds are taking generic drugs. The mean time of use is 491 days with approximately 510 DDD. This means approximately 1 DDD/day. For estimated secondary prevention, which represents 12% of the patients, the majority of patients are between 60 and 80 years old. Their mean time of use is 518 days with on average 766 DDD. This results in 1.5 DDD/day.

The average out-of-pocket cost of a statin for an individual patient was about € 30/year in 2016. Some packagings are cheaper such as low doses (*atorvastatin* 10mg or *simvastatin* 20mg), but some are more expensive such as high doses (*simvastatin* 80mg) or drugs without an available generic alternative in 2016, such as *rosuvastatin*, or associations of statins with other drugs. In 2018, the average out-of-pocket cost of a statin for an individual patient remains about € 25/year for big packagings. However, lower dosages such as *atorvastatin* 10mg and *rosuvastatin* 15mg, the average out-of-pocket cost for an individual patient is < € 12/year.

Therapy adherence is rather bad. In regular new users, the mean time of use is 648 days with a consumption of 800 DDD. This corresponds to 1.24 DDD/day. The EPS shows that 28% of new users in 2014-2015 only had one purchase registered. This high proportion was challenged by some of our external experts because they stated that in some cases (for instance because of side effects) patients are sometimes advised to take only 1 statin every three days. Then, one big packaging might theoretically be sufficient for almost a whole year, while our definition of a new user was *'a user which did not purchase a statin during the previous 365 days'*. When we defined a single package user as *'an individual who did not purchase a statin since 2002, purchasing at least one packaging in a given year, and not purchasing a single packaging later'*, the results are very similar, as shown in section 3.13. Apart from this observation of individuals buying just one packaging, we observed that less than 50% of patients had a mean possession ratio of 80% or above, which we used as a threshold for adherence.

Also in previous studies adherence in real life was reported to be bad. In Belgium, it was shown that 65% of the statin users are non-adherent.[19] In the UK, it was shown that 40% of patients who received a prescription of statins in primary prevention never got a second prescription.[20] This is explained by the fact that the patient doesn't see immediate benefit and also by the media reporting side effects such as muscular pain. For patients with more than one statin prescription, it has been shown that 47% of patients in primary prevention discontinued statin treatment, and 28% of them never restarted.[21] In a Finnish registry, studying the adherence of new users of statins and after exclusion of one-purchase only patients, it is reported that 55% of new users are adherent.[22] In the review of Lemstra et al. the adherence in observational studies and randomized trials was compared. It was shown that 49% of patients are adherent at 1 year of follow up in observational studies, as compared with 90% in randomized trials.[23] This underlines the important differences between observational studies in real life compared to controlled randomized trials.

Factors associated with low adherence in our analysis for the years 2014-2015 are young age, GP prescribers, female gender and using statins for

primary prevention. Factors associated with good adherence are male gender, age group of 60 to 69 years, use of concomitant antidiabetic or cardiovascular drugs, and using atorvastatin.

It is difficult to predict the adherence to statin treatment. With the variables age, gender and diabetes, we calculated the 2-year risk of death (all-cause mortality) in Belgium for new users of statins in the years 2014-2015. With this estimated 2-year risk of death we classified patients according to three levels of risk. The patients with the highest level of mortality risk are those with the highest levels of adherence. It can be hypothesised that adherent patients have a higher burden of disease, and this could explain why adherence is associated with prescription by a specialist and with using statins at a higher intensity.

- The total number of statin users has been growing until 2012 but is stable since: about the same number quit using a statin as those who start, leading to a stable number of 1.5 million users each year in Belgium. But the number of new users of simvastatin is decreasing, while the number of new users of atorvastatin is growing.
- The estimated number of patients in secondary prevention is around 12% and is stable over the years.
- Slightly less than half of new users are regular users (adherent), and factors associated with low adherence are young age, GP prescribers and female gender.
- Patients with higher adherence are those with a higher 2-year risk of death (all causes).

6.3 Risk assessment

All current guidelines on the prevention of CVD in clinical practice recommend the assessment of CVD risk, because atherosclerotic CVD is usually the result of a number of risk factors, and prevention of CVD in a given person should be adapted to the global CVD risk: the higher the risk, the more intense the treatment should be.[1] In Belgium, the European Systemic Coronary Risk Estimation (SCORE) risk chart system is used to assess the individual risk of fatal CVD.[17] Figure 11 shows an example of the graphical representation of this risk estimate from a document/booklet which was widely distributed among Belgian physicians by the pharmaceutical companies. In the past electronic risk calculators have also been distributed by pharmaceutical companies, although it is unclear on what scale these were used.

Besides this simple assessment based on only a few parameters, other conditions are considered *'qualifiers for risk',* (such as physical inactivity, family history of premature CVD, triglyceride levels, diabetes, obesity, social deprivation etc.) i.e. they can increase the risk as assessed with the SCORE risk chart.

It is often discussed whether this Belgian SCORE should be used, or whether to European SCORE (low risk countries) should be used. In practice however, the differences are small.[115, 116] Currently, the SCORE model is being updated and in the coming months we may expect SCORE charts re-calibrated for all European countries separately and predicting total CVD events instead of only fatal CVD events.[117] There is also discussion about whether to use total cholesterol or LDL-C in the guidelines, but again, differences are marginal.

Figure 15 – Belgian SCORE risk chart

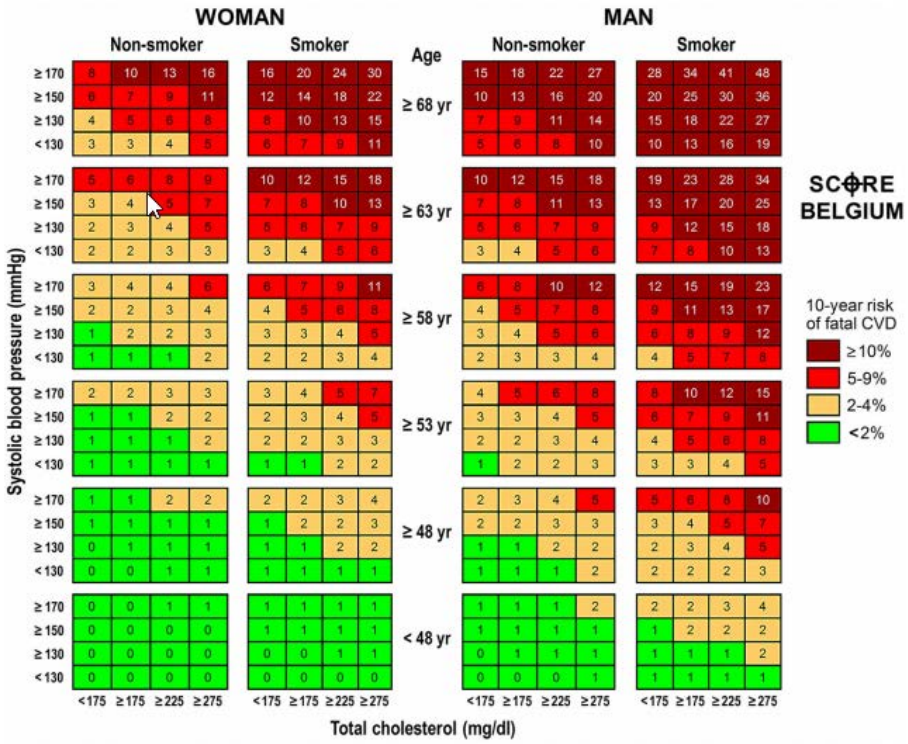


Fig. 1. The SCORE Belgium risk chart for 10-year cardiovascular mortality.

However, recently doubt was expressed about those risk estimates since these are largely based on historical cohorts such as the Framingham Heart Study that started in 1948, or historical European studies, while prevention, therapy and survival have improved since. A recent article by Yadlowsky et al. estimated from newer cohort data in the US that previous risk estimates overestimated cardiovascular risk by 20% on average across risk groups.[118] It is unclear whether the same is true for European countries.

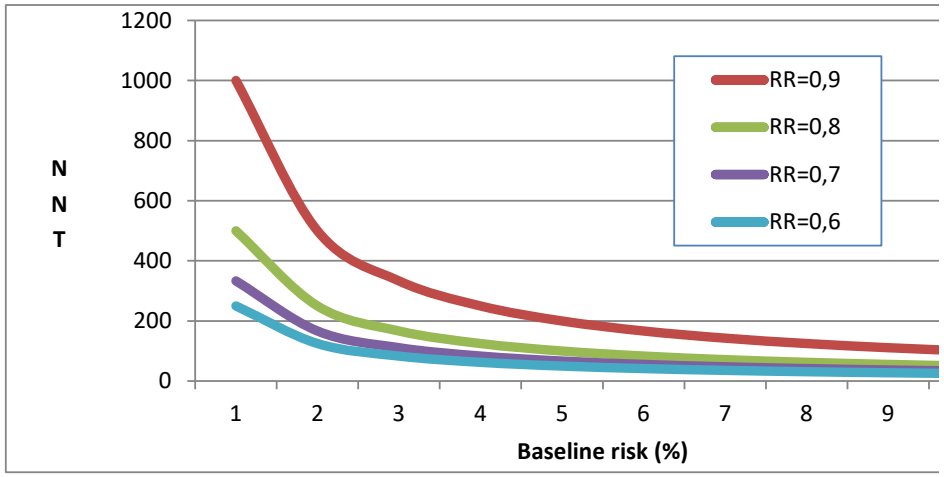
As shown in section 4.5, meta-analyses of RCT's have reported that primary prevention with statins reduces cardiovascular mortality, but with a number needed to treat (NNT) to prevent one cardiovascular death of 233 after 2 to 6 years in this low risk population.[2] The NNT varied in individual trials depending on factors such as the baseline risk of the population – individuals with the highest risk have the most to gain – and the duration of follow-up. Occurrence of adverse events appears to be low, but there are inconsistencies in meta-analyses, particularly regarding the occurrence of myalgia and diabetes.

The conversion of risk estimates into numbers NNT obviously depends on the estimated relative risk (RR) as a result of the intervention (depending also upon the intensity of the treatment), but is especially dependent upon the baseline risk. Figure 16 shows a theoretical example of baseline risks (for any outcome) running from 1 to 10 % and with RR of an intervention ranging from 0.6 to 0.9 (for any outcome chosen) which is in line with the RR point estimates observed in the selected systematic review,[2] and in our sensitivity analyses (see section 4.5). It clearly shows that the baseline risk is the main driver for the NNT. It should be noted that in this theoretical example, the x-axis could be any kind of risk (SCORE, risk for a CVD event, risk for re-intervention etc.).

To avoid one death due to CVD the meta-analysis found that 233 persons should be treated during 2 to 6 years. This NNT varied between the studies due to different baseline risks and different durations of the studies.

According to our theoretical example, a baseline risk of 5% according to the SCORE table and a 28% risk reduction for CVD death due to statin treatment would mean that 71 individuals should be treated to avoid one CVD death over 10 years. However at a baseline risk of 1%, 357 individuals should take statins to avoid this one CVD death over the same time period. In the meantime, those who will not benefit from the intervention are exposed to potential harms.

Figure 16 – NNT as a function of RR and baseline risk (theoretical example)



6.4 Efficacy and harms of statin use in primary prevention

6.4.1 Efficacy

In the systematic review by Chou et al. including 19 individual studies, statin use in primary prevention is associated with a reduced risk of overall and cardiovascular mortality, myocardial infarction, stroke, revascularization and composite CVD outcomes compared with placebo:[2]

- All-cause mortality: 15 trials; RR 0.86 [95% CI 0.80 to 0.93], I^2=0%, ARD -0.40%, NNT 250.
- CVD mortality: 10 trials; RR 0.72 [95% CI 0.59 to 0.88], I^2=38%, ARD -0.43% NNT 233.
- Fatal and non-fatal MI: 12 trials, RR 0.64 [95% CI 0.57 to 0.71], I^2=0%, ARD -0.81%, NNT 123.
- Fatal and non-fatal stroke: 13 trials, RR, 0.71 [95% CI 0.61 to 0.81], I^2=0%, ARD -0.38%, NNT 263.
- Revascularization: 7 trials, RR 0.63 [95% CI 0.54 to 0.72], I^2=8%, ARD -0.66%, NNT 152.
- Composite cardiovascular outcomes: 13 trials, RR 0.70 [95% CI 0.63 to 0.78], I^2 36%, ARD -1.39%, NNT 72.

In spite of the presence of risk of bias in some of the included studies, inclusion of secondary prevention patients in some trials, and early termination of three trials, the sensitivity analyses show that these results are nevertheless robust (see section 4.5.4). Therefore, the evidence was rated as good for all-outcomes, except for cardiovascular mortality, which was downgraded in the systematic review to moderate quality because of significant heterogeneity among studies.

A further sensitivity analysis performed by us, showed that the relative risks were lower (= better) for the high intensity treatment. However, this concerned mainly one single trial, the JUPITER trial with rosuvastatin from 2008.

Although this meta-analysis included the results of the recent (2016) large HOPE-3 trial (which accounted for 24% of the information for cardio-vascular mortality, see Figure 29 in appendix) and in spite of the fact that the effect of statin prevention did not reach statistical significance in that trial (RR=0.90 [95%CI: 0.72 to 1.11]), the findings are consistent with previous other high-quality systematic reviews of statins in primary prevention,[6, 7, 14, 36, 47, 50] as well as in secondary prevention.[91] Only one SR did not find statistically significant results for all-cause mortality (RR=0.91 [95%CI: 0.83; 1.01]).[30] The latter review had access to individual patient data which allowed to exclude individuals in secondary prevention. However, this was also the case in the CTT 2012 review in which a RR=0·91, 95% CI 0·85–0·97) for all-cause mortality was reported. In fact, the difference in results might relate to the proportion of cardiovascular deaths in deaths from all causes.[6]

Although the trials evaluated diverse patient populations (e.g., patients with hyperlipidaemia, diabetes, hypertension, early-onset cerebrovascular

disease, or elevated CRP levels), there was no evidence that the effect of statin prevention varied according to demographic and/or clinical characteristics (e.g. diabetes or renal dysfunction) of patients. In particular, benefits did not appear to be restricted to patients with severely elevated lipid levels, as similar effects were observed in subgroups stratified according to baseline total cholesterol or LDL-C level and trials that excluded patients with severe dyslipidaemia but included those who had other cardiovascular risk factors.[2] Similarly, trials that stratified participants according to a baseline global cardiovascular risk score reported similar relative risk estimates in those classified as higher or lower assessed risk.[52, 59, 76] This is consistent with the results of the CTT meta-analysis on individual data, which showed that in participants without a history of vascular disease, the proportional reductions in vascular and all-cause mortality were similar, whatever the baseline risk.[6]

Most of the trials included participants aged between 45 and 75 and none of the trials that enrolled participants older than age 75 years reported results in these specific subgroups. We found little evidence for the efficacy of statin use for primary prevention, neither for CVD morbidity, CVD mortality nor for all-cause mortality in individuals aged 75 years and older.[114, 119]

6.4.2 Harms

Statins are relatively safe and evaluating harms is not straightforward. In RCT's harms are poorly reported and moreover, RCT's are not powered to report those rare events. On the other hand, in observational studies the reporting might be biased. Therefore, figures on reported harms differ widely and are not consistent between studies (see section 4.6).

Those diverging results are caused by different study designs, different statistical measures (cumulative incidences, incidence/person-year, etc.) and especially by the different definitions and assessment methods used. In general the incidence of harms appears to be higher in observational evidence than in RCTs.

Muscle symptoms are difficult to quantify and are reported by 7% to 30% of patients taking statins. The symptoms are minor and disappear upon abandoning statin use. However, the precise increased incidence attributable to statin use is difficult to quantify because these symptoms are also very frequently reported by patients not taking statins and can be caused by the so-called *'nocebo effect'*.[53] More severe myopathy would occur in about 5 cases/10 000 but estimates vary (see section 4.6).

Mild myalgia with normal CK value ranges from 50-100/10 000 in 5 years in RCTs,[91] 70 – 290/10 000 persons in observational studies and registries,[90] to 100-500/10 000 in RCTs and 500-1000/10 000 in observational studies and clinical settings.[94]

Severe myopathy, myositis with CK elevation and rhadomyolisis are considered 'rare' by a consensus panel,[94] 5/10 000 over five years in RCTs by Collins et al.,[91] and 1-10/10 000 by Stroes et al.[90]

Numbers for diabetes as an unwanted side effect are equally divergent: 50-100/10 000 over five years in RCTs, [91] *'depends on population'*,[94] and 10/10 000 in Mach et al.[95] It is often claimed that diabetes as a side effect occurs mainly in individuals with so-called pre-diabetes.

For haemorrhagic stroke the numbers are: 5-10/10 000 over five years in RCTs, [91] *'unclear'*,[94] and *'no evidence for increased risk in individuals without cerebrovascular disease*'.[95]

6.5 Cost-effectiveness of statins in primary prevention

We first evaluated two systematic reviews. The first, relatively old, was a KCE report from 2007,[97] and the second was a NICE review from 2014.[14]

Then, a review of additional primary economic evaluations (see section 5.5) was performed and ten primary studies were selected.[99-108]

Discrepancies can be found in the results of cost-effectiveness studies and conclusions were mostly influenced by the following parameters:

- **The level of CHD/CVD risk, gender and age**: all these parameters must be taken into account during the decision process. The higher the risk, the more cost-effective statin therapy is. Statins therapy in primary prevention are more cost-effective in men than women at the same age and CVD risk level. The way the risk is assessed (QRISK2,

Framingham, SCORE, …) and the output used (CHD or CVD) also impacted results.

- **The interventions compared:** according to KCE guidelines on economic evaluation,[120] an intervention should be compared to all relevant alternatives. While statins were only compared to no treatment or current practice, other interventions such as smoking cessation programs should be considered. When other interventions than only statins are taken into account, statin is not the first strategy to consider. Indeed, lifestyle modification such as smoking cessations interventions should first be considered. Aspirin was also considered in the KCE model nevertheless recent evidence does not support aspirin in primary prevention anymore.
- **The price of statins**: the lower the treatment costs are, the more cost-effective statins becomeand the lower optimal risk threshold is. It is important to note that oldest studies used elevated prices for statin and conclusions from these studies are no longer relevant in the current context of "generic" products. Results from the review of primary studies performed in section 5.5 are more relevant.
- **Conflict of interest**: potential conflict of interest could explain differences in cost-effectiveness results. A study published in 2013(Catala-Lopez et al.[121]) showed that industry-sponsored studies have generally more favourable cost-effectiveness results for statins in primary prevention than non-sponsorded studies.
- **Lack of transparency in health economic modelling:** differences in methodology and model design are also a main cause of heterogeneity between studies.[122]
- **The adherence to the treatment**: non-adherence has negative impact on the ICER. In section 3.11 it was shown that compliance of younger and low risk patients is expected to be lower than in patients at higher risks.
- **Adverse events:** when adverse events are taken into account then the ICER is worse. However, the evidence on potential adverse events related to statin use is confusing.
- **Disutility of taking a daily medicine:** assumptions on disutility of taken a daily medicine impacted results. Other options could be envisaged for patients burdened by daily pill use which impact both their adherence and quality of life.

Even if no optimal risk threshold can be recommended based on these studies, the following conclusions can be made:

- before considering statin therapy in primary prevention, other interventions should be considered (e.g. lifestyle modification, stopping smoking, change in CVD risk factors…) and the patient should be informed on the importance of these life style modification,
- it seems important to assess the CVD risk before deciding to start statin therapy,
- for the decision to start statin therapy, information should be given to the patient on the necessity to be adherent to the treatment and the patient's acceptance to take a pill every day should also be assessed,
- even if no optimal risk threshold can be recommended, there is an agreement that statins are cost-effective in primary prevention for high risk patients, but more uncertainties remain on the cost-effectiveness of statin in primary prevention for intermediate and low risk patients,
- diabetic patients and patients with CKD are considered as higher risk patients and therefore, statins are likely to be more cost-effective for this specific population,
- based on one RCT only, cost-effectiveness seems to be different in primary prevention between high- and moderate-intensity statin therapy but further evidence is needed to confirm this,
- there is little and inconclusive evidence about the clinical effectiveness of statin use in primary prevention in patients aged over 75 and therefore no conclusion on the cost-effectiveness of statins for this group of patients can be made.

6.6 Applicability of the findings to Belgium

Although the trials and the economic evaluations evaluated diverse patient populations, the sensitivity analyses for efficacy showed that the results were robust. In particular, when studies with a substantial proportion of secondary prevention patients or restricted to high-risk patients (diabetes, presence of cerebrovascular disease) were excluded, the relative reduction of cardiovascular events remained consistent.

A second difficulty is that none of the trials included patients specifically on the basis of their CV risk. Nonetheless, it appears that the relative risk reduction is quite stable across baseline risks and depends mainly of the size of the reduction in LDL-C).[6]

There is also no evidence that the RR varies over the years of treatment. Therefore, it appears reasonable to multiply the RR obtained from the systematic review by the baseline risk of the patient to compute the absolute risk reduction obtained with statins.

Given similar RR estimates, the absolute benefit of statins prevention will be greater in patients at higher baseline risk. Individual baseline CV risk can be assessed first by clinical characteristics. Persons with documented CVD, type 1 or type 2 diabetes, very high levels of individual risk factors, and chronic kidney disease (CKD) are automatically at high total CV risk.[1]

For persons not presenting these specific clinical characteristics, the baseline CVD risk is computed on the basis of the SCORE taking into consideration potential *'qualifiers for risk'* (see section 6.3). The SCORE system estimates the 10-year cumulative risk of a fatal atherosclerotic event, whether heart attack, stroke or other occlusive arterial disease, including sudden cardiac death.[1] The SCORE data indicate that the total risk for a CVD event is about three times higher than the risk of a fatal CVD in men, and four times in women.[1]

Although the benefits of any preventive therapy accrue according to the risk of disease (greater benefit in higher-risk patients), the harms of therapy are distributed equally over the risk levels. Thus, persons at low risk have little chance to benefit but have an equal chance of harms and thus are more likely to suffer a net harm.

Most evidence regarding benefits and harms of statin therapy is available for ages 45 to 75 years, and in trials that did enrol participants older than age 75 results were not reported separately for those subgroups.

6.7 Who should receive statin-based primary prevention?

Although this health technology assessment is not a practice guideline, we repeat here some of the conclusions from the RIZIV – INAMI consensus conference in 2014.[5] New evidence in this HTA does not contradict these recommendations.

The evaluation of the risk is a task for the physician. The SCORE has to be considered as a guide to help the physician in planning preventive strategies with his patients and to manage the total risk. For each patient, the risk score should be interpreted within its unique context and by referring to underlying risk factors, life style, family history, socio-economic status and psychosocial risk factors.

In clinical practice, the prediction models (for example the SCORE model in Europe) are used to predict CVD risk in an individual patient and to guide decision making whether or not to start treatment. Almost no efficacy study included participants specifically based on such a risk prediction model.[5]

Statins can also be recommended in patients without prior CVD but who are at high risk. It is important that the treating physician determines individual risk and explains it to the patient in terms of number of individuals needed to treat to avoid an event.

In all cases, life-style and dietary measures have to be recommended and evaluated on a regular basis with the patient. These lifestyle modifications needed are in no way replaced by taking a statin.[5]

Some practice guidelines mention target values for LDL-C to determine whether the treatment dose with statins needs to be increased. These target values vary largely between practice guidelines and are not based on solid evidence. However, since there is considerable individual variability in the LDL-C response to dietary and drug treatment a tailored and individual approach to risk management might be advocated. The use of targets might

also enhance adherence and compliance through the physician-patient interaction.

It should also be repeated that most evidence is available for individuals aged between 45 and 75, and that evidence for other age groups is highly uncertain.

6.8 Limitations of the current evidence

Meta-analyses combine heterogeneous studies. This is a problem when evaluating the efficacy of a statin in an individual patient. Also *'primary prevention'* is ill defined. In the selected meta-analysis the definition is based on a simple clinical element; i.e. no prior clinical CVD. But how to handle patients with atherosclerosis (for example asymptomatic aortic or carotid stenosis) diagnosed with imaging techniques? The selected SR from Chou et al. included studies with patients with aortic or carotid stenosis. It also included some studies with a small number of patients with a previous clinical CVD event.

Statins have been studied in relatively young populations (average age lower than 60 years of age in most of the studies) and we do not have sufficient evidence in older patients (over 75 years).

The placebo controlled studies evaluating statins often include a pre-inclusion period with placebo. Studies comparing a low dose statin vs. a high dose often have a pre-inclusion period based on statins. In this case (like with patients having received statins before the inclusion in the study) it is impossible to evaluate side effects reliably, since the patients having had side effects previously are unlikely to be included in these studies.[5]

The ascertainment of harms in the studies is poor. The meta-analyses do not always analyse all side effects and they are often poorly reported. The use of a pre-inclusion period additionally induces an important bias. An evaluation of the benefit/harm ratio will include an evaluation of the magnitude of the effect of treatment, its side effects, the cost of treatment and societal choices. It also needs to address the concept of *'medicalisation'* of a population in relatively good health. Many of these elements have not been studied well or are difficult to quantify.

There is no evidence that the association of a statin with a fibrate has a greater efficacy compared to a statin alone in patients with type 2 diabetes mellitus.[5]

6.9 Overall conclusion

The decision to start with a statin treatment for primary prevention should be a cautious one, i.e. a decision that is made by an informed patient together with his/her physician. In a follow-up trajectory of this report we aim to develop a tool to aid this joint decision-making.

An individual considering taking a statin for primary prevention should be aware of the potential benefits and the potential harms. She/he should be aware that the first approach, before even considering a statin, is a healthier lifestyle. Furthermore, she/he should be aware that taking a statin is a long-term endeavour. Our data from Belgium show that current adherence to statin use is often substandard.

Finally, the patient should be aware that taking a statin is no guarantee for not having a future CVD event.

APPENDICES

APPENDIX 1. HISTORICAL AND CURRENT USE OF STATINS IN BELGIUM

Appendix 1.1. Subgroups analyses for Users and New users

Table 24 – Users and new users per statin per year in age [0-49] years (in thousand)

		2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
Simvastatin	Users	8,1	10,8	27,0	37,5	41,3	47,9	56,8	60,5	62,0	62,8	61,4	52,3	45,4	41,6	38,2
	New Users		4,9	19,5	19,6	19,5	22,6	28,2	27,0	26,6	26,1	24,9	18,2	15,7	15,4	14,3
	% New Users		45,0%	72,1%	52,2%	47,2%	47,2%	49,6%	44,7%	42,9%	41,5%	40,5%	34,8%	34,6%	37,0%	37,3%
Pravastatin	Users	7,8	8,2	8,6	9,4	9,0	9,1	8,6	9,0	8,7	8,1	7,9	6,3	5,9	5,1	5,0
	New Users		3,2	3,64	4,2	3,6	3,36	3,4	4,04	2,96	2,48	2,56	2,12	1,96	1,6	1,64
	% New Users		39,2%	42,1%	44,5%	39,8%	36,8%	39,7%	44,9%	33,9%	30,5%	32,3%	33,5%	33,1%	31,3%	33,1%
Fluvastatin	Users	1,9	3,5	3,2	2,4	1,2	1,2	1,2	0,8	0,8	0,6	0,4	0,5	0,4	0,3	0,2
	New Users		2,1	1,1	0,6	0,2	0,4	0,4	0,1	0,1	0,1	0,04	0,1	0,0	0,1	0,1
	% New Users		59,1%	34,2%	26,7%	20,7%	32,3%	35,5%	10,0%	14,3%	12,5%	9,1%	25,0%	0,0%	25,0%	50,0%
Atorvastatin	Users	25,2	24,4	24,3	22,0	20,0	18,9	21,2	20,5	20,6	18,8	24,7	28,4	31,2	34,4	34,7
	New Users		5,6	6,8	6,0	4,8	5,3	8,4	6,0	6,5	5,4	11,5	11,8	13,6	14,6	14,0
	% New Users		23,0%	28,0%	27,3%	24,2%	28,1%	39,9%	29,5%	31,7%	28,5%	46,6%	41,5%	43,8%	42,4%	40,4%
Rosuvastatin	Users			5,6	10,8	14,0	15,4	22,2	24,1	26,4	25,7	25,3	23,7	21,8	19,3	17,2
	New Users			4,8	5,1	5,6	5,5	10,6	8,0	8,4	6,7	6,8	6,1	5,6	5,1	5,0
	% New Users			85,1%	47,4%	40,3%	35,5%	47,5%	33,4%	31,7%	26,2%	27,0%	25,7%	25,9%	26,5%	29,3%
Associations	Users							0,7	1,7	2,0	2,0	2,0	2,2	1,8	1,5	1,7
	New Users							0,2	0,2	0,4	0,2	0,2	0,2	0,2	0,2	0,4
	% New Users							33,3%	11,6%	19,6%	12,2%	12,2%	10,9%	13,3%	10,5%	20,9%
Total	Users	43,0	46,9	68,8	82,1	85,5	92,6	110,7	116,6	120,5	118,0	121,8	113,4	106,4	102,3	97,0
	New Users		15,8	35,8	35,5	33,8	37,2	51,2	45,4	44,9	41,0	46,1	38,5	37,2	36,9	35,4
	% New Users		33,6%	52,1%	43,3%	39,5%	40,2%	46,3%	39,0%	37,3%	34,7%	37,8%	34,0%	34,9%	36,1%	36,5%

Figure 17 – Evolution of number of users (left) and new users (right) per statin and per year in age [0-49] years (in thousand)

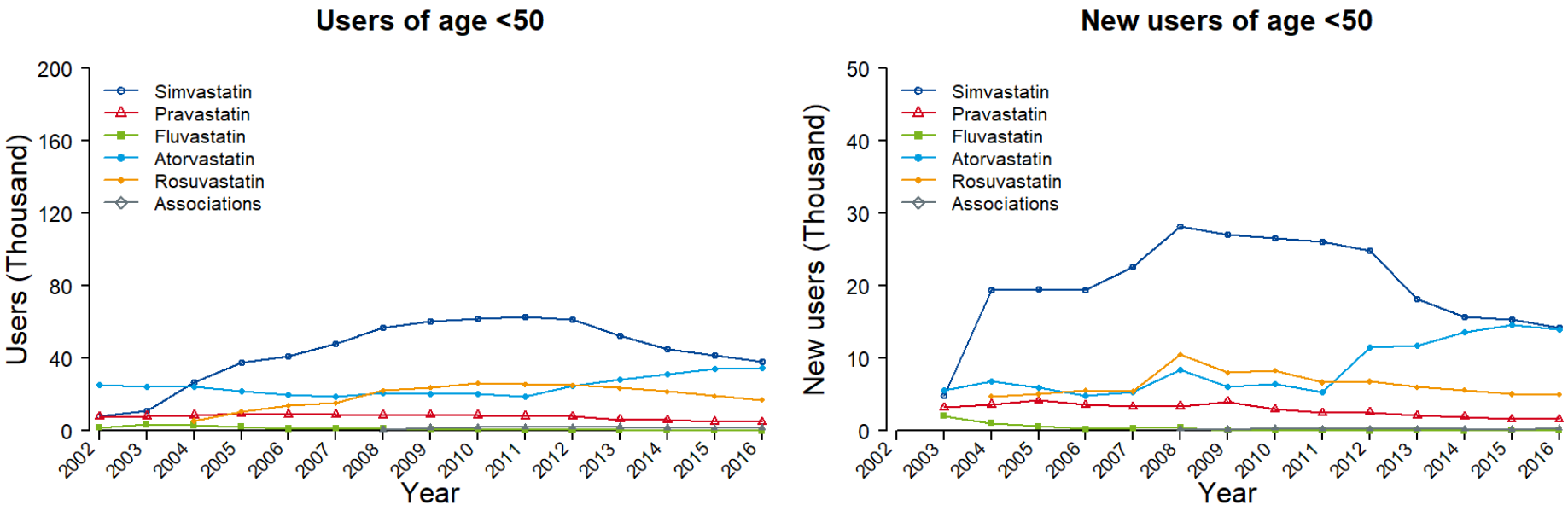


Table 25 – Users and new users per statin per year in age [50-59] years (in thousand)

		2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
Simvastatin	Users	17,9	25,0	56,8	81,2	91,6	99,6	118,2	126,8	130,6	137,6	135,2	120,7	112,3	105,6	97,7
	New Users		9,6	35,5	33,5	31,5	31,7	44,1	41,1	37,5	42,2	35,7	26,7	23,4	24,3	21,4
	% New Users		38,5%	62,5%	41,2%	34,4%	31,8%	37,3%	32,4%	28,7%	30,7%	26,4%	22,1%	20,8%	23,0%	21,9%
Pravastatin	Users	18,8	19,3	22,2	22,4	22,2	22,1	21,5	20,5	19,3	18,8	18,0	17,5	15,7	13,8	12,8
	New Users		4,84	7,64	6,2	5,68	5,8	5,68	5,28	4,16	4,8	3,36	3,16	3,32	2,6	2,6
	% New Users		25,1%	34,4%	27,6%	25,6%	26,3%	26,4%	25,7%	21,5%	25,6%	18,6%	18,0%	21,2%	18,9%	20,4%
Fluvastatin	Users	2,9	5,1	5,1	4,1	3,6	3,9	2,8	2,4	1,9	1,8	1,5	1,2	1,1	1,0	1,0
	New Users		2,2	1,6	1,0	0,4	0,9	0,4	0,3	0,2	0,3	0,20	0,0	0,0	0,2	0,2
	% New Users		43,3%	31,3%	23,5%	12,1%	23,7%	14,1%	11,7%	10,6%	17,4%	13,2%	3,2%	3,6%	15,4%	23,1%
Atorvastatin	Users	50,2	53,4	54,2	50,5	46,4	47,6	54,0	53,9	51,7	50,2	59,6	67,0	74,3	79,6	89,1
	New Users		10,2	11,9	9,4	7,0	9,6	15,0	10,0	9,1	8,2	16,3	18,0	20,6	21,2	25,7
	% New Users		19,2%	21,9%	18,7%	15,2%	20,3%	27,8%	18,6%	17,6%	16,3%	27,4%	26,8%	27,7%	26,7%	28,8%
Rosuvastatin	Users			10,1	18,4	26,4	33,1	47,0	54,8	60,7	62,5	63,2	62,2	59,0	56,5	52,0
	New Users			8,6	8,0	8,5	9,1	17,4	13,0	13,1	11,8	9,2	8,8	9,6	8,9	7,8
	% New Users			85,0%	43,3%	32,3%	27,6%	36,9%	23,7%	21,5%	18,9%	14,6%	14,1%	16,3%	15,7%	15,1%
Associations	Users							1,8	3,8	5,0	6,1	6,1	6,2	5,8	5,2	6,1
	New Users							0,6	0,6	0,6	0,3	0,5	0,7	0,3	0,4	0,7
	% New Users							31,1%	14,9%	12,0%	5,2%	7,8%	10,9%	5,5%	7,6%	11,8%
Total	Users	89,8	102,8	148,5	176,7	190,2	206,3	245,3	262,1	269,2	277,0	283,7	275,0	268,2	261,7	258,7
	New Users		26,9	65,2	58,0	53,2	57,2	83,1	70,2	64,6	67,6	65,3	57,3	57,2	57,6	58,5
	% New Users		26,1%	43,9%	32,9%	28,0%	27,7%	33,9%	26,8%	24,0%	24,4%	23,0%	20,8%	21,3%	22,0%	22,6%

Figure 18 – Evolution of number of users (left) and new users (right) per statin and per year in age [50-59] years (in thousand)

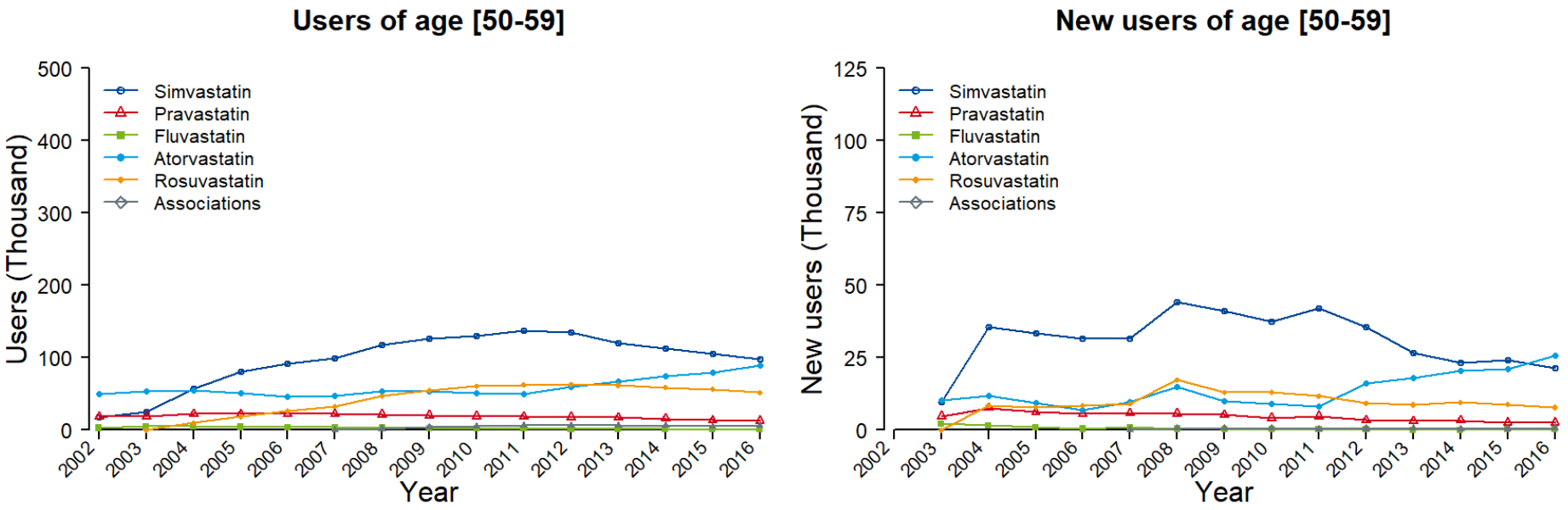


Table 26 – Users and new users per statin per year in age [60-69] years (in thousand)

		2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
Simvastatin	Users	32,3	38,7	80,3	111,3	129,1	141,2	163,2	176,2	185,8	195,7	202,3	194,0	183,8	179,2	172,3
	New Users		12,9	47,7	42,3	39,8	38,9	51,9	49,1	45,5	48,8	47,3	37,5	33,9	33,2	33,8
	% New Users		33,4%	59,4%	38,0%	30,8%	27,6%	31,8%	27,9%	24,5%	24,9%	23,4%	19,3%	18,5%	18,5%	19,6%
Pravastatin	Users	26,4	28,0	30,9	33,4	33,8	33,9	33,1	32,9	31,8	32,4	30,2	28,7	27,4	26,9	24,6
	New Users		6,94	10,1	10,1	7,38	7,12	8,04	6,78	6,62	6,8	5,32	5,48	4,82	4,36	4,26
	% New Users		24,8%	32,7%	30,3%	21,8%	21,0%	24,3%	20,6%	20,8%	21,0%	17,6%	19,1%	17,6%	16,2%	17,3%
Fluvastatin	Users	4,4	8,1	8,3	6,8	5,5	5,2	5,0	5,0	4,5	4,0	3,4	2,9	2,6	2,4	2,6
	New Users		3,6	2,8	1,4	0,7	0,9	0,8	1,0	0,4	0,5	0,44	0,5	0,4	0,4	0,4
	% New Users		44,9%	34,1%	20,5%	13,5%	18,1%	15,5%	19,3%	9,4%	13,1%	13,0%	17,1%	16,2%	16,4%	17,2%
Atorvastatin	Users	71,6	72,6	78,1	74,1	73,5	74,7	79,2	79,4	81,5	83,4	94,6	106,7	118,4	125,8	136,1
	New Users		13,3	19,0	13,7	12,5	13,5	18,3	13,6	13,9	13,9	22,5	22,5	27,7	27,8	33,2
	% New Users		18,4%	24,3%	18,5%	17,0%	18,1%	23,1%	17,2%	17,1%	16,7%	23,8%	21,1%	23,4%	22,1%	24,4%
Rosuvastatin	Users			11,8	20,7	28,4	40,3	55,3	67,4	78,6	86,5	92,9	94,5	93,3	93,0	89,1
	New Users			9,7	8,8	8,7	13,1	18,1	15,8	16,0	14,7	16,0	14,2	13,8	14,0	13,6
	% New Users			82,0%	42,7%	30,8%	32,4%	32,8%	23,4%	20,3%	17,0%	17,2%	15,0%	14,8%	15,1%	15,2%
Associations	Users							2,7	4,7	6,0	7,4	8,8	9,8	10,7	10,6	11,7
	New Users							0,8	0,7	0,7	1,0	0,9	0,8	1,3	1,0	1,2
	% New Users							30,8%	15,2%	11,1%	13,8%	10,2%	8,2%	12,0%	9,1%	10,3%
Total	Users	134,7	147,5	209,4	246,3	270,3	295,3	338,4	365,6	388,2	409,4	432,1	436,6	436,2	437,9	436,5
	New Users		36,8	89,3	76,3	69,1	73,6	98,0	87,0	83,1	85,8	92,4	81,0	82,0	80,7	86,5
	% New Users		25,0%	42,7%	31,0%	25,6%	24,9%	28,9%	23,8%	21,4%	20,9%	21,4%	18,6%	18,8%	18,4%	19,8%

Figure 19 – Evolution of number of users (left) and new users (right) per statin and per year in age [60-69] years (in thousand)

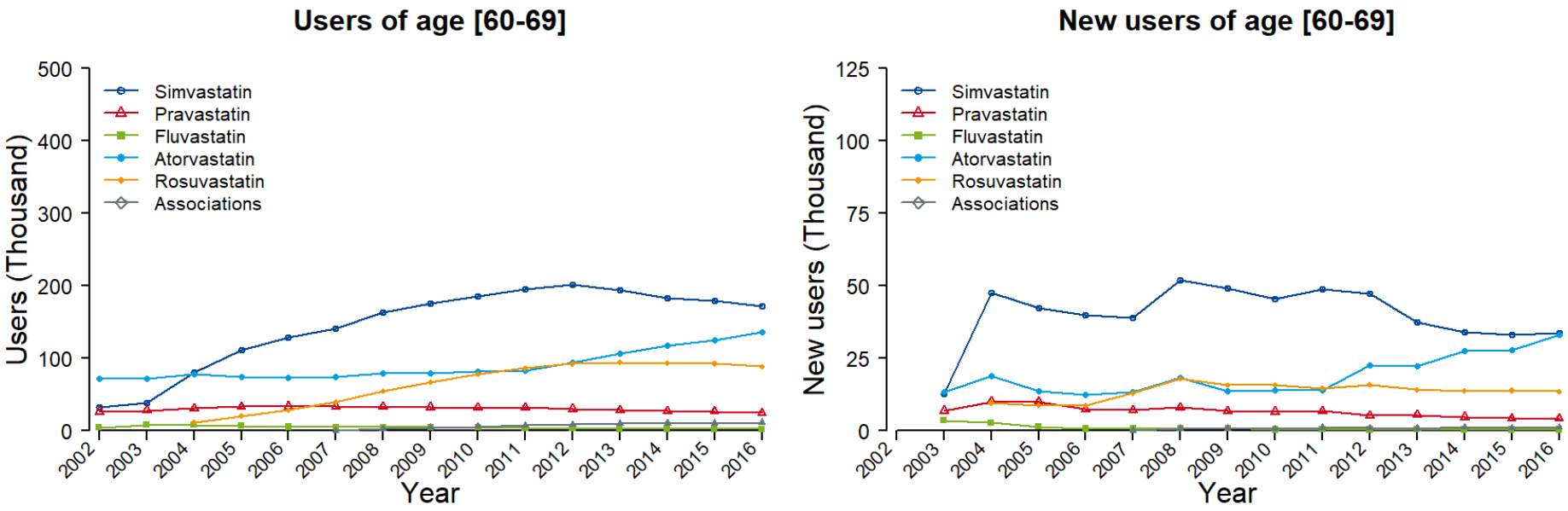


Table 27 – Users and new users per statin per year in age [70-79] years (in thousand)

		2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
Simvastatin	Users	34,4	43,4	86,8	117,0	136,2	148,7	164,2	176,3	179,3	182,6	182,7	176,1	169,3	167,2	164,2
	New Users		12,3	46,4	37,1	32,2	29,9	37,0	33,1	29,9	29,9	25,8	20,3	19,2	19,4	18,2
	% New Users		28,3%	53,5%	31,7%	23,7%	20,1%	22,5%	18,8%	16,7%	16,4%	14,1%	11,5%	11,3%	11,6%	11,1%
Pravastatin	Users	25,0	28,0	33,0	34,4	35,2	34,9	36,3	36,2	34,6	33,6	32,7	30,9	28,8	27,7	27,2
	New Users		4,72	9,06	6,86	5,9	5,4	5,84	5,24	4,12	4,36	3,78	3,14	2,74	2,9	2,98
	% New Users		16,9%	27,5%	19,9%	16,8%	15,5%	16,1%	14,5%	11,9%	13,0%	11,5%	10,2%	9,5%	10,5%	10,9%
Fluvastatin	Users	4,5	7,0	7,9	7,1	6,7	6,6	6,9	6,2	5,8	5,3	4,8	4,4	3,7	3,4	3,1
	New Users		2,7	1,9	1,1	0,7	0,7	1,0	0,5	0,3	0,3	0,26	0,3	0,2	0,2	0,1
	% New Users		38,5%	23,6%	15,8%	10,5%	10,0%	15,1%	8,7%	5,5%	6,0%	5,4%	6,8%	6,0%	6,4%	4,6%
Atorvastatin	Users	58,3	64,4	75,3	75,2	74,4	77,6	85,6	88,7	88,3	86,6	89,7	95,8	102,4	110,2	119,1
	New Users		7,6	15,3	9,6	8,4	8,9	13,6	8,9	8,3	7,0	11,5	12,0	13,6	14,7	17,2
	% New Users		11,8%	20,3%	12,8%	11,3%	11,5%	15,9%	10,1%	9,4%	8,1%	12,8%	12,5%	13,3%	13,3%	14,5%
Rosuvastatin	Users			10,1	16,1	23,9	33,7	45,2	53,8	62,0	66,6	68,9	72,6	75,3	75,4	76,0
	New Users			8,6	5,2	6,4	8,2	10,7	8,9	8,6	7,9	6,7	6,4	6,6	6,1	6,1
	% New Users			85,5%	32,4%	26,9%	24,2%	23,7%	16,6%	13,8%	11,8%	9,7%	8,8%	8,8%	8,1%	8,1%
Associations	Users							1,8	3,5	5,1	5,9	6,3	7,1	7,3	8,0	9,0
	New Users							0,4	0,3	0,4	0,3	0,3	0,3	0,3	0,3	0,5
	% New Users							21,7%	8,0%	7,1%	5,5%	4,7%	4,8%	4,6%	3,8%	6,0%
Total	Users	122,2	142,8	213,0	249,8	276,4	301,6	340,1	364,7	375,1	380,5	385,1	386,9	386,9	391,8	398,6
	New Users		27,3	81,2	59,9	53,6	53,1	68,6	57,0	51,7	49,8	48,3	42,4	42,7	43,6	45,2
	% New Users		19,1%	38,1%	24,0%	19,4%	17,6%	20,2%	15,6%	13,8%	13,1%	12,5%	11,0%	11,0%	11,1%	11,3%

Figure 20 – Evolution of number of users (left) and new users (right) per statin and per year in age [70-79] years (in thousand)

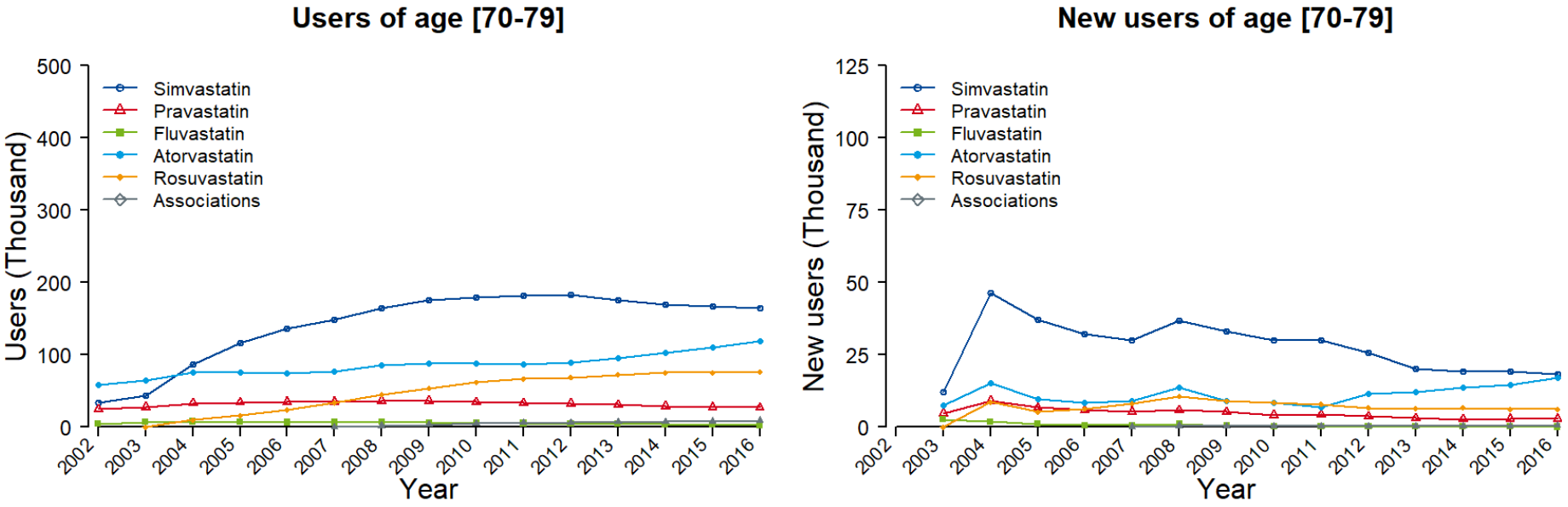


Table 28 – Users and new users per statin per year in age [80+[years (in thousand)

		2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
Simvastatin	Users	9,3	12,7	28,9	44,3	56,2	66,5	82,0	93,0	103,7	112,4	121,3	121,8	122,6	123,8	113,0
	New Users		3,1	15,6	13,1	13,0	12,7	16,8	15,3	14,8	14,7	14,6	12,0	11,4	11,3	10,0
	% New Users		24,2%	53,9%	29,6%	23,1%	19,1%	20,5%	16,5%	14,3%	13,1%	12,0%	9,9%	9,3%	9,1%	8,9%
Pravastatin	Users	5,5	7,1	9,4	11,4	13,4	15,5	17,2	18,2	19,8	20,1	20,4	20,2	20,1	20,3	19,3
	New Users		1,32	2,46	2,5	1,96	1,94	2,72	2,16	2,22	1,66	1,76	1,52	1,48	2	1,62
	% New Users		18,5%	26,1%	21,9%	14,6%	12,5%	15,9%	11,9%	11,2%	8,2%	8,6%	7,5%	7,4%	9,8%	8,4%
Fluvastatin	Users	0,8	1,5	1,8	1,9	2,1	2,3	2,3	2,6	2,8	2,9	3,0	3,0	3,1	3,2	2,9
	New Users		0,5	0,6	0,2	0,3	0,4	0,2	0,2	0,1	0,2	0,32	0,1	0,1	0,2	0,1
	% New Users		33,8%	33,7%	9,3%	15,4%	15,9%	8,7%	6,8%	4,2%	6,2%	10,7%	3,4%	3,9%	5,6%	2,7%
Atorvastatin	Users	12,2	15,3	20,7	23,6	26,3	30,6	35,7	39,9	44,0	48,4	54,5	61,1	65,3	71,4	74,2
	New Users		1,9	4,8	3,1	3,1	3,5	4,9	4,0	4,1	3,4	6,1	6,5	6,8	7,8	8,2
	% New Users		12,5%	23,3%	13,1%	11,9%	11,6%	13,7%	9,9%	9,4%	7,0%	11,2%	10,6%	10,5%	10,9%	11,0%
Rosuvastatin	Users			2,2	4,3	7,1	10,6	15,2	19,7	24,6	28,9	32,6	35,0	38,6	39,7	38,6
	New Users			1,9	1,5	1,9	2,4	4,1	3,0	3,3	3,4	3,0	3,1	3,6	2,8	3,5
	% New Users			86,1%	34,9%	27,2%	22,9%	27,2%	15,4%	13,3%	11,7%	9,1%	8,7%	9,3%	7,0%	9,1%
Associations	Users							0,3	0,8	1,2	1,6	2,3	3,0	3,3	3,8	4,2
	New Users							0,1	0,1	0,1	0,1	0,1	0,1	0,1	0,1	0,2
	% New Users							23,1%	18,4%	8,2%	5,1%	4,4%	3,3%	3,0%	3,7%	4,8%
Total	Users	27,8	36,7	63,0	85,5	105,1	125,5	152,6	174,3	196,1	214,4	234,0	244,0	253,0	262,3	252,2
	New Users		6,8	25,3	20,4	20,3	20,9	28,8	24,8	24,6	23,4	25,8	23,3	23,5	24,2	23,6
	% New Users		18,6%	40,2%	23,8%	19,3%	16,7%	18,9%	14,2%	12,6%	10,9%	11,0%	9,5%	9,3%	9,2%	9,3%

Figure 21 – Evolution of number of users (left) and new users (right) per statin and per year in age [80+[years (in thousand)

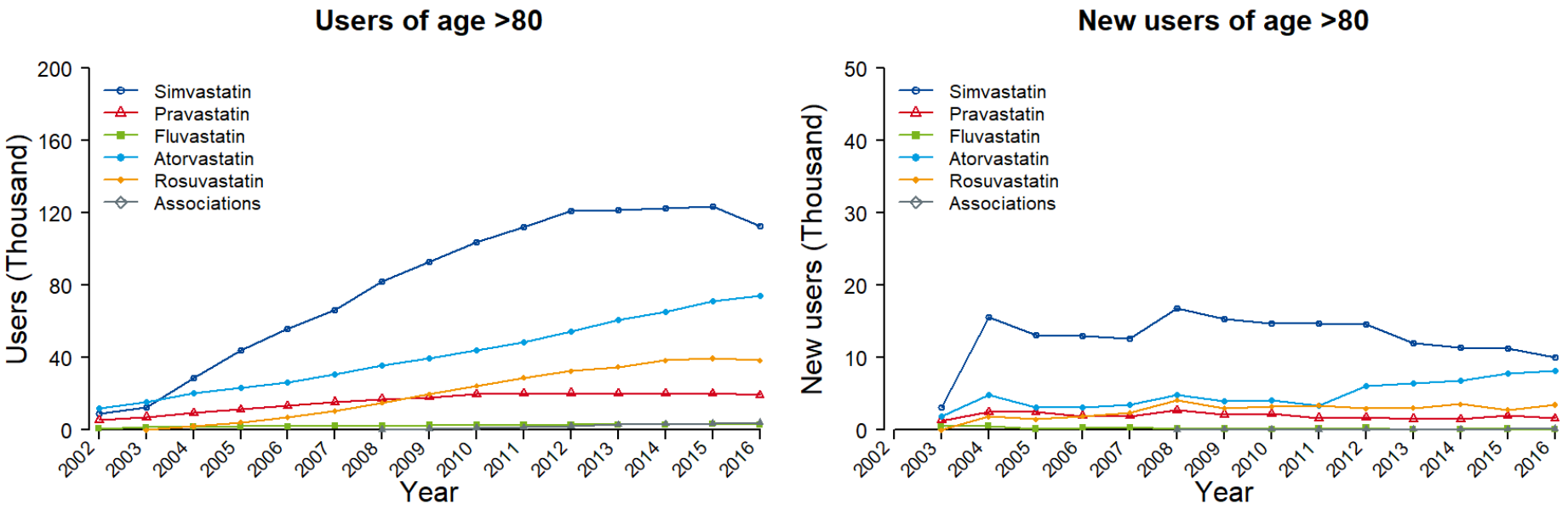


Table 29 – Users and new users per statin per year in male gender (in thousand)

		2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
Simvastatin	Users	47,7	66,6	142,1	191,0	222,0	246,8	290,2	312,1	326,6	342,3	348,7	329,7	315,4	308,9	295,6
	New Users		25,0	82,5	68,0	65,3	65,9	89,7	79,8	74,6	79,8	74,5	58,1	51,4	51,6	48,2
	% New Users		37,5%	58,1%	35,6%	29,4%	26,7%	30,9%	25,6%	22,9%	23,3%	21,4%	17,6%	16,3%	16,7%	16,3%
Pravastatin	Users	36,0	38,9	47,9	50,9	51,0	51,8	52,3	51,8	50,1	49,8	48,5	46,2	44,1	42,8	41,3
	New Users		8,66	16,54	12,34	10,26	10,12	11,8	10,3	8,86	8,42	7,14	6,68	6,26	5,82	5,88
	% New Users		22,3%	34,5%	24,2%	20,1%	19,5%	22,6%	19,9%	17,7%	16,9%	14,7%	14,5%	14,2%	13,6%	14,2%
Fluvastatin	Users	6,4	10,9	12,4	11,0	9,3	9,3	9,2	8,7	8,0	7,5	6,7	6,3	5,6	5,1	4,8
	New Users		4,5	4,0	2,2	1,0	1,4	1,3	1,0	0,7	0,7	0,62	0,5	0,4	0,4	0,4
	% New Users		41,4%	31,9%	19,9%	10,3%	15,1%	14,3%	11,5%	8,3%	9,8%	9,3%	8,0%	7,9%	8,6%	8,4%
Atorvastatin	Users	99,1	104,8	122,8	126,7	124,3	130,5	147,5	149,8	153,0	153,7	172,8	194,0	213,8	232,7	254,1
	New Users		17,0	31,3	21,9	18,0	21,8	34,0	21,4	22,0	20,3	34,2	37,2	44,6	46,9	53,2
	% New Users		16,2%	25,5%	17,3%	14,5%	16,7%	23,0%	14,3%	14,4%	13,2%	19,8%	19,2%	20,8%	20,1%	20,9%
Rosuvastatin	Users			21,5	37,9	52,0	68,9	98,4	116,8	135,1	145,3	152,2	155,9	156,5	156,1	150,6
	New Users			18,2	14,8	15,6	19,7	33,8	25,5	25,8	22,9	22,1	20,8	20,1	19,4	18,4
	% New Users			84,4%	38,9%	30,1%	28,6%	34,4%	21,8%	19,1%	15,7%	14,5%	13,3%	12,9%	12,4%	12,2%
Associations	Users							3,9	8,1	10,3	12,3	13,1	15,1	15,5	15,7	17,6
	New Users							1,2	1,0	1,3	1,0	1,1	1,2	1,4	0,9	1,7
	% New Users							29,9%	12,8%	12,2%	8,5%	8,1%	7,8%	9,3%	5,7%	9,7%
Total	Users	189,2	221,2	346,6	417,5	458,6	507,4	601,5	647,3	683,2	710,9	742,0	747,2	750,9	761,3	763,9
	New Users		55,1	152,4	119,2	110,2	119,0	171,8	139,0	133,3	133,1	139,6	124,5	124,2	125,0	127,8
	% New Users		24,9%	44,0%	28,6%	24,0%	23,5%	28,6%	21,5%	19,5%	18,7%	18,8%	16,7%	16,5%	16,4%	16,7%

Figure 22 – Evolution of number of users (left) and new users (right) per statin and per year in male gender (in thousand)

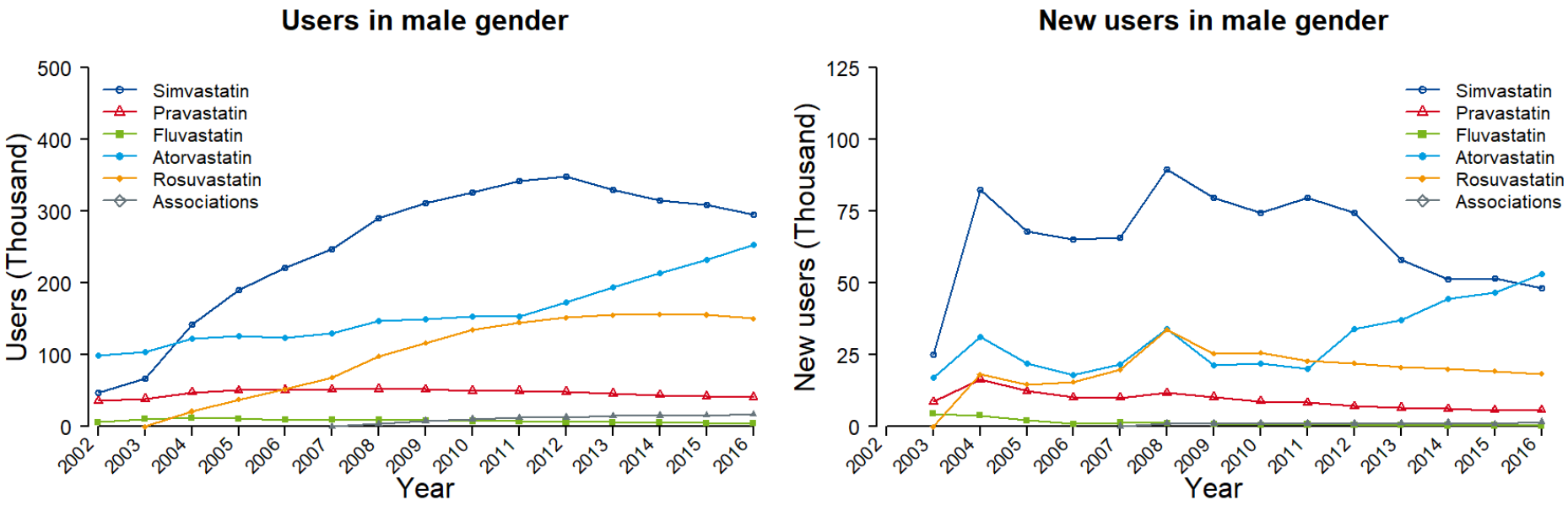


Table 30 – Users and new users per statin per year in female gender (in thousand)

		2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
Simvastatin	Users	54,2	64,1	137,7	200,3	232,3	257,1	294,2	320,8	334,6	348,8	354,3	335,2	317,9	308,4	289,9
	New Users		17,8	82,2	77,5	70,7	70,0	88,3	85,9	79,7	82,0	73,7	56,6	52,3	51,9	49,5
	% New Users		27,7%	59,7%	38,7%	30,4%	27,2%	30,0%	26,8%	23,8%	23,5%	20,8%	16,9%	16,4%	16,8%	17,1%
Pravastatin	Users	47,5	51,7	56,3	60,2	62,7	63,7	64,3	64,9	64,1	63,1	60,8	57,4	53,8	51,0	47,5
	New Users		12,36	16,36	17,52	14,26	13,5	13,88	13,2	11,22	11,68	9,64	8,74	8,06	7,64	7,22
	% New Users		23,9%	29,1%	29,1%	22,8%	21,2%	21,6%	20,3%	17,5%	18,5%	15,9%	15,2%	15,0%	15,0%	15,2%
Fluvastatin	Users	8,0	14,3	13,8	11,3	9,7	9,9	9,1	8,4	7,8	7,1	6,4	5,7	5,3	5,4	5,0
	New Users		6,6	4,0	2,1	1,5	1,9	1,5	1,0	0,5	0,7	0,64	0,6	0,4	0,6	0,6
	% New Users		46,2%	29,0%	18,6%	15,2%	19,0%	17,0%	12,4%	6,6%	9,5%	10,0%	9,8%	6,8%	11,2%	11,6%
Atorvastatin	Users	118,6	125,3	129,9	118,7	116,3	118,9	128,1	132,5	133,1	133,8	150,2	164,9	177,7	188,7	199,2
	New Users		21,7	26,6	19,9	17,9	19,1	26,2	21,2	20,0	17,5	33,8	33,5	37,8	39,3	45,2
	% New Users		17,3%	20,5%	16,8%	15,4%	16,1%	20,5%	16,0%	15,0%	13,1%	22,5%	20,3%	21,3%	20,8%	22,7%
Rosuvastatin	Users			18,2	32,4	47,8	64,3	86,6	103,0	117,2	125,0	130,7	132,1	131,6	127,8	122,3
	New Users			15,4	13,9	15,6	18,5	27,1	23,3	23,4	21,6	19,6	17,7	19,1	17,5	17,6
	% New Users			84,2%	42,8%	32,7%	28,8%	31,3%	22,6%	20,0%	17,3%	15,0%	13,4%	14,5%	13,7%	14,4%
Associations	Users							3,4	6,4	9,0	10,6	12,4	13,3	13,5	13,4	15,2
	New Users							0,9	0,9	0,9	0,9	1,0	1,0	0,8	1,1	1,3
	% New Users							27,1%	13,4%	9,6%	8,9%	7,8%	7,4%	6,2%	7,9%	8,7%
Total	Users	228,3	255,4	355,9	422,9	468,7	513,9	585,7	635,9	665,8	688,5	714,7	708,6	699,8	694,7	679,1
	New Users		58,5	144,5	130,9	119,9	123,0	157,9	145,4	135,7	134,4	138,3	118,1	118,5	118,1	121,5
	% New Users		22,9%	40,6%	31,0%	25,6%	23,9%	27,0%	22,9%	20,4%	19,5%	19,3%	16,7%	16,9%	17,0%	17,9%

Figure 23 – Evolution of number of users (left) and new users (right) per statin and per year in female gender (in thousand)

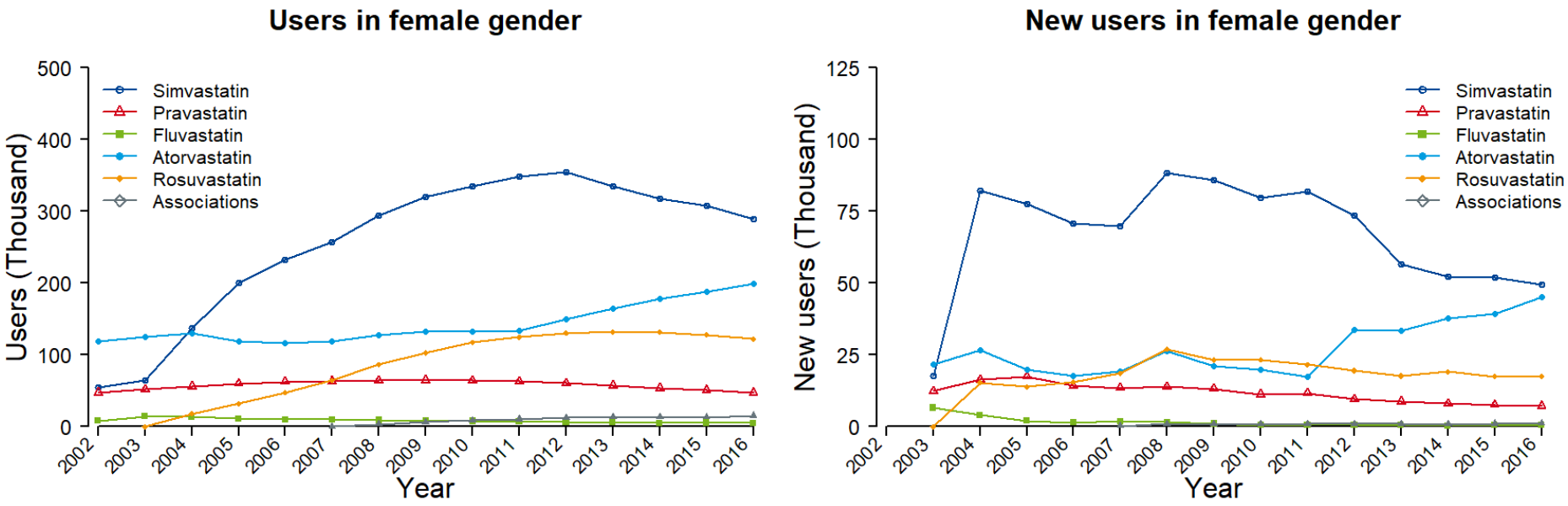
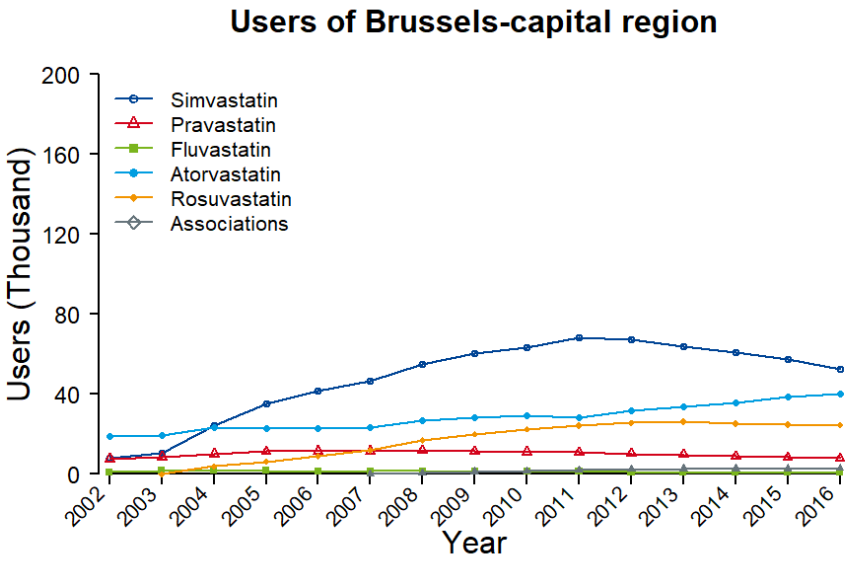


Table 31 – Users and new users per statin per year in Brussels-capital region (in thousand)

		2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
Simvastatin	Users	8,2	10,7	24,3	35,5	41,7	46,8	54,8	60,5	63,4	68,4	67,4	64,0	60,8	57,5	52,6
	New Users		4,0	15,2	14,4	13,8	14,3	18,7	18,1	17,1	19,7	16,4	14,4	13,2	11,8	10,3
	% New Users		37,8%	62,6%	40,7%	33,2%	30,6%	34,1%	29,9%	27,0%	28,7%	24,3%	22,5%	21,7%	20,6%	19,7%
Pravastatin	Users	7,7	8,7	10,2	11,4	11,5	11,7	11,7	11,5	11,2	10,8	10,3	9,8	8,9	8,5	7,9
	New Users		2,34	3,82	3,64	2,8	2,62	2,9	2,5	2,62	2,44	1,44	1,92	1,4	1,2	1,32
	% New Users		26,8%	37,6%	32,0%	24,3%	22,5%	24,8%	21,8%	23,5%	22,6%	14,0%	19,7%	15,7%	14,2%	16,7%
Fluvastatin	Users	1,0	1,7	1,9	1,9	1,4	1,6	1,5	1,4	1,3	1,3	1,0	0,9	0,8	0,8	0,8
	New Users		0,7	0,8	0,4	0,2	0,3	0,2	0,1	0,0	0,1	0,12	0,0	0,0	0,1	0,1
	% New Users		41,9%	40,6%	21,3%	12,7%	20,5%	15,8%	5,8%	1,5%	6,3%	12,2%	2,3%	5,3%	13,2%	17,9%
Atorvastatin	Users	18,9	19,6	23,3	22,9	22,7	23,5	26,7	28,3	29,1	28,3	31,8	33,8	35,6	38,5	40,2
	New Users		4,1	7,3	4,5	3,9	3,7	6,8	5,5	5,3	4,4	7,2	7,3	8,0	9,7	10,5
	% New Users		21,1%	31,5%	19,7%	17,1%	15,8%	25,5%	19,5%	18,1%	15,6%	22,8%	21,6%	22,5%	25,3%	26,2%
Rosuvastatin	Users			4,0	6,3	9,0	12,1	17,0	20,0	22,6	24,4	25,8	26,4	25,4	24,9	24,6
	New Users			3,4	2,6	3,1	3,6	6,2	5,0	4,9	4,9	4,4	4,7	4,4	3,7	4,4
	% New Users			85,4%	41,1%	34,1%	29,9%	36,7%	25,2%	21,8%	20,1%	17,0%	17,7%	17,5%	14,9%	18,1%
Associations	Users							0,5	1,1	1,6	2,0	2,4	2,6	2,7	2,7	3,0
	New Users							0,2	0,2	0,3	0,3	0,3	0,2	0,3	0,2	0,4
	% New Users							29,6%	15,8%	17,7%	13,3%	12,7%	7,6%	10,3%	7,4%	12,0%
Total	Users	35,7	40,7	63,7	77,9	86,3	95,5	112,2	122,7	129,2	135,2	138,6	137,4	134,2	132,8	129,0
	New Users		11,2	30,5	25,6	23,8	24,6	35,0	31,4	30,3	31,8	29,9	28,5	27,3	26,8	27,1
	% New Users		27,6%	48,0%	32,8%	27,5%	25,7%	31,2%	25,6%	23,4%	23,5%	21,6%	20,7%	20,4%	20,2%	21,0%

Figure 24 – Evolution of number of users (left) and new users (right) per statin and per year in Brussels-capital region (in thousand)



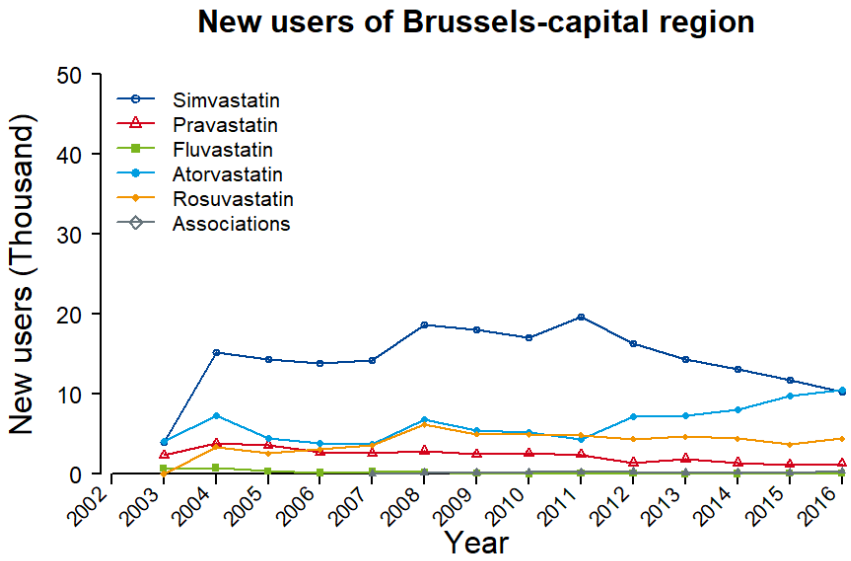


Table 32 – Users and new users per statin per year in Flemish region (in thousand)

		2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
Simvastatin	Users	66,4	82,5	170,3	237,2	276,4	305,4	353,0	379,5	397,0	414,0	424,6	405,9	389,3	384,2	370,6
	New Users		24,8	96,7	84,6	78,9	78,2	102,2	92,2	86,0	88,9	84,4	64,7	58,8	59,9	58,0
	% New Users		30,1%	56,8%	35,7%	28,5%	25,6%	28,9%	24,3%	21,7%	21,5%	19,9%	15,9%	15,1%	15,6%	15,7%
Pravastatin	Users	49,2	54,6	58,7	61,0	63,1	65,6	67,5	69,2	68,0	68,2	67,0	64,6	61,3	59,5	56,8
	New Users		13,12	15,24	14,78	12,98	12,84	14,54	13,36	11,06	11,72	10,62	9,32	8,22	8,22	7,94
	% New Users		24,0%	26,0%	24,2%	20,6%	19,6%	21,5%	19,3%	16,3%	17,2%	15,9%	14,4%	13,4%	13,8%	14,0%
Fluvastatin	Users	8,8	15,7	16,5	14,1	12,2	12,5	12,1	11,1	10,4	9,7	9,1	8,3	7,5	7,2	6,8
	New Users		7,1	4,9	2,7	1,7	2,1	2,0	1,4	0,8	0,9	0,84	0,7	0,6	0,8	0,6
	% New Users		45,3%	29,5%	19,2%	13,7%	16,7%	16,8%	12,8%	8,1%	8,9%	9,2%	8,9%	7,4%	10,5%	8,3%
Atorvastatin	Users	137,7	147,0	157,9	155,9	156,0	161,6	178,2	181,0	181,3	183,3	202,9	226,9	248,9	270,9	295,7
	New Users		24,1	32,8	27,0	23,0	26,3	37,8	24,8	23,5	21,9	39,2	43,0	49,3	52,7	60,2
	% New Users		16,4%	20,8%	17,3%	14,7%	16,3%	21,2%	13,7%	12,9%	11,9%	19,3%	18,9%	19,8%	19,4%	20,4%
Rosuvastatin	Users			20,4	37,6	53,9	71,7	101,5	120,5	140,8	151,8	161,0	166,9	169,7	166,6	160,4
	New Users			16,7	15,3	16,4	19,3	33,1	25,7	27,1	23,1	21,9	20,1	21,5	19,5	19,0
	% New Users			82,1%	40,7%	30,4%	26,9%	32,6%	21,4%	19,3%	15,2%	13,6%	12,1%	12,7%	11,7%	11,8%
Associations	Users							4,3	8,7	12,0	14,1	15,4	17,2	17,2	17,0	19,3
	New Users							1,4	0,9	1,1	1,1	0,9	1,3	1,2	1,1	1,8
	% New Users							33,0%	10,8%	9,2%	8,1%	5,7%	7,3%	6,7%	6,4%	9,1%
Total	Users	262,0	299,7	423,9	505,9	561,6	616,7	716,7	770,0	809,6	841,2	880,0	889,8	894,0	905,5	909,5
	New Users		69,1	166,3	144,5	132,9	138,8	191,0	158,4	149,6	147,5	157,8	139,1	139,6	142,1	147,5
	% New Users		23,1%	39,2%	28,6%	23,7%	22,5%	26,7%	20,6%	18,5%	17,5%	17,9%	15,6%	15,6%	15,7%	16,2%

Figure 25 – Evolution of number of users (left) and new users (right) per statin and per year in Flemish region (in thousand)

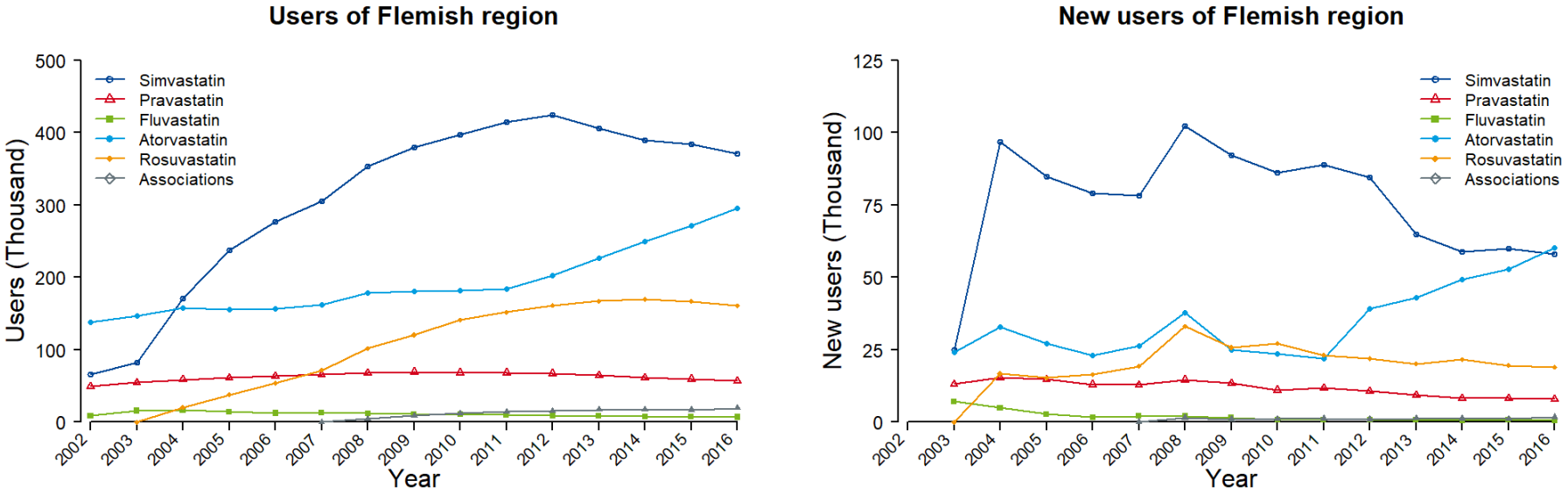
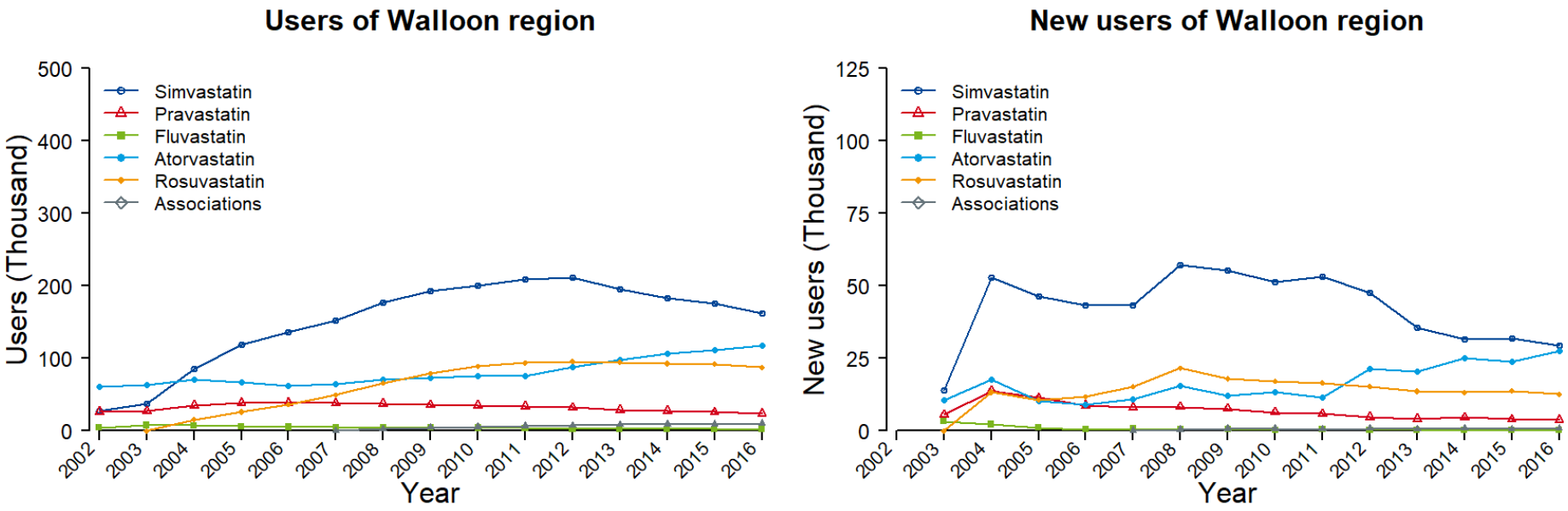


Table 33 – Users and new users per statin per year in Walloon region (in thousand)

		2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
Simvastatin	Users	27,4	37,5	85,2	118,6	136,2	151,8	176,6	192,9	200,8	208,7	211,0	195,1	183,2	175,6	162,3
	New Users		13,9	52,8	46,5	43,3	43,4	57,1	55,4	51,2	53,2	47,5	35,6	31,6	31,8	29,3
	% New Users		37,1%	61,9%	39,2%	31,8%	28,6%	32,4%	28,7%	25,5%	25,5%	22,5%	18,2%	17,3%	18,1%	18,1%
Pravastatin	Users	26,6	27,3	35,3	38,7	39,0	38,3	37,4	36,1	35,0	33,9	32,0	29,2	27,7	25,8	24,1
	New Users		5,56	13,84	11,44	8,74	8,16	8,24	7,64	6,4	5,94	4,72	4,18	4,7	4,04	3,84
	% New Users		20,4%	39,2%	29,5%	22,4%	21,3%	22,0%	21,2%	18,3%	17,5%	14,8%	14,3%	17,0%	15,6%	15,9%
Fluvastatin	Users	4,7	7,8	7,7	6,3	5,4	5,1	4,7	4,6	4,1	3,7	3,0	2,8	2,6	2,5	2,2
	New Users		3,3	2,3	1,2	0,6	0,9	0,6	0,5	0,3	0,5	0,30	0,3	0,2	0,2	0,3
	% New Users		42,2%	29,7%	18,7%	10,7%	17,1%	12,4%	11,8%	7,8%	13,0%	9,9%	10,6%	7,8%	7,2%	12,8%
Atorvastatin	Users	61,1	63,5	71,4	66,5	62,0	64,3	70,7	73,0	75,7	75,9	88,4	98,3	107,0	112,0	117,4
	New Users		10,5	17,7	10,3	9,0	10,9	15,6	12,2	13,2	11,5	21,5	20,5	25,1	23,8	27,6
	% New Users		16,5%	24,8%	15,4%	14,6%	16,9%	22,1%	16,7%	17,5%	15,2%	24,3%	20,8%	23,4%	21,2%	23,5%
Rosuvastatin	Users			15,4	26,4	36,8	49,4	66,5	79,3	88,9	94,1	96,0	94,7	93,0	92,4	88,0
	New Users			13,4	10,8	11,8	15,4	21,6	18,0	17,2	16,5	15,3	13,7	13,3	13,7	12,6
	% New Users			86,9%	40,7%	32,0%	31,1%	32,5%	22,7%	19,3%	17,6%	16,0%	14,4%	14,3%	14,9%	14,4%
Associations	Users							2,4	4,6	5,7	6,8	7,7	8,5	9,0	9,3	10,5
	New Users							0,5	0,8	0,7	0,6	0,8	0,7	0,8	0,7	0,9
	% New Users							20,5%	16,9%	12,9%	8,6%	10,9%	8,2%	9,3%	7,3%	8,6%
Total	Users	119,8	136,1	215,0	256,6	279,5	309,0	358,3	390,5	410,2	423,1	438,2	428,6	422,5	417,7	404,5
	New Users		33,2	100,0	80,2	73,4	78,7	103,7	94,6	89,1	88,3	90,2	74,9	75,7	74,2	74,6
	% New Users		24,4%	46,5%	31,2%	26,3%	25,5%	28,9%	24,2%	21,7%	20,9%	20,6%	17,5%	17,9%	17,8%	18,4%

Figure 26 – Evolution of number of users (left) and new users (right) per statin and per year in Walloon region (in thousand)



Appendix 1.2. Adherence

Table 34 – Adherence assessment of second definition of new users (each user is a new user)

	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
New Users	103,96	269,44	211,88	176,22	176,32	247,56	195,34	174,86	165,3	166,5	134,78	128,54	126,26	127,92
One pack recorded during full period	4,32	12,68	17,1	16,04	17,4	21,9	22,48	21,14	23,6	28,2	24,1	27,2	30,72	54,78
	4,2%	4,7%	8,1%	9,1%	9,9%	8,8%	11,5%	12,1%	14,3%	16,9%	17,9%	21,2%	24,3%	42,8%
Regular users	59660	159680	110980	90960	92160	131900	100720	89820	84700	85320	67760	63880	62600	55280
	57,4%	59,3%	52,4%	51,6%	52,3%	53,3%	51,6%	51,4%	51,2%	51,2%	50,3%	49,7%	49,6%	43,2%
Occasional users	44300	109760	100900	85260	84160	115660	94620	85040	80600	81180	67020	64660	63660	72640
	42,6%	40,7%	47,6%	48,4%	47,7%	46,7%	48,4%	48,6%	48,8%	48,8%	49,7%	50,3%	50,4%	56,8%

Table 35 – Adherence assessment of new users in Brussels-capital region	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
New Users	11,3	30,5	25,6	23,8	24,6	35,0	31,4	30,3	31,8	29,9	28,5	27,3	26,8	27,1
One pack recorded	1,5	4,1	5,2	5,3	6,2	7,7	7,7	8,1	8,5	8,6	8,5	8,0	7,7	14,4
	13,3%	13,6%	20,2%	22,4%	25,3%	21,9%	24,4%	26,6%	26,8%	28,7%	29,7%	29,2%	28,7%	53,1%
Regular users	5,4	15,8	10,5	9,1	9,7	14,9	12,3	10,8	11,9	11,2	10,7	10,7	12,0	10,7
	47,5%	51,8%	41,2%	38,2%	39,2%	42,7%	39,3%	35,8%	37,5%	37,6%	37,5%	39,1%	44,9%	39,3%
Defaulters	2,8	8,0	5,9	5,0	4,4	6,6	5,0	3,9	4,6	3,4	3,2	2,1	1,0	0,1
	53,0%	50,8%	55,6%	55,1%	46,0%	43,9%	40,2%	36,4%	38,3%	30,6%	30,1%	19,3%	8,7%	0,8%
Occasional users	5,9	14,7	15,0	14,7	15,0	20,1	19,1	19,4	19,9	18,6	17,8	16,7	14,7	16,5
	52,5%	48,2%	58,8%	61,8%	60,8%	57,3%	60,7%	64,2%	62,5%	62,4%	62,5%	60,9%	55,1%	60,7%
Quitters	1,3	3,7	4,3	3,7	3,3	5,1	4,9	5,7	6,2	5,9	5,9	6,0	5,8	7,0
	21,6%	25,1%	28,5%	24,9%	21,8%	25,5%	25,6%	29,4%	31,1%	31,9%	33,1%	35,9%	39,1%	42,7%

Table 36 – Adherence assessment of new users in Flemish region

	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
New Users	69,1	166,3	144,5	132,9	138,9	191,0	158,4	149,6	147,5	157,8	139,1	139,6	142,1	147,5
One pack recorded	9,5 13,8%	21,2 12,7%	29,0 20,1%	29,7 22,4%	30,1 21,7%	34,7 18,2%	35,4 22,4%	33,1 22,1%	33,4 22,6%	38,0 24,1%	34,3 24,6%	36,5 26,2%	35,4 24,9%	68,5 46,4%
Regular users	33,8 48,9%	89,0 53,5%	64,6 44,7%	58,3 43,8%	60,7 43,7%	89,7 46,9%	66,2 41,8%	63,0 42,1%	64,6 43,8%	69,3 43,9%	60,6 43,6%	63,8 45,7%	74,1 52,1%	66,8 45,3%
Defaulters	17,3 51,1%	43,2 48,5%	30,5 47,2%	25,8 44,3%	26,7 43,9%	36,6 40,8%	25,5 38,6%	20,9 33,1%	21,6 33,5%	19,3 27,8%	14,4 23,7%	10,5 16,5%	6,3 8,5%	0,5 0,8%
Occasional users	35,3 51,1%	77,3 46,5%	79,9 55,3%	74,6 56,2%	78,2 56,3%	101,3 53,1%	92,3 58,2%	86,5 57,9%	82,9 56,2%	88,5 56,1%	78,5 56,4%	75,8 54,3%	68,0 47,9%	80,7 54,7%
Quitters	7,7 21,7%	21,0 27,1%	21,4 26,7%	17,3 23,2%	19,4 24,8%	27,7 27,3%	24,7 26,8%	23,3 26,9%	23,8 28,7%	28,1 31,8%	25,2 32,2%	26,2 34,5%	27,6 40,6%	36,8 45,6%

Table 37 – Adherence assessment of new users in Walloon region

	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
New Users	33,3	100,0	80,2	73,4	78,8	103,7	94,6	89,1	88,3	90,2	74,9	75,7	74,2	74,6
One pack recorded	5,4 16,2%	14,8 14,8%	18,4 23,0%	17,5 23,8%	20,5 26,0%	23,3 22,5%	25,1 26,6%	24,8 27,8%	22,6 25,6%	26,1 28,9%	21,0 28,0%	22,4 29,5%	23,3 31,4%	37,8 50,6%
Regular users	15,5 46,6%	48,3 48,3%	32,6 40,7%	28,7 39,0%	29,3 37,2%	42,9 41,4%	36,3 38,4%	32,9 36,9%	34,1 38,6%	35,8 39,7%	29,5 39,4%	32,2 42,5%	34,2 46,1%	30,5 40,9%
Defaulters	8,7 56,4%	23,6 48,8%	15,9 48,8%	13,4 46,8%	12,5 42,7%	19,1 44,5%	14,3 39,5%	11,9 36,0%	8,9 26,0%	9,8 27,3%	5,8 19,7%	5,6 17,5%	3,0 8,7%	0,3 0,9%
Occasional users	17,8 53,4%	51,7 51,7%	47,5 59,3%	44,7 61,0%	49,5 62,8%	60,8 58,6%	58,3 61,6%	56,2 63,1%	54,2 61,4%	54,4 60,3%	45,4 60,6%	43,6 57,5%	40,0 53,9%	44,1 59,1%
Quitters	3,7 21,0%	11,5 22,2%	12,4 26,0%	11,3 25,3%	12,1 24,5%	16,7 27,4%	15,7 27,0%	15,4 27,4%	16,2 29,9%	17,1 31,4%	13,6 30,0%	15,2 34,8%	16,1 40,3%	19,5 44,3%

Appendix 1.3. Current prices of statins in Belgium

Table 38 – Comparison of prices in 2018 vs. 2016

	Consumption and prices 2016							Prices 2018			
	Number of DDD (million)	Total price		Third party payer		Co-payement		small boxes (<90)		big boxes (≥90)	
Atorvastatin		/ day	/year	/ day	/year	/ day	/year	/ day	/year	/ day	/year
10	15.5	0.20	73.67	0.16	58.46	0.04	15.20	0.06	20.86	0.03	11.94
20	60.3	0.37	134.56	0.28	103.75	0.08	30.81	0.08	29.13	0.07	25.65
40	69.4	0.37	135.57	0.29	104.34	0.09	31.23	0.08	28.06	0.07	25.90
80	37.1	0.34	125.02	0.26	95.84	0.08	29.17	0.08	28.23	0.07	25.03
Fluvastatin		/ day	/year	/ day	/year	/ day	/year	/ day	/year	/ day	/year
40	0.37	0.23	83.80	0.15	54.07	0.08	29.73	-	-	-	-
80	3.3	0.28	102.16	0.19	69.89	0.09	32.27	-	-	0.10	37.77
Pravastatin		/ day	/year	/ day	/year	/ day	/year	/ day	/year	/ day	/year
20	5.6	0.27	99.82	0.20	73.13	0.07	26.70	0.07	26.56	0.06	23.13
30	0	0.36	129.61	0.26	96.32	0.09	33.3	-	-	-	-
40	23.8	0.40	146.21	0.29	107.64	0.11	38.58	0.17	62.31	0.10	35.59
Rosuvastatin		/ day	/year	/ day	/year	/ day	/year	/ day	/year	/ day	/year
5	0	0.95	345.71	0.70	254.85	0.25	90.86	0.06	20.24	0.03	11.67
10	59.1	0.76	278.19	0.63	229.17	0.13	49.02	0.08	27.54	0.07	23.97
20	42.2	1.16	424.61	1.03	375.96	0.13	48.65	0.08	27.64	0.07	24.29
40	19.8	1.80	658.79	1.68	613.13	0.13	45.66	0.08	27.64	0.07	24.87
Simvastatin		/ day	/year	/ day	/year	/ day	/year	/ day	/year	/ day	/year
20	68.9	0.19	68.90	0.15	54.13	0.04	14.77	0.06	22.43	0.05	17.12
40	90.1	0.23	83.13	0.17	63.73	0.05	19.41	0.08	28.68	0.06	22.11
80	0.71	0.74	268.29	0.61	222.41	0.13	45.87	-	-	0.15	54.02
Associations		/ day	/year	/ day	/year	/ day	/year	/ day	/year	/ day	/year
INEGY® 10/20	0.65	1.74	635.54	1.62	591.71	0.13	47.48	-	-	0.14	51.12
INEGY® 10/40	2.34	2.02	737.81	1.89	690.32	0.13	47.48	-	-	0.14	51.12
INEGY® 10/80	0.5	2.12	774.33	2.01	734.15	0.12	43.83	-	-	0.15	55.12

ATOZET® 10/10	*0.01*	*1.50*	*547.88*	*1.39*	*507.70*	*0.11*	*40.18*	*-*	*-*	*0.16*	*60.02*
ATOZET® 10/20	*0.03*	*1.61*	*588.05*	*1.46*	*533.27*	*0.15*	*54.79*	*-*	*-*	*0.16*	*60.02*
ATOZET® 10/40	*0.17*	*1.61*	*588.05*	*1.48*	*540.57*	*0.13*	*47.48*	*-*	*-*	*0.16*	*60.02*
ATOZET® 10/80	*0.08*	*1.61*	*588.05*	*1.47*	*536.92*	*0.14*	*51.14*	*-*	*-*	*0.16*	*60.02*
Trinomia® 20/2.5	*0.01*	*0.44*	*160.71*	*0.33*	*120.53*	*0.11*	*40.18*	*0.13*	*48.23*	*0.09*	*32.89*
Trinomia® 20/5	*0*	*0.61*	*222.80*	*0.52*	*189.93*	*0.09*	*32.87*	*0.16*	*56.84*	*0.10*	*37.10*
Trinomia® 20/10	*0.01*	*0.62*	*226.46*	*0.52*	*189.93*	*0.10*	*36.53*	*0.20*	*74.69*	*0.13*	*45.85*

APPENDIX 2. CLINICAL BENEFITS AND HARMS

Appendix 2.1. Search strategies for systematic reviews and RCTs

Both strategies were run at the same time. As we already had a good systematic review for which literature review ended in 2016, we decided to look for RCTs published after those included in this SR (2016), but for other SRs we have searched from 2010 onwards.

Table 39 – Search strategy for Medline

Date	
Database	Medline
Segments	Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE and Versions(R) <1946 to February 21, 2018>
Database provider	OvidSp
Search Strategy	1 exp *Hydroxymethylglutaryl-CoA Reductase Inhibitors/ (25023) 2 *Hypolipidemic Agents/ (9368) 3 *Anticholesteremic Agents/ (10654) 4 1 or 2 or 3 (39868) 5 Hydroxymethylglutaryl-CoA Reductase Inhibitors.ti,kw. (184) 6 hmg-coa reductase inhibitors.ti,kw. (687) 7 hydroxymethylglutaryl-coa inhibitors.ti,kw. (0) 8 hydroxymethylglutaryl-coenzyme a inhibitors.ti,kw. (1) 9 statin?.ti,kw. (14723) 10 Hypolipidemic Agents.ti,kw. (158) 11 Anticholesteremic Agents.ti,kw. (94) 12 (anticholesteremic adj2 (drugs or agents)).ti,kw. (12) 13 (hypocholesteremic adj2 (drugs or agents)).ti,kw. (43) 14 anticholesteremics.ti,kw. (0) 15 cholesterol inhibitors.ti,kw. (2) 16 (hypolipidemic adj2 (agents or drugs)).ti,kw. (255) 17 (antilipemic adj2 (drugs or agents)).ti,kw. (59)

18	antihyperlipemics.ti,kw. (0)
19	antihyperlipidemics.ti,kw. (9)
20	antilipemics.ti,kw. (10)
21	((lipid or LDL or cholesterol) adj2 lowering adj3 (treatment? or therapy or therapies)).ti,kw. (1189)
22	Atorvastatin.ti,kw. (4082)
23	lipitor.ti,kw. (62)
24	liptonorm.ti,kw. (1)
25	ci-981.ti,kw. (2)
26	ci981.ti,kw. (0)
27	Lovastatin.ti,kw. (1552)
28	6-methylcompactin.ti,kw. (0)
29	mk-803.ti,kw. (2)
30	mk803.ti,kw. (0)
31	mevacor.ti,kw. (19)
32	mevinolin.ti,kw. (111)
33	monacolin.ti,kw. (74)
34	Meglutol.ti,kw. (0)
35	beta hydroxy beta methylglutarate.ti,kw. (0)
36	3 hydroxy 3 methylglutaric acid.ti,kw. (31)
37	3 hydroxy 3 methylpentanedioic acid.ti,kw. (0)
38	Pravastatin.ti,kw. (1646)
39	bristacol.ti,kw. (0)
40	cs 514.ti,kw. (18)
41	cs514.ti,kw. (0)
42	elisor.ti,kw. (1)
43	eptastatin.ti,kw. (2)
44	lipemol.ti,kw. (0)
45	liplat.ti,kw. (0)
46	lipostat.ti,kw. (9)
47	mevalotin.ti,kw. (2)
48	prareduct.ti,kw. (0)
49	pravachol.ti,kw. (8)
50	pravacol.ti,kw. (0)
51	pravasin.ti,kw. (0)

52	rms-431.ti,kw. (1)
53	rms431.ti,kw. (0)
54	sq-31000.ti,kw. (0)
55	sq31000.ti,kw. (0)
56	selektine.ti,kw. (0)
57	vasten.ti,kw. (1)
58	Rosuvastatin.ti,kw. (1663)
59	zd 4522.ti,kw. (0)
60	zd4522.ti,kw. (0)
61	crestor.ti,kw. (12)
62	Simvastatin.ti,kw. (4494)
63	mk-733.ti,kw. (21)
64	mk733.ti,kw. (0)
65	simvastatin.ti,kw. (4494)
66	synvinolin.ti,kw. (4)
67	zocor.ti,kw. (42)
68	pitavastatin.ti,kw. (441)
69	mevinolin.ti,kw. (111)
70	glenvastatin.ti,kw. (0)
71	fluindostatin.ti,kw. (0)
72	dalvastatin.ti,kw. (2)
73	crilvastatin.ti,kw. (4)
74	tenivastatin.ti,kw. (0)
75	cerivastatin.ti,kw. (265)
76	bervastatin.ti,kw. (0)
77	compactin.ti,kw. (97)
78	or/5-77 (29339)
79	4 or 78 (46189)
80	exp *Cardiovascular Diseases/ (1839722)
81	cardiovascular disease?.ti,kw. (39232)
82	(coronary adj2 disease?).ti,kw. (48155)
83	(vascular adj2 disease?).ti,kw. (10144)
84	(heart adj2 disease?).ti,kw. (58849)
85	(cardiac adj2 disease?).ti,kw. (3255)

	86 81 or 82 or 83 or 84 or 85 (141149) 87 80 or 86 (1859054) 88 79 and 87 (14418) 89 *primary prevention/ (7942) 90 (primary adj5 prevention).ab,ti,kw. (24002) 91 primary prevention.kw. (852) 92 ((individuals or persons or people or adults) adj1 without adj2 (prior or previous)).ab,ti,kw. (335) 93 ((individuals or persons or people or adults) adj1 with no adj2 (prior or previous)).ab,ti,kw. (218) 94 ((individuals or persons or people or adults) adj3 risk?).ab,ti,kw. (38936) 95 89 or 90 or 91 or 92 or 93 or 94 (68196) 96 88 and 95 (1669) 97 (statins adj3 primary adj3 prevent*).ab,ti,kw. (384) 98 87 and 97 (287) 99 96 or 98 (1702) 100 limit 99 to systematic reviews (221) 101 limit 100 to yr="2010-2018" (132)
Note	Separate search for RCTs, see Table 42

Table 40 – Search strategy for Embase

Date	**28/02/2018**
Database	Embase
Database provider	Embase.com
Search Strategy	#105 #104 AND [2016-2018]/py 22 #104 #101 AND (random*:ab,ti OR placebo*:de,ab,ti OR ((double NEXT/1 blind*):ab,ti)) 137 #103 #102 AND ('meta-analysis'/exp OR 'meta-analysis' OR 'systematic review'/exp OR 'systematic review') 46 #102 #101 AND [2010-2018]/py 215 #101 #100 NOT [medline]/lim 405 #100 #99 NOT ([conference abstract]/lim OR [conference paper]/lim OR [conference review]/lim OR [editorial]/lim) 1788 #99 #96 OR #98 2102 #98 #87 AND #97 377 #97 (statins NEAR/3 primary NEAR/3 prevent*):ab,ti,kw 566 #96 #88 AND #95 2064

#95	#89 OR #90 OR #91 OR #92 OR #93 OR #94 91167
#94	((individuals OR persons OR people OR adults) NEAR/3 (risk OR risks)):ab,ti,kw 51186
#93	(((individuals OR persons OR people OR adults) NEAR/1 with):ab,ti,kw) AND ((no NEAR/2 (prior OR previous)):ab,ti,kw) 1860
#92	((individuals OR persons OR people OR adults) NEAR/1 without NEAR/2 (prior OR previous)):ab,ti,kw 465
#91	'primary prevention':kw 2636
#90	(primary NEAR/5 prevention):ab,ti,kw 35888
#89	'primary prevention'/mj 6986
#88	#79 AND #87 21047
#87	#80 OR #86 2548363
#86	#81 OR #82 OR #83 OR #84 OR #85 234895
#85	((cardiac NEAR/2 disease):ti,kw) OR ((cardiac NEAR/2 diseases):ti,kw) 5819
#84	((heart NEAR/2 disease):ti,kw) OR ((heart NEAR/2 diseases):ti,kw) 96700
#83	((vascular NEAR/2 disease):ti,kw) OR ((vascular NEAR/2 diseases):ti,kw) 18567
#82	((coronary NEAR/2 disease):ti,kw) OR ((coronary NEAR/2 diseases):ti,kw) 88292
#81	'cardiovascular disease':ti,kw OR 'cardiovascular diseases':ti,kw 62273
#80	'cardiovascular diseases'/exp/mj 2514086
#79	#4 OR #78 61234
#78	#5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60 OR #61 OR #62 OR #63 OR #64 OR #65 OR #66 OR #67 OR #68 OR #69 OR #70 OR #71 OR #72 OR #73 OR #74 OR #75 OR #76 OR #77 45131
#77	'compactin':ti,kw 172
#76	'bervastatin':ti,kw 1
#75	'cerivastatin':ti,kw 358
#74	'tenivastatin':ti,kw 0
#73	'crilvastatin':ti,kw 4
#72	'dalvastatin':ti,kw 3
#71	'fluindostatin':ti,kw 3
#70	'glenvastatin':ti,kw 0
#69	'mevinolin':ti,kw 186
#68	'pitavastatin':ti,kw 744
#67	'zocor':ti,kw 70
#66	'synvinolin':ti,kw 5

#65	'simvastatin':ti,kw 6821
#64	'mk733':ti,kw 0
#63	'mk-733':ti,kw 29
#62	'simvastatin':ti,kw 6821
#61	'crestor':ti,kw 32
#60	'zd4522':ti,kw 0
#59	'zd 4522':ti,kw 2
#58	'rosuvastatin':ti,kw 2747
#57	'vasten':ti,kw 3
#56	'selektine':ti,kw 1
#55	'sq31000':ti,kw 0
#54	'sq-31000':ti,kw 0
#53	'rms431':ti,kw 0
#52	'rms-431':ti,kw 1
#51	'pravasin':ti,kw 1
#50	'pravacol':ti,kw 0
#49	'pravachol':ti,kw 12
#48	'prareduct':ti,kw 0
#47	'mevalotin':ti,kw 8
#46	'lipostat':ti,kw 12
#45	'liplat':ti,kw 0
#44	'lipemol':ti,kw 0
#43	'eptastatin':ti,kw 6
#42	'elisor':ti,kw 5
#41	'cs514':ti,kw 0
#40	'cs 514':ti,kw 35
#39	'bristacol':ti,kw 0
#38	'pravastatin':ti,kw 2459
#37	'3 hydroxy 3 methylpentanedioic acid':ti,kw 0
#36	'3 hydroxy 3 methylglutaric acid':ti,kw 46
#35	'beta hydroxy beta methylglutarate':ti,kw 0
#34	'meglutol':ti,kw 1
#33	'monacolin':ti,kw 128
#32	'mevinolin':ti,kw 186

	#31 'mevacor':ti,kw 37 #30 'mk803':ti,kw 0 #29 'mk-803':ti,kw 2 #28 '6-methylcompactin':ti,kw 0 #27 'lovastatin':ti,kw 2233 #26 'ci981':ti,kw 0 #25 'ci-981':ti,kw 17 #24 'liptonorm':ti,kw 1 #23 'lipitor':ti,kw 81 #22 'atorvastatin':ti,kw 6451 #21 ((lipid OR ldl OR cholesterol) NEAR/2 lowering NEAR/3 (treatment? OR therapy OR therapies)):ti,kw 1513 #20 'antilipemics':ti,kw 6 #19 'antihyperlipidemics':ti,kw 16 #18 'antihyperlipemics':ti,kw 0 #17 (antilipemic NEAR/2 (drugs OR agents)):ti,kw 160 #16 (hypolipidemic NEAR/2 (agents OR drugs)):ti,kw 416 #15 'cholesterol inhibitors':ti,kw 8 #14 'anticholesteremics':ti,kw 0 #13 (hypocholesteremic NEAR/2 (drugs OR agents)):ti,kw 42 #12 (anticholesteremic NEAR/2 (drugs OR agents)):ti,kw 52 #11 'anticholesteremic agents':ti,kw 51 #10 'hypolipidemic agents':ti,kw 204 #9 'statin':ti,kw OR 'statins':ti,kw 25130 #8 'hydroxymethylglutaryl-coenzyme a inhibitors':ti,kw 4 #7 'hydroxymethylglutaryl-coa inhibitors':ti,kw 0 #6 'hmg-coa reductase inhibitors':ti,kw 1486 #5 'hydroxymethylglutaryl-coa reductase inhibitors':ti,kw 393 #4 #1 OR #2 OR #3 53011 #3 'hypocholesterolemic agent'/mj 4422 #2 'antilipemic agent'/mj 8057 #1 'hydroxymethylglutaryl coenzyme a reductase inhibitor'/exp/mj 42821
Note	Line #102 for SRs, line #105 for RCTs.

Table 41 – Search strategy for Cochrane

Date	**28/02/18 14:07:26.977**	
Database	Cochrane Database or Systematic Reviews	
Database provider	Wiley.com	
Search Strategy	#1	[mh "Hydroxymethylglutaryl-CoA Reductase Inhibitors" [mj]] 460
	#2	[mh ^"Hypolipidemic Agents" [mj]] 8
	#3	[mh ^"Anticholesteremic Agents" [mj]] 7
	#4	#1 or #2 or #3 474
	#5	Hydroxymethylglutaryl-CoA Reductase Inhibitors:ab,ti,kw 3596
	#6	hmg-coa reductase inhibitors:ab,ti,kw 589
	#7	hydroxymethylglutaryl-coa inhibitors:ab,ti,kw 3603
	#8	hydroxymethylglutaryl-coenzyme a inhibitors:ab,ti,kw 700
	#9	statin:ti,kw or statins:ab,ti,kw 5073
	#10	Hypolipidemic Agents:ab,ti,kw 1600
	#11	Anticholesteremic Agents:ab,ti,kw 2541
	#12	(anticholesteremic near/2 (drugs or agents)):ab,ti,kw 2540
	#13	(hypocholesteremic near/2 (drugs or agents)):ab,ti,kw 2
	#14	anticholesteremics:ab,ti,kw 1
	#15	cholesterol inhibitors:ab,ti,kw 3284
	#16	(hypolipidemic near/2 (agents or drugs)):ab,ti,kw 1576
	#17	(antilipemic near/2 (drugs or agents)):ab,ti,kw 79
	#18	antihyperlipemics:ab,ti,kw 1
	#19	antihyperlipidemics:ab,ti,kw 3
	#20	antilipemics:ab,ti,kw 1
	#21	((lipid or LDL or cholesterol) near/2 lowering near/3 (treatment? or therapy or therapies)):ab,ti,kw 964
	#22	Atorvastatin:ab,ti,kw 3745
	#23	lipitor:ab,ti,kw 29
	#24	liptonorm:ab,ti,kw 0
	#25	ci-981:ab,ti,kw 7
	#26	ci981:ab,ti,kw 0
	#27	Lovastatin:ab,ti,kw 817
	#28	6-methylcompactin:ab,ti,kw 2
	#29	mk-803:ab,ti,kw 1

#30	mk803:ab,ti,kw	0
#31	mevacor:ab,ti,kw	9
#32	mevinolin:ab,ti,kw	252
#33	monacolin:ab,ti,kw	22
#34	Meglutol:ab,ti,kw	2
#35	beta hydroxy beta methylglutarate:ab,ti,kw	0
#36	3 hydroxy 3 methylglutaric acid:ab,ti,kw	9
#37	3 hydroxy 3 methylpentanedioic acid:ab,ti,kw	0
#38	Pravastatin:ab,ti,kw	1690
#39	bristacol:ab,ti,kw	0
#40	cs 514:ab,ti,kw	17
#41	cs514:ab,ti,kw	0
#42	elisor:ab,ti,kw	1
#43	eptastatin:ab,ti,kw	3
#44	lipemol:ab,ti,kw	0
#45	liplat:ab,ti,kw	0
#46	lipostat:ab,ti,kw	1
#47	mevalotin:ab,ti,kw	3
#48	prareduct:ab,ti,kw	0
#49	pravachol:ab,ti,kw	5
#50	pravacol:ab,ti,kw	0
#51	pravasin:ab,ti,kw	0
#52	rms-431:ab,ti,kw	0
#53	rms431:ab,ti,kw	0
#54	sq-31000:ab,ti,kw	0
#55	sq31000:ab,ti,kw	0
#56	selektine:ab,ti,kw	0
#57	vasten:ab,ti,kw	0
#58	Rosuvastatin:ab,ti,kw	1521
#59	zd 4522:ab,ti,kw	0
#60	zd4522:ab,ti,kw	20
#61	crestor:ab,ti,kw	15
#62	Simvastatin:ab,ti,kw	2915
#63	mk-733:ab,ti,kw	18

#64	mk733:ab,ti,kw	1
#65	simvastatin:ab,ti,kw	2915
#66	synvinolin:ab,ti,kw	8
#67	zocor:ab,ti,kw	33
#68	pitavastatin:ab,ti,kw	267
#69	mevinolin:ab,ti,kw	252
#70	glenvastatin:ab,ti,kw	0
#71	fluindostatin:ab,ti,kw	256
#72	dalvastatin:ab,ti,kw	0
#73	crilvastatin:ab,ti,kw	0
#74	tenivastatin:ab,ti,kw	4
#75	cerivastatin:ab,ti,kw	162
#76	bervastatin:ab,ti,kw	0
#77	compactin:ab,ti,kw	4
#78	#5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40 or #41 or #42 or #43 or #44 or #45 or #46 or #47 or #48 or #49 or #50 or #51 or #52 or #53 or #54 or #55 or #56 or #57 or #58 or #59 or #60 or #61 or #62 or #63 or #64 or #65 or #66 or #67 or #68 or #69 or #70 or #71 or #72 or #73 or #74 or #75 or #76 or #77	14178
#79	#4 or #78	14178
#80	[mh "Cardiovascular Diseases" [mj]]	19023
#81	cardiovascular disease:ti,kw or cardiovascular diseases:ab,ti,kw	28694
#82	(coronary near/2 disease):ti,kw or (coronary near/2 diseases):ab,ti,kw	16193
#83	(vascular near/2 disease):ti,kw or (vascular near/2 diseases):ab,ti,kw	3201
#84	(heart near/2 disease):ti,kw or (heart near/2 diseases):ab,ti,kw	11731
#85	(cardiac near/2 disease):ti,kw or (cardiac near/2 diseases):ab,ti,kw	362
#86	#81 or #82 or #83 or #84 or #85	46616
#87	#80 or #86	60006
#88	#79 and #87	4570
#89	[mh ^"primary prevention" [mj]]	61
#90	(primary near/5 prevention):ab,ti,kw	4390
#91	primary prevention:kw	11091
#92	((individuals or persons or people or adults) near/1 without near/2 (prior or previous)):ab,ti,kw	19
#93	((individuals or persons or people or adults) near/1 with no near/2 (prior or previous)):ab,ti,kw	189
#94	((individuals or persons or people or adults) near/3 (risk or risks)):ab,ti,kw	3432

	#95	#89 or #90 or #91 or #92 or #93 or #94	16086	
	#96	#88 and #95	592	
	#97	(statins near/3 primary near/3 prevent*):ab,ti,kw		53
	#98	#87 and #97	39	
	#99	#96 or #98	593	
	#100	#99 Publication Year from 2010 to 2018	335	
	#101	#99 Publication Year from 2016 to 2018	105	
Note	Line #100 was used to export SRs and line #101 to extract RCTs as Wiley allows to search both databases with the same strategy, and to select the database at the end.			

Appendix 2.2. Search strategy for RCTs in Medline

Only the search in Medline was slightly adapted for the search for RCTs. For the others databases, see notes under each search strategy in the previous section.

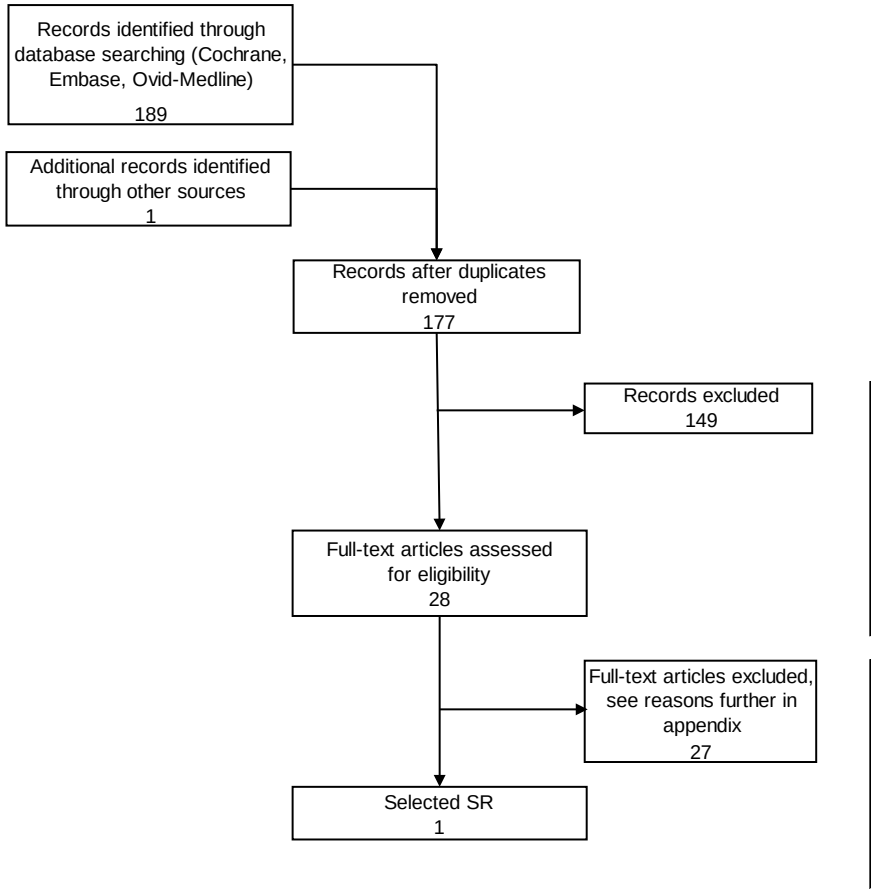
Table 42 – Search strategy for RCTs in Medline

Date	
Database	Medline
Segments	
Database provider	OvidSp
Search Strategy	1 *Hydroxymethylglutaryl-CoA Reductase Inhibitors/ (18913) 2 *Hypolipidemic Agents/ (9368) 3 *Anticholesteremic Agents/ (10654) 4 1 or 2 or 3 (36194) 5 Hydroxymethylglutaryl-CoA Reductase Inhibitors.ti,kw. (184) 6 hmg-coa reductase inhibitors.ti,kw. (687) 7 hydroxymethylglutaryl-coa inhibitors.ti,kw. (0) 8 hydroxymethylglutaryl-coenzyme a inhibitors.ti,kw. (1) 9 statin?.ti,kw. (14723) 10 Hypolipidemic Agents.ti,kw. (158) 11 Anticholesteremic Agents.ti,kw. (94) 12 (anticholesteremic adj2 (drugs or agents)).ti,kw. (12) 13 (hypocholesteremic adj2 (drugs or agents)).ti,kw. (43) 14 anticholesteremics.ti,kw. (0) 15 cholesterol inhibitors.ti,kw. (2) 16 (hypolipidemic adj2 (agents or drugs)).ti,kw. (255) 17 (antilipemic adj2 (drugs or agents)).ti,kw. (59) 18 antihyperlipemics.ti,kw. (0) 19 antihyperlipidemics.ti,kw. (9) 20 antilipemics.ti,kw. (10) 21 ((lipid or LDL or cholesterol) adj2 lowering adj3 (treatment? or therapy or therapies)).ti. (1189) 22 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 (16839) 23 4 or 22 (40124) 24 exp *Cardiovascular Diseases/ (1839722)

	25	cardiovascular disease?.ti,kw. (39232)
	26	(coronary adj2 disease?).ti,kw. (48155)
	27	(vascular adj2 disease?).ti,kw. (10144)
	28	25 or 26 or 27 (96901)
	29	24 or 28 (1854540)
	30	23 and 29 (13343)
	31	*primary prevention/ (7942)
	32	(primary adj5 prevention).ab,ti,kw. (24002)
	33	primary prevention.kw. (852)
	34	((individuals or persons or people or adults) adj1 without adj1 prior).ab,ti,kw. (128)
	35	((individuals or persons or people or adults) adj3 "low risk").ab,ti,kw. (780)
	36	31 or 32 or 33 or 34 or 35 (30758)
	37	36 and 30 (1452)
	38	(statins adj3 primary adj3 prevent*).ab,ti,kw. (384)
	39	38 or 37 (1584)
	40	randomized controlled trial.pt. (454399)
	41	controlled clinical trial.pt. (92180)
	42	randomized.ti,ab. (435238)
	43	placebo.ti,ab. (191846)
	44	clinical trials as topic/ (182690)
	45	randomly.ti,ab. (286641)
	46	trial?.ti. (239846)
	47	40 or 41 or 42 or 43 or 44 or 45 or 46 (1164286)
	48	exp animal/ not humans/ (4429349)
	49	47 not 48 (1073046)
	50	39 and 49 (560)
	51	limit 50 to yr="2016-2018" (53)
Note		

Appendix 2.3. Selection of studies from search strategy

Figure 27 – Flow chart of literature search for SRs



In total we retrieved 133 references for new primary studies since 2016 (including 8 duplicates). However, none of these references fulfilled the inclusion criteria, i.e. no new RCT's for the efficacy of statins in primary prevention.

Appendix 2.4. Inclusion and exclusion criteria

Table 43 – Inclusion criteria for studies in the systematic review on clinical outcomes

Item	Inclusion	Exclusion
Population	• Adult individuals without established CVD (including individuals with type1/type2 diabetes, CKD, and family hypercholesterolemia)	• Secondary prevention
Intervention	• Atorvastatin (alone or in combination with fibrate or ezetimibe) • Fluvastatin (alone or in combination with fibrate or ezetimibe) • Pravastatin (alone or in combination with fibrate or ezetimibe) • Rosuvastatin (alone or in combination with fibrate or ezetimibe) • Simvastatin (alone or in combination with fibrate or ezetimibe)	
Comparison	• Other interventions (diet, physical activity) • Placebo	
Outcomes	• All-cause mortality • CV mortality • Fatal and non-fatal myocardial infarction • Fatal and non-fatal stroke • Quality of life • Adverse events: myalgia; rhabdomyolysis (CK more than 10 times the upper limit of normal); liver (transaminases more than 3 times the upper limit of normal); new-onset diabetes; others	• Atrial fibrillation • Venous thrombo-embolism • Dementia
Study design	• SRs of RCTs published since 2010 • RCTs with minimum 1 year follow up published since the last search of the most recent SR	

Table 44 – Excluded SR and reasons

Studies	Reasons for exclusion
Kamran 2018[51]	No other outcomes than new-onset diabetes
Nunes 2017[50]	No other outcomes than mortality
Kunustor 2017[49]	Main outcome is venous thromboembolism
Pandit 2016[48]	Main outcome is intracerebral haemorrhage
Karmali 2016[47]	Overview of reviews with review by Chou 2016 not included

Appendix 2.5. Quality appraisal

Table 45 – Quality appraisal of the SR by Chou et al.[46] based on AMSTAR-2(Shea et al.)

1. Did the research questions and inclusion criteria for the review include the components of PICO?

For Yes:

- ☒ **Population**
- ☒ **Intervention**
- ☒ **Comparator group**
- ☒ **Outcome**

Optional (recommended)

- ☐ Timeframe for follow-up

- ☒ Yes
- ☐ NO

2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?

For Partial Yes:

The authors state that they had a written protocol or guide that included ALL the following:

- ☒ **review question(s)**
- ☒ **a search strategy**
- ☒ **inclusion/exclusion criteria**
- ☒ **a risk of bias assessment**

For Yes:

As for partial yes, plus the protocol should be registered and should also have specified:

- ☒ a meta-analysis/synthesis plan, if appropriate, and
- ☒ a plan for investigating causes of heterogeneity
- ☒ justification for any deviations from the protocol

- ☒ Yes
- ☐ Partial Yes
- ☐ No

3. Did the review authors explain their selection of the study designs for inclusion in the review?

For Yes, the review should satisfy ONE of the following:

☐ **Explanation for including only RCTs** ☐ **OR Explanation for including only Non Randomised Study of Intervention (NRSI)** ☒ **OR Explanation for including both RCTs and NRSI**	☒ Yes ☐ No
4. Did the review authors use a comprehensive literature search strategy?	
For Partial Yes (all the following): ☒ **searched at least 2 databases (relevant to research question)** ☒ **provided key word and/or search strategy** ☒ **justified publication restrictions (e.g. language)**	For Yes, should also have (all the following): ☒ searched the reference lists / bibliographies of included studies ☒ searched trial/study registries ☒ included/consulted content experts in the field ☐ where relevant, searched for grey literature ☒ conducted search within 24 months of completion of the review
	☒ Yes ☐ Partial Yes ☐ No
4. **Did the review authors perform study selection in duplicate?**	
For Yes, either ONE of the following: ☒ **at least two reviewers independently agreed on selection of eligible studies and achieved consensus on which studies to include** ☐ **OR two reviewers selected a sample of eligible studies and achieved good agreement (at least 80 percent), with the remainder selected by one reviewer.**	☒ Yes ☐ No
5. **Did the review authors perform data extraction in duplicate?**	
For Yes, either ONE of the following: ☐ **at least two reviewers achieved consensus on which data to extract from included studies** ☐ **OR two reviewers extracted data from a sample of eligible studies and achieved good agreement (at least 80 percent), with the remainder extracted by one reviewer.**	☐ Yes ☒ No
6. **Did the review authors provide a list of excluded studies and justify the exclusions?**	
For Partial Yes ☒ **provided a list of all potentially relevant studies that were read in full-text form but excluded from the review**	For Yes, must also have: ☒ Justified the exclusion from the review of each potentially relevant study
	☒ Yes ☐ Partial Yes ☐ No

7. Did the review authors describe the included studies in adequate detail?		
For Partial Yes (ALL the following): ☒ **described populations** ☒ **described interventions** ☒ **described comparators** ☒ **described outcomes** ☒ **described research design**	For Yes, should also have ALL the following: ☒ described population in detail ☒ described intervention in detail (including doses where relevant) ☒ described comparator in detail (including doses where relevant) ☒ described study's setting ☒ timeframe for follow-up	☒ Yes ☐ Partial Yes ☐ No

8. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?		
RCTs **For Partial Yes, must have assessed RoB from** ☒ **unconcealed allocation, and** ☒ **lack of blinding of patients and assessors when assessing outcomes (unnecessary for objective outcomes such as all- cause mortality)**	For Yes, must also have assessed RoB from: ☒ allocation sequence that was not truly random, and ☒ selection of the reported result from among multiple measurements or analyses of a specified outcome	☒ Yes ☐ Partial Yes ☐ No ☐ Includes only NRSI
NRSI **For Partial Yes, must have assessed RoB:** ☒ **from confounding, and** ☒ **from selection bias**	For Yes, must also have assessed RoB: ☒ methods used to ascertain exposures and outcomes, and ☒ selection of the reported result from among multiple measurements or analyses of a specified outcome	☒ Yes ☐ Partial Yes ☐ No ☐ Includes only RCTs

9. Did the review authors report on the sources of funding for the studies included in the review?	
For Yes ☒ **Must have reported on the sources of funding for individual studies included in the review. Note: Reporting that the reviewers looked for this information. No but it was not reported by study authors also qualifies**	☒ Yes ☐ No

10. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?

RCTs

For Yes:

- ☒ **The authors justified combining the data in a meta-analysis**
- ☒ **AND they used an appropriate weighted technique to combine study results and adjusted for heterogeneity if present.**
- ☒ **AND investigated the causes of any heterogeneity**

☒ Yes
☐ No
☐ No meta-analysis conducted

For NRSI

For Yes:

- ☐ **The authors justified combining the data in a meta-analysis**
- ☐ **AND they used an appropriate weighted technique to combine study results, adjusting for heterogeneity if present**
- ☐ **AND they statistically combined effect estimates from NRSI that were adjusted for confounding, rather than combining raw data, or justified combining raw data when adjusted effect estimates were not available**
- ☐ **AND they reported separate summary estimates for RCTs and NRSI separately when both were included in the review**

☐ Yes
☐ No
☒ No meta-analysis conducted

11. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?

For Yes:

- ☐ **included only low risk of bias RCTs**
- ☒ **OR, if the pooled estimate was based on RCTs and/or NRSI at variable RoB, the authors performed analyses to investigate possible impact of RoB on summary estimates of effect.**

☒ Yes
☐ No
☐ No meta-analysis conducted

12. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?

For Yes:

- ☐ **included only low risk of bias RCTs**
- ☒ **OR, if RCTs with moderate or high RoB, or NRSI were included the review provided a discussion of the likely impact of RoB on the results**

☒ Yes
☐ No

13. **Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?**	
For Yes: ☐ **There was no significant heterogeneity in the results** ☒ **OR if heterogeneity was present the authors performed an investigation of sources of any heterogeneity in the results and discussed the impact of this on the results of the review**	☒ Yes ☐ No
14. **If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?**	
For Yes: ☒ **performed graphical or statistical tests for publication bias and discussed the likelihood and magnitude of impact of publication bias**	☒ Yes ☐ No ☐ No meta-analysis conducted
15. **Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?**	
For Yes: ☒ **The authors reported no competing interests OR** ☐ **The authors described their funding sources and how they managed potential conflicts of interest**	☒ Yes ☐ No

Appendix 2.6. Characteristics of included RCTs

Table 46 – Characteristics of included RCTs

Study	Year	Inclusion Criteria	N	Intervention (md/day)	Intensity	Duration (year)	Run in	Early termination	Comments
ACAPS[65]	1994	-Ages 40 to 79 years -LDL-C 160 to 189 mg/dL with ≤1 risk factors, 130 to 159 mg/dL with >1 risk factor at baseline, or TG ≤400 mg/dL after intensive dietary treatment -Early-onset carotid atherosclerosis	919 (n=460)	Lovastatin 20 Lovastatin 40[jj]	Low Moderate	3	Yes/P	No	Not primary prevention in general population (asymptomatic Carotid Plaque)
AFCAPS/TexCAPS[59]	1998	-Ages 45 to 73 years (men) or 55 to 73 years (women) -TC 180 to 264 mg/dL; LDL-C 130 to 190 mg/dL; HDL-C ≤45 mg/dL (men) or ≤47 mg/dL (women) TG ≤400 mg/dL[kk].	6605 (n=3304)	Lovastatin 20 Lovastatin 40[ll]	Low Moderate	5	Yes/P	No	>20% overall loss to followup
ASCOT-LLA[73]	2003	-Ages 40 to 79 years -TC ≤251 mg/dL; TG <399 mg/dL -Untreated or treated hypertension -No current fibrate or statin use -≥3 CVD risk factors[mm]	10335 (n=5168)	Atorvastatin10[nn]	Moderate	3	Yes/NR	Yes	18% with history of CVD (History of stroke or TIA: 10%; PVD: 5%; Other CVD: 4%
ASPEN[69]	2006	- Ages 40 to 75 years - LDL-C <160 mg/dL	1905[oo] (n=959)	Atorvastatin 10	Moderate	4	Yes/P	No	22% drop-outs; <10% with clinical evidence of CVD

[jj] Titrated to 40 mg/day for target LDL-C of 90 to 110 mg/dL

[kk] Also included patients with LDL-C 125 to 129 mg/dL if TC-to-HDL-C ratio >6.0

[ll] Titrated to 20 to 40 mg/day for target LDL-C of ≤110 mg/dL

[mm] Left-ventricular hypertrophy, other ECG abnormalities, type 2 diabetes, peripheral arterial disease, previous stroke or transient ischaemic attack, male sex, age >55 years, microalbuminuria or proteinuria, smoking, ratio TC/HDL-C≥6, premature family history of CHD.

[nn] 2x2 factorial trial : participants also randomized to ß-blocker vs. Ca channel blocker

[oo] 2410 individuals were included, but 1905 were in primary prevention (no prior myocardial infarction)

		- Diabetes							
ASTRONOMER[68]	2010	- Ages 18 to 82 years - Lipids within target levels for respective risk categories according to Canadian guidelines - Asymptomatic mild or moderate aortic stenosis (aortic valve velocity, 2.5 to 4.0 m/s) -No clinical indications for statin use (CAD, cerebrovascular disease, PVD, diabetes)	271 (n=136)	Rosuvastatin 40	High	4	No	No	Not primary prevention in general population (asymptomatic mild or moderate aortic stenosis)
Beishuizen[70]	2004	- Ages 30 to 80 years - TC 155 to 267 mg/dL; TG ≤531 mg/dL - Type 2 diabetes (duration ≥1 year) - No history of CVD	250 (n=125)	Cerivastatin 0.4[pp]	Moderate	2	No	No	
Bone[60]	2007	-Women ages 40 to 75 years -LDL-C ≥130 to <190 mg/dL[qq] -No history of diabetes or CHD	626 (n=507)	Atorvastatin 10 Atorvastatin 20 Atorvastatin 40 Atorvastatin 80	Moderate Moderate High High	1	Yes	No	Outcome is change in bone mineral density
CAIUS[66]	1996	-Ages 45 to 65 years -LDL-C 150 to 250 mg/dL; TG <250 mg/dL -No symptomatic CAD - ≥1 carotid artery lesion	305 (n=151)	Pravastatin 40	Moderate	3	Yes/P	No	Not primary prevention in general population (increased carotid intima thickness); family history of CVD: 45%
CARDS[71]	2004	-Ages 40 to 75 years -LDL-C ≤160 mg/dL;TG ≤600 mg/dL - Diabetes and ≥1 additional risk factor for CHD[rr];	2838 (n=1428)	Atorvastatin 10	Moderate	4	No	Yes	

[pp] After mean of 15 months, switched to simvastatin 20 mg/day

[qq] Criteria modified during trial to women with LDL- C ≥160 mg/dL and ≥2 CVD risk factors

[rr] Hypertension (treated or not ; retinopathy ; micor/macro-albuminuria ; smoking

		- No previous CVD events; BMI <35 kg/m2 ; HbA1c <12%; SBP <200 mm Hg; DBP <110 mm Hg -Not receiving any other lipid-lowering medication							
Heljic[72]	2009	-Obese patients with diabetes - TG ≤266 mg/dL[ss] -No preexisting CHD	95 (n=45)	Simvastatin 40	Moderate	1	No	No	
HOPE-3[52]	2016	-Men age ≥55 years and women age ≥65 years -≥1 CV risk factors[tt] or women age ≥60 years with ≥2 CV risk factors	12705 (n=6361)	Rosuvastatin 10	Moderate	6	Yes[uu]	No	Family history of early CHD: 26%; low HDL-C: 36%; Asian: 50%
HYRIM[74]	2005	-Men ages 40 to 74 years -TC 174 to 309 mg/dL; TG <399 mg/dL -Treatment for hypertension - BMI 25 to 35 kg/m2 - <1 hour/week of regular exercise	568 (n=283)	Fluvastatin 40[vv]	Low	4	NR	No	
JUPITER[76]	2008	-Men age ≥50 years or women age ≥60 years - LDL-C <130 mg/dL; TG <500 mg/dL -CRP ≥2.0 mg/L -No history of CVD	17802 (n=8901)	Rosuvastatin 20	High	2	Yes/P	Yes	Family history of CHD: 12%; metabolic syndrome: 42%; elevated CRP
KAPS[61]	1995	-Men aged 42-60 years -LDL-C ≥164 mg/dL; TC <308 mg/dL -BMI <32 kg/m2 -ALT <1.5 ULN	447 (n=224)	Pravastatin 40	Moderate	3	Yes/P	No	7.5% with prior MI. High risk of bias (ITT not used, 17% patient dropped out)

ss States LDL-C used as entry criterion but values NR

tt Including elevated waist- to-hip ratio, low HDL-C, current or recent tobacco use, dysglycemia, family history of premature CHD, or mild renal dysfunction)

uu Eligible participants entered a single-blind run-in phase, during which they received active treatments (both for blood-pressure lowering and for cholesterol lowering) for 4 weeks. Participants who adhered to the assigned regimen and who did not have an unacceptable level of adverse events were randomly assigned

vv This was a 2x2 factorial trial. Participants were also randomized to lifestyle intervention (physical activity plus dietary intervention) vs. usual care.

MEGA[62]	2006	-Ages 40 to 70 years -TC 220 to 270 mg/dL -No history of CHD or stroke	7832 (n=3866)	Pravastatin 10[ww]	Low	5	No	No	High risk of bias (single blinded; not all adverse events reported)
METEOR[67]	2007	-Men aged 45 to 70 years or women aged 55 to 70 years -LDL-C 120 to <190 mg/dL if age only risk factor or LDL-C 120 to <160 mg/dL if ≥2 CHD risk factors and 10-year CHD risk <10% -HDL-C ≤60 mg/dL; TG <500 mg/dL - Maximum CIMT 1.2 to <3.5 mm	984 (n=702)	Rosuvastatin 40	High	2	No	No	Outcome is progression of carotid atherosclerosis; Family history of CHD: 9.6% 25-6% dropped out.
Muldoon[63]	2004	-ages 35 to 70 years -LDL-C between160 and 220 mg/dL	308 (n=206)	Simvastatin 10 Simvastatin 40	Low Moderate	0.5	No	No	Outcome is cognitive performance/treatment length is 6 months/small sample size 30% of participants dropped-out
PREVEND-IT[75]	2004	-Ages 28 to 75 years - TC <309 mg/dL or <193 mg/dL if previous MI -Persistent microalbuminuria -BP <160/100 mm Hg and no antihypertensive medication -No lipid-lowering medications	864 (n=433)	Pravastatin 40	Moderate	4	No	No	3% with history of CVD
WOSCOPS [64]	1995	-Men ages 45 to 64 years - LDL-C >155 mg/dL; TC >251 mg/dL -No significant CAD	6995 (n=3302)	Pravastatin 40	Moderate	5	No	No	5% with angina, 3% with intermittent claudication, 8 with minor ECG abnormality; 30% drop-outs

** As assessed by Chou et al. [2]*

[ww] Titrated to 20 mg/day for target TC of <220 mg/dL. All participants also received intensive lipid control with diet. No placebo (single blind).

Table 47 – Pooled estimates for statins versus placebo and sensitivity analyses (adapted from Chou et al.)

Analysis	All-cause mortality	CV mortality	Stroke	Myocardial infarction	Revascularization	Composite CV outcomes
All trials						
RR (95% CI)	0.86 (0.80 to 0.93) I^2=0%	0.69 (0.54 to 0.88) I^2=54%	0.71 (0.62 to 0.82) I^2=0%	0.64 (0.57 to 0.71) I^2=0%	0.63 (0.56 to 0.72) I^2=0%	0.70 (0.63 to 0.78) I^2=37%
ARD (95% CI)	-0.40% (-0.64 to -0.17)	-0.43% (-0.75 to -0.11)	-0.38% (-0.53 to -0.23)	-0.81% (-1.19 to -0.43)	-0.66% (-0.87 to -0.45)	-1.39% (-1.79 to -0.99)
Number of trials	14	10	13	12	7	13
Excluding trials stopped early						
RR (95% CI)	0.89 (0.80 to 0.99) I^2=0%	0.70 (0.52 to 0.94) I^2=38%	0.75 (0.63 to 0.90) I^2=0%	0.65 (0.57 to 0.74) I^2=0%	0.66 (0.57 to 0.77) I^2=0%	0.71 (0.63 to 0.81) I^2=35%
ARD (95% CI)	-0.39% (-0.75 to -0.03)	-0.39% (-0.78 to 0.01)	-0.40% (-0.63 to 0.16)	-0.90% (-1.43 to -0.37)	-0.70% (-1.03 to -0.37)	-1.54% (-2.16 to -0.93)
Number of trials	12	8	11	10	5	11
Good-quality trials						
RR (95% CI)	0.85 (0.77 to 0.94) I^2=0%	0.64 (0.44 to 0.93) I^2=73%	0.68 (0.56 to 0.83) I^2=0%	0.61 (0.51 to 0.72) I^2=8%	0.62 (0.52 to 0.74) I^2=0%	0.69 (0.61 to 0.78) I^2=28%
ARD (95% CI)	-0.59% (-0.94 to -0.24)	-0.63% (-1.24 to 0.02)	-0.36% (-0.54 to -0.19)	-1.05% (-1.71 to -0.39)	-0.60% (-0.82 to -0.39)	-1.35% (-1.81 to -0.88)
Number of trials	5	5	6	6	5	4
Follow-up >3 years						
RR (95% CI)	0.88 (0.80 to 0.98) I^2=0%	0.71 (0.53 to 0.96) I^2=42%	0.77 (0.64 to 0.92) I^2=0%	0.65 (0.56 to 0.74) I^2=0%	0.66 (0.57 to 0.77) I^2=0%	0.74 (0.67 to 0.81) I^2=8%
ARD (95% CI)	-0.43% (-0.77 to -0.10)	-0.32% (-0.72 to 0.08)	-0.36% (-0.61 to 0.12)	-1.00% (-1.59 to -0.41)	-0.73% (-1.10 to -0.36)	-1.35% (-1.81 to -0.90)
Number of trials	8	6	7	7	5	8
Patients with prior CV disease excluded						
RR (95% CI)	0.87 (0.79 to 0.95) I^2=8%	0.59 (0.39 to 0.88) I^2=71%	0.70 (0.60 to 0.83) I^2=0%	0.63 (0.55 to 0.72) I^2=0%	0.63 (0.55 to 0.72) I^2=0%	0.69 (0.60 to 0.78) I^2=45%
ARD (95% CI)	-0.46% (-0.76 to -0.16)	-0.52% (-0.98 to -0.06)	-0.37% (-0.53 to -0.21)	-0.73% (-1.12 to -0.34)	-0.68% (-0.92 to -0.43)	-1.45% (-1.94 to -0.96)
Number of trials	11	6	10	10	6	11
Baseline mean LDL-C <160 mg/dL						
RR (95% CI)	0.87 (0.80 to 0.95) I^2=0%	0.67 (0.50 to 0.91) I^2=64%	0.70 (0.60 to 0.81) I^2=0%	0.61 (0.54 to 0.70) I^2=0%	0.63 (0.55 to 0.73) I^2=0%	0.70 (0.61 to 0.79) I^2=46%

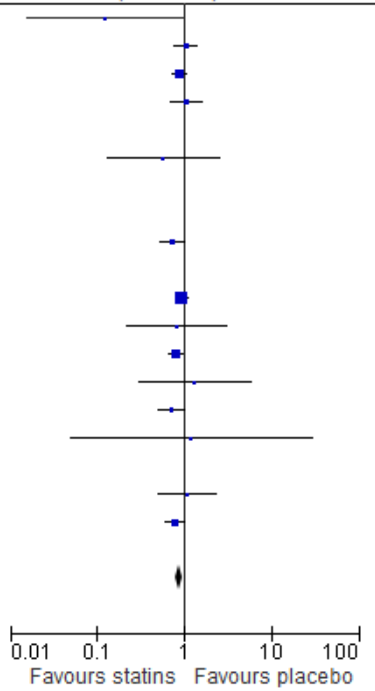
ARD (95% CI)	-0.38% (-0.63 to -0.13)	-0.41% (-0.77 to -0.06)	-0.40% (-0.56 to -0.24)	-0.67% (-0.99 to -0.34)	-0.66% (-0.94 to -0.38)	-1.29% (-1.68 to -0.90)
Number of trials	13	8	9	9	5	11
Excluding trials restricted to patients with diabetes						
RR (95% CI)	0.87 (0.80 to 0.94) I^2=0%	0.69 (0.54 to 0.88) I^2=54%				
ARD (95% CI)	-0.39% (-0.63 to -0.15)	-0.43% (-0.75 to -0.11)				
Number of trials	11	10				
Excluding trials restricted to patients with early cerebrovascular disease or aortic stenosis						
RR (95% CI)	0.86 (0.80 to 0.93) I^2=0%	0.73 (0.60 to 0.83) I^2=39%				
ARD (95% CI)	-0.45% (-0.70 to -0.21)	-0.37% (-0.61 to -0.12)				
Number of trials	12	7				

Appendix 2.7. Meta-analyses

Figure 28 – Meta-analysis of all-cause mortality

Study or Subgroup	Statin Events	Statin Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F G
ACAPS{Furberg, 1994 #12}	1	460	8	459	0.1%	0.12 [0.02, 0.99]	+ ? + ? + + ?
AFCAPS/TexCAPS{Downs, 1998 #13}	80	3304	77	3301	6.6%	1.04 [0.76, 1.41]	? ? + + + + ?
ASCOT-LLA{Sever, 2003 #14}	185	5168	212	5137	17.0%	0.87 [0.71, 1.05]	? ? ? ? + + −
ASPEN{Knopp, 2006 #15}	44	959	41	946	3.7%	1.06 [0.70, 1.60]	? ? + ? + ? ?
ASTRONOMER{Chan, 2010 #16}	0	0	0	0		Not estimable	+ ? + + + + ?
Beishuizen{Beishuizen, 2004 #17}	3	103	4	79	0.3%	0.58 [0.13, 2.50]	+ ? ? + − + ?
Bone{Bone, 2007 #18}	0	485	0	119		Not estimable	+ ? ? ? + + ?
CAIUS{Mercuri, 1996 #19}	0	0	0	0		Not estimable	+ + ? ? + + ?
CARDS{Colhoun, 2004 #20}	61	1428	82	1410	6.1%	0.73 [0.53, 1.01]	+ + + + + + −
Heljic{Heljic, 2009 #21}	0	0	0	0		Not estimable	− ? ? ? ? + +
HOPE-3{Yusuf, 2016 #23}	334	6361	357	6344	30.2%	0.93 [0.81, 1.08]	+ + + + + + +
HYRIM{Anderssen, 2005 #22}	4	283	5	285	0.4%	0.81 [0.22, 2.97]	? ? ? ? ? − ?
JUPITER{Ridker, 2008 #24}	198	8901	247	8901	18.6%	0.80 [0.67, 0.96]	+ + + + + + −
KAPS{Salonen, 1995 #25}	4	214	3	212	0.3%	1.32 [0.30, 5.83]	+ ? + + − + ?
MEGA{Nakamura, 2006 #26}	55	3866	79	3966	5.4%	0.71 [0.51, 1.00]	+ + − ? + − ?
METEOR{Crouse, 2007 #27}	1	700	0	281	0.1%	1.21 [0.05, 29.54]	+ ? + + + + ?
Muldoon{Muldoon, 2004 #28}	0	0	0	0		Not estimable	? ? ? ? + + +
PREVEND-IT{Asselbergs, 2004 #29}	13	433	12	431	1.1%	1.08 [0.50, 2.34]	+ + + + ? + ?
WOSCOPS{Shepherd, 1995 #30}	106	3302	135	3293	10.2%	0.78 [0.61, 1.01]	+ ? + + ? + ?
Total (95% CI)		**35967**		**35164**	**100.0%**	**0.86 [0.80, 0.93]**	
Total events	1089		1262				

Heterogeneity: Tau² = 0.00; Chi² = 11.07, df = 13 (P = 0.60); I² = 0%
Test for overall effect: Z = 3.63 (P = 0.0003)



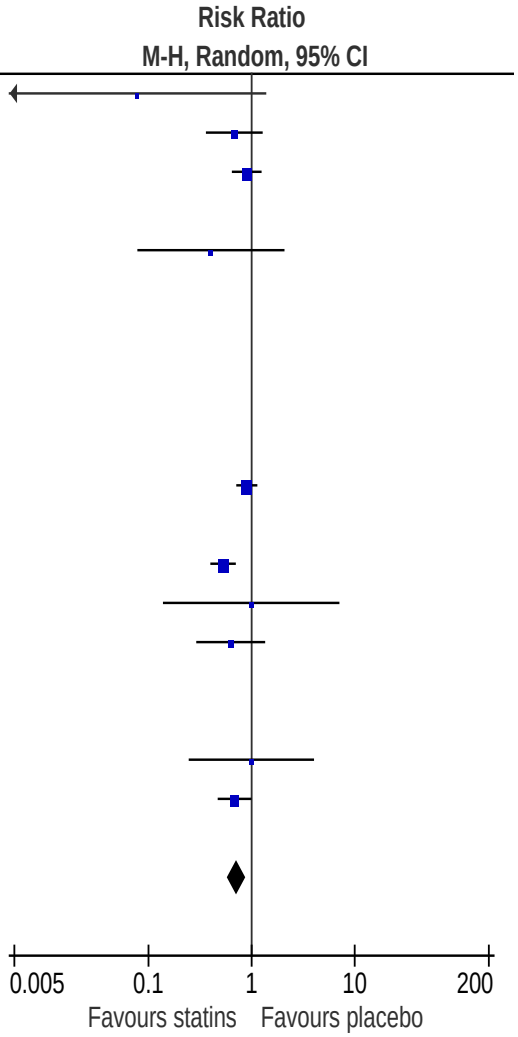
Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Figure 29 – Corrected meta-analysis of CVD mortality

Study or Subgroup	Statin Events	Statin Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
ACAPS{Furberg, 1994 #12}	0	460	6	459	0.5%	0.08 [0.00, 1.36]
AFCAPS/TexCAPS{Downs, 1998 #13}	17	3304	25	3301	8.2%	0.68 [0.37, 1.26]
ASCOT-LLA{Sever, 2003 #14}	74	5168	82	5137	18.7%	0.90 [0.66, 1.23]
ASPEN{Knopp, 2006 #15}	0	0	0	0		Not estimable
ASTRONOMER{Chan, 2010 #16}	2	134	5	135	1.5%	0.40 [0.08, 2.04]
Beishuizen{Beishuizen, 2004 #17}	0	0	0	0		Not estimable
Bone{Bone, 2007 #18}	0	0	0	0		Not estimable
CAIUS{Mercuri, 1996 #19}	0	0	0	0		Not estimable
CARDS{Colhoun, 2004 #20}	0	0	0	0		Not estimable
Heljic{Heljic, 2009 #21}	0	0	0	0		Not estimable
HOPE-3{Yusuf, 2016 #23}	154	6361	171	6344	24.4%	0.90 [0.72, 1.11]
HYRIM{Anderssen, 2005 #22}	0	0	0	0		Not estimable
JUPITER{Ridker, 2008 #24}	83	8901	157	8901	21.4%	0.53 [0.41, 0.69]
KAPS{Salonen, 1995 #25}	2	214	2	212	1.0%	0.99 [0.14, 6.97]
MEGA{Nakamura, 2006 #26}	11	3866	18	3966	6.0%	0.63 [0.30, 1.33]
METEOR{Crouse, 2007 #27}	0	0	0	0		Not estimable
Muldoon{Muldoon, 2004 #28}	0	0	0	0		Not estimable
PREVEND-IT{Asselbergs, 2004 #29}	4	433	4	431	2.0%	1.00 [0.25, 3.95]
WOSCOPS{Shepherd, 1995 #30}	50	3302	73	3293	16.4%	0.68 [0.48, 0.98]
Total (95% CI)		**32143**		**32179**	**100.0%**	**0.72 [0.59, 0.88]**
Total events	397		543			

Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 14.48$, df = 9 (P = 0.11); $I^2 = 38\%$

Test for overall effect: Z = 3.22 (P = 0.001)



APPENDIX 3. COST-EFFECTIVENESS

Appendix 3.1. Search strategies of reviews of economic evaluations

In March 2018, the websites of HTA institutes (Table 48 and Table 49) were searched using free text such as statins and primary prevention. The aim was to find both reviews and primary studies. The combination of these two words depended on the number of hits and was determined in a pragmatic way. E.g. if there were no hits with statins, the search was stopped. If a limited number of results was found, the references were looked at to identify relevant reports. If the number of hits per website was high from a pragmatic point of view, a combination with statins and primary prevention was applied.

Table 48 – List of INAHTA member websites searched for HTA reports

Abbreviation	Institute	Country
ACE	Agency for Care Effectiveness	Singapore
AETS	Agencia de Evaluación de Tecnologias Sanitarias	Spain
AETSA	Andalusian Agency for Health Technology Assessment	Spain
Agenas	The Agency for Regional Healthcare	Italy
AHRQ	Agency for Healthcare Research and Quality	USA
AHTA	Adelaide Health Technology Assessment	Australia
AHTAPol	Agency for Health Technology Assessment in Poland	Poland
AQuAS	Agència de Qualitat i Avaluació Sanitàries de Catalunya	Spain
ASERNIP-S	Australian Safety and Efficacy Register of New Interventional Procedures -Surgical	Australia
ASSR	Agenzia Sanitaria e Sociale Regionale (Regional Agency for Health and Social Care)	Italy
AVALIA-T	Galician Agency for Health Technology Assessment	Spain
CADTH	Canadian Agency for Drugs and Technologies in Health	Canada
CDE	Center for Drug Evaluation	Republic of China
CEDIT	Comité d´Evaluation et de Diffusion des Innovations Technologiques	France
CEM	Inspection générale de la sécurité sociale (IGSS), Cellule d'expertise médicale	Luxembourg
CENETEC	Centro Nacional de Excelencia Tecnológica en Salud	Mexico
CONITEC	National Committee for Technology Incorporation	Brazil
CMeRC	Department of Internal Medicine	South Africa
DAHTA @ DIMDI	German Agency for HTA at the German Institute for Medical Documentation and Information	Germany

Abbreviation	Institute	Country
DECIT-CGATS	Secretaria de Ciência, Tecnologia e Insumos Estratégicos, Departamento de Ciência e Tecnologia	Brazil
DEFACTUM	Social & Health Services and Labour Market	Denmark
G-BA	The German Health Care System and the Federal Joint Committee	Germany
GÖG	Gesunheit Österreich	Austria
HAD-MSP	Health Assessment Division, Ministry of Public Health	Uruguay
HAS	Haute Autorité de Santé	France
HCT-NHSRC	Division of Healthcare Technology, National Health Systems Resource Center	India
HealthPACT	Health Policy Advisory Committee on Technology	Australia
HIQA	Health Information and Quality Authority	Ireland
HIS	Healthcare Improvement Scotland	United Kingdom
HQO	Evidence Development and Standards Branch	Canada
HSAC	Health Services Assessment Collaboration	New Zealand
IACS	Health Sciences Institute in Aragon	Spain
IECS	Institute for Clinical Effectiveness and Health Policy	Argentina
IETS	Instituto de Evaluación Tecnológica en Salud	Colombia
IHE	Institute of Health Economics	Canada
INASanté	National Instance for Accreditation in Health Care	Tunisia
INESSS	Institut national d'excellence en santé et en services sociaux	Canada
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen	Germany
KCE	Belgian Federal Health Care Knowledge Centre	Belgium
LBI-HTA	Ludwig Boltzmann Institut für Health Technology Assessment	Austria
MaHTAS	Health Technology Assessment Section at Ministry of Health of Malaysia	Malaysia
MTU-SFOPH	Medical Technology Unit - Swiss Federal Office of Public Health	Switzerland
NECA	National Evidence-based healthcare Collaborating Agency	Korea
NIHR	National Institute for Health Research	United Kingdom
NIPH	Norwegian Institute of Public Health	Norway
OSTEBA	Basque Office for Health Technology Assessment	Spain

Abbreviation	Institute	Country
RCHD-CS	Ministry of Public Health of the Republic of Kazakhstan, Republican Centre for Health Development, Centre of Standardization, HTA department	Kazakhstan
SBU	Swedish Council on Technology Assessment in Health Care	Sweden
UVT	HTA Unit in A. Gemelli Teaching Hospital	Italy
ZIN	Zorginstituut Nederland	The Netherlands
ZonMw	The Medical and Health Research Council of The Netherlands	The Netherlands

Table 49 – Selection of ex or non-member websites

Abbreviation	Institute	Country
CHE	Centre for Health Economics	United Kingdom
CMT	Center for Medical Technology Assessment	Sweden
EUnetHTA	European Network for HealthTechnology Assessment	Europe
HTAi	Health Technology Assessment International	International
iHEA	International Health Economics Association	International
INAHTA	International Network of Agencies for Health Technology Assessment	International
ISPOR	International Society for Pharmacoeconomics and Outcomes Research	International
NICE	National Institute for Health and Care Excellence	United Kingdom
PHARMAC	Pharmaceutical Management Agency	New Zealand

The following databases were searched in March 2018 for reviews of economic evaluations: Centre for Reviews and Dissemination Health Technology Assessment databases (CRD-HTA, NHS Health Technology Assessments), Medline, and Embase. Table 50 up to Table 53 provide an overview of the applied search strategies.

Table 50 – Search strategy and results of reviews of economic evaluations for CRD HTA

Database	CRD HTA		
Date			26 February 2018
Date covered			No restriction
Search Strategy	**#**	**Searches**	**Results**
	1	MeSH DESCRIPTOR cardiovascular diseases EXPLODE ALL TREES IN HTA	1865
	2	MeSH DESCRIPTOR primary prevention EXPLODE ALL TREES IN HTA	105
	3	MeSH DESCRIPTOR hydroxymethylglutaryl-coa reductase inhibitors EXPLODE ALL TREES IN HTA	23
	4	#1 AND #2	8
	5	#3 OR #4	30
	6	* FROM 2008 TO 2018	52709
	7	#5 AND #6	15
Note	According to the number of hits we choose to not focus on the last 10 years and to export line 5 (30 articles).		

Table 51 – Search strategy and results of economic systematic reviews for Medline @ OVID

Database	Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE and Versions(R) 1946 to March 21 2018		
Date			27 March 2018
Date covered			1946 to March 21 2018
Search Strategy	**#**	**Searches**	**Results**
	1	economics/	26978
	2	exp "Costs and Cost Analysis"/	213172
	3	"Value of Life"/ec [Economics]	242
	4	Economics, Dental/	1891
	5	exp Economics, Hospital/	22715
	6	Economics, Medical/	8940
	7	Economics, Nursing/	3978

	8	Economics, Pharmaceutical/	2743
	9	(econom$ or cost$ or pric$ or pharmacoeconomic$).tw.	718225
	10	(expenditure$ not energy).tw.	25145
	11	(value adj1 money).tw.	30
	12	budget$.tw.	25303
	13	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12	857428
	14	(metabolic adj cost).ti,ab,sh.	1201
	15	((energy or oxygen) adj cost).ti,ab,sh.	3640
	16	13 not (14 or 15)	852710
	17	letter.pt.	981443
	18	editorial.pt.	453767
	19	historical article.pt.	343872
	20	17 or 18 or 19	1761620
	21	16 not 20	818131
	22	Animals/	6171929
	23	human/	16953819
	24	22 not (22 and 23)	4403503
	25	21 not 24	760152
	26	exp Hydroxymethylglutaryl-CoA Reductase Inhibitors/	35850
	27	Hydroxymethylglutaryl-CoA Reductase Inhibitors.ti,kw.	186
	28	hmg-coa reductase inhibitors.ti,kw.	686
	29	hydroxymethylglutaryl-coa inhibitors.ti,kw.	0
	30	hydroxymethylglutaryl-coenzyme a inhibitors.ti,kw.	1
	31	statin?.ti,kw.	14790
	32	Hypolipidemic Agents.ti,kw.	158
	33	Anticholesteremic Agents.ti,kw.	94
	34	(anticholesteremic adj2 (drugs or agents)).ti,kw.	12

	35	(hypocholesteremic adj2 (drugs or agents)).ti,kw.	43
	36	anticholesteremics.ti,kw.	0
	37	cholesterol inhibitors.ti,kw.	2
	38	(hypolipidemic adj2 (agents or drugs)).ti,kw.	255
	39	(antilipemic adj2 (drugs or agents)).ti,kw.	59
	40	antihyperlipemics.ti,kw.	0
	41	antihyperlipidemics.ti,kw.	9
	42	antilipemics.ti,kw.	10
	43	((lipid or LDL or cholesterol) adj2 lowering adj3 (treatment? or therapy or therapies)).ti.	1193
	44	27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43	16910
	45	26 or 44	40153
	46	exp Cardiovascular Diseases/	2175404
	47	cardiovascular disease?.ti,kw.	39515
	48	(coronary adj2 disease?).ti,kw.	48259
	49	(vascular adj2 disease?).ti,kw.	10167
	50	47 or 48 or 49	97309
	51	46 or 50	2188656
	52	exp primary prevention/	137719
	53	(primary adj5 prevention).ab,ti,kw.	24094
	54	primary prevention.kw.	864
	55	((individuals or persons or people or adults) adj1 without adj1 prior).ab,ti,kw.	128
	56	((individuals or persons or people or adults) adj3 "low risk").ab,ti,kw.	783
	57	53 or 54 or 55 or 56	25436
	58	52 or 57	158471
	59	(statins adj3 primary adj3 prevent*).ab,ti,kw.	384
	60	51 and 58	14452
	61	45 or 59 or 60	52807

	62	25 and 61	2796
	63	limit 62 to systematic reviews	315
	64	limit 63 to yr="2008-2018"	193
	65	remove duplicates from 64	191
Note			

Table 52 – Search strategy and results of economic systematic reviews for Embase @ Embase.com

Database	**Embase**		
Date			9 March 2018
Date covered	Embase		No restriction
Search Strategy	**#**	**Searches**	**Results**
	1	'socioeconomics'/exp	332428
	2	'cost benefit analysis'/exp	76384
	3	'cost-effectiveness analysis'/exp	129839
	4	'cost of illness'/exp	17161
	5	'cost control'/exp	60942
	6	'economic aspect'/exp	1479904
	7	'financial management'/exp	378452
	8	'health care cost'/exp	257491
	9	'health care financing'/exp	12596
	10	'health economics'/exp	759634
	11	'hospital cost'/exp	33155
	12	'finance'/exp OR 'funding'/exp OR fiscal OR financial	238969
	13	'cost minimization analysis'/exp	3084
	14	cost*:de,cl,ab,ti	889027
	15	estimate*:de,cl,ab,ti	990242
	16	variable*:de,cl,ab,ti	923424
	17	unit:de,cl,ab,ti	564093
	18	('#14' NEAR/1 '#15') OR ('#15' NEAR/1 '#14')	114051

	19	('#14' NEAR/1 '#16') OR ('#16' NEAR/1 '#14')	280054
	20	('#14' NEAR/1 '#17') OR ('#17' NEAR/1 '#14')	55323
	21	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #18 OR #19 OR #20	1957606
	22	'hydroxymethylglutaryl-coa reductase inhibitors'/exp	125756
	23	'hydroxymethylglutaryl-coa reductase inhibitors':ti,kw	393
	24	'hmg-coa reductase inhibitors':ti,kw	1486
	25	'hydroxymethylglutaryl-coa inhibitors':ti,kw	0
	26	'hydroxymethylglutaryl-coenzyme a inhibitors':ti,kw	4
	27	statin:ti,kw OR statins:ti,kw	25124
	28	'anticholesteremic agents':ti,kw	51
	29	'hypolipidemic agents':ti,kw	204
	30	(anticholesteremic NEAR/2 (drugs OR agents)):ti,kw	52
	31	(hypocholesteremic NEAR/2 (drugs OR agents)):ti,kw	42
	32	anticholesteremics:ti,kw	0
	33	'cholesterol inhibitors':ti,kw	8
	34	(hypolipidemic NEAR/2 (agents OR drugs)):ti,kw	416
	35	(antilipemic NEAR/2 (drugs OR agents)):ti,kw	160
	36	antihyperlipemics:ti,kw	0
	37	antihyperlipidemics:ti,kw	16
	38	antilipemics:ti,kw	6
	39	((lipid OR ldl OR cholesterol) NEAR/2 lowering NEAR/3 (treatment? OR therapy OR therapies)):ti	1268
	40	#23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39	27790
	41	#22 OR #40	128330
	42	'cardiovascular diseases'/exp	3851201
	43	'cardiovascular disease':ti,kw	47681
	44	(coronary NEAR/2 disease*):ti,kw	88379
	45	(vascular NEAR/2 disease*):ti,kw	18571
	46	#43 OR #44 OR #45	151356

	47	#42 OR #46	3858526
	48	'primary prevention'/de	35329
	49	(primary NEAR/5 prevention):ab,ti,kw	35873
	50	'primary prevention':kw	2634
	51	((individuals OR persons OR people OR adults) NEAR/1 without NEAR/1 prior):ab,ti,kw	186
	52	((individuals OR persons OR people OR adults) NEAR/3 'low risk'):ab,ti,kw	1049
	53	#48 OR #49 OR #50 OR #51 OR #52	57749
	54	#47 AND #53	26600
	55	(statins NEAR/3 primary NEAR/3 prevent*):ab,ti,kw	567
	56	#41 OR #54 OR #55	149665
	57	#21 AND #56	14815
	58	#57 AND ('meta-analysis'/exp OR 'meta-analysis' OR 'systematic review'/exp OR 'systematic review')	1066
	59	#58 NOT ([conference abstract]/lim OR [conference paper]/lim OR [conference review]/lim OR [editorial]/lim OR [letter]/lim OR [note]/lim)	847
	60	#59 NOT [medline]/lim	209
	61	#60 AND [2008-2018]/py	126
Note			

Table 53 – Results of search strategy of reviews of economic evaluations

Database	
CRD HTA	30
Medline@OVID	191
Embase	126
Total (incl. duplicates)	**347**
Duplicates	12
Total (excl. duplicates)	**335**

Appendix 3.2. Search strategies of primary economic evaluation

The following databases were searched between April and May 2018: Centre for Reviews and Dissemination (CRD) databases (NHS Economic Evaluation Database (NHS EED) and Health Technology Assessments (HTA)), Medline, and Embase. Table 54 up to Table 57 provide an overview of the applied search strategies.

Table 54 – Search strategy and results of primary economic evaluation for CRD NHS EED

Database	CRD EED		
Date			29 May 2018
Date covered			No restriction
Search Strategy	**#**	**Searches**	**Results**
	1	MeSH DESCRIPTOR Cardiovascular Diseases EXPLODE ALL TREES IN NHSEED	2855
	2	MeSH DESCRIPTOR primary prevention EXPLODE ALL TREES IN NHSEED	539
	3	MeSH DESCRIPTOR Hydroxymethylglutaryl-CoA Reductase Inhibitors EXPLODE ALL TREES IN NHSEED	195
	4	#1 AND #2	61
	5	#3 OR #4	230
	6	* FROM 2013 TO 2018	25075
	7	#5 AND #6	**28**
Note			

Table 55 – Search strategy and results of primary economic evaluation for Medline @ OVID

Database	Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE and Versions(R) <1946 to April 11 2018>		
Date			12 April 2018
Date covered			1946 to April 11 2018
Search Strategy	**#**	**Searches**	**Results**
	1	economics/	26902
	2	exp "Costs and Cost Analysis"/	214045
	3	"Value of Life"/ec [Economics]	242
	4	Economics, Dental/	1892
	5	exp Economics, Hospital/	22771
	6	Economics, Medical/	8947
	7	Economics, Nursing/	3979
	8	Economics, Pharmaceutical/	2748
	9	(econom$ or cost$ or pric$ or pharmacoeconomic$).tw.	721760
	10	(expenditure$ not energy).tw.	25265
	11	(value adj1 money).tw.	30
	12	budget$.tw.	25412
	13	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12	861207
	14	(metabolic adj cost).ti,ab,sh.	1210
	15	((energy or oxygen) adj cost).ti,ab,sh.	3652
	16	13 not (14 or 15)	856468
	17	letter.pt.	982869
	18	editorial.pt.	454899
	19	historical article.pt.	344317
	20	17 or 18 or 19	1764597
	21	16 not 20	821834
	22	Animals/	6188401

	23	human/	17008649
	24	22 not (22 and 23)	4413281
	25	21 not 24	763428
	26	exp Hydroxymethylglutaryl-CoA Reductase Inhibitors/	36010
	27	Hydroxymethylglutaryl-CoA Reductase Inhibitors.ti,kw.	190
	28	hmg-coa reductase inhibitors.ti,kw.	687
	29	hydroxymethylglutaryl-coa inhibitors.ti,kw.	0
	30	hydroxymethylglutaryl-coenzyme a inhibitors.ti,kw.	1
	31	statin?.ti,kw.	14852
	32	Hypolipidemic Agents.ti,kw.	158
	33	Anticholesteremic Agents.ti,kw.	94
	34	(anticholesteremic adj2 (drugs or agents)).ti,kw.	12
	35	(hypocholesteremic adj2 (drugs or agents)).ti,kw.	43
	36	anticholesteremics.ti,kw.	0
	37	cholesterol inhibitors.ti,kw.	2
	38	(hypolipidemic adj2 (agents or drugs)).ti,kw.	255
	39	(antilipemic adj2 (drugs or agents)).ti,kw.	59
	40	antihyperlipemics.ti,kw.	0
	41	antihyperlipidemics.ti,kw.	9
	42	antilipemics.ti,kw.	10
	43	((lipid or LDL or cholesterol) adj2 lowering adj3 (treatment? or therapy or therapies)).ti.	1193
	44	27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43	16972
	45	26 or 44	40294
	46	exp Cardiovascular Diseases/	2180942
	47	cardiovascular disease?.ti,kw.	39722
	48	(coronary adj2 disease?).ti,kw.	48347
	49	(vascular adj2 disease?).ti,kw.	10178

	50	47 or 48 or 49	97612
	51	46 or 50	2194126
	52	exp primary prevention/	138190
	53	(primary adj5 prevention).ab,ti,kw.	24188
	54	primary prevention.kw.	878
	55	((individuals or persons or people or adults) adj1 without adj1 prior).ab,ti,kw.	129
	56	((individuals or persons or people or adults) adj3 "low risk").ab,ti,kw.	783
	57	53 or 54 or 55 or 56	25539
	58	52 or 57	159016
	59	(statins adj3 primary adj3 prevent*).ab,ti,kw.	385
	60	51 and 58	14501
	61	45 or 59 or 60	52990
	62	25 and 61	2808
	63	limit 62 to yr="2008-2018"	819
	64	remove duplicates from 63	**808**
Note			

Table 56 – Search strategy and results of primary economic evaluation for Embase @ Embase.com

Database	**Embase**		
Date			13 April 2018
Date covered	Embase		No restriction
Search Strategy	**#**	**Searches**	**Results**
	1	'socioeconomics'/exp	332428
	2	'cost benefit analysis'/exp	76384
	3	'cost-effectiveness analysis'/exp	129839
	4	'cost of illness'/exp	17161
	5	'cost control'/exp	60942
	6	'economic aspect'/exp	1479904

	7	'financial management'/exp	378452
	8	'health care cost'/exp	257491
	9	'health care financing'/exp	12596
	10	'health economics'/exp	759634
	11	'hospital cost'/exp	33155
	12	'finance'/exp OR 'funding'/exp OR fiscal OR financial	238969
	13	'cost minimization analysis'/exp	3084
	14	cost*:de,cl,ab,ti	889027
	15	estimate*:de,cl,ab,ti	990242
	16	variable*:de,cl,ab,ti	923424
	17	unit:de,cl,ab,ti	564093
	18	('#14' NEAR/1 '#15') OR ('#15' NEAR/1 '#14')	114051
	19	('#14' NEAR/1 '#16') OR ('#16' NEAR/1 '#14')	280054
	20	('#14' NEAR/1 '#17') OR ('#17' NEAR/1 '#14')	55323
	21	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #18 OR #19 OR #20	1957606
	22	'hydroxymethylglutaryl-coa reductase inhibitors'/exp	125756
	23	'hydroxymethylglutaryl-coa reductase inhibitors':ti,kw	393
	24	'hmg-coa reductase inhibitors':ti,kw	1486
	25	'hydroxymethylglutaryl-coa inhibitors':ti,kw	0
	26	'hydroxymethylglutaryl-coenzyme a inhibitors':ti,kw	4
	27	statin:ti,kw OR statins:ti,kw	25124
	28	'anticholesteremic agents':ti,kw	51
	29	'hypolipidemic agents':ti,kw	204
	30	(anticholesteremic NEAR/2 (drugs OR agents)):ti,kw	52
	31	(hypocholesteremic NEAR/2 (drugs OR agents)):ti,kw	42
	32	anticholesteremics:ti,kw	0
	33	'cholesterol inhibitors':ti,kw	8

	34	(hypolipidemic NEAR/2 (agents OR drugs)):ti,kw	416
	35	(antilipemic NEAR/2 (drugs OR agents)):ti,kw	160
	36	antihyperlipemics:ti,kw	0
	37	antihyperlipidemics:ti,kw	16
	38	antilipemics:ti,kw	6
	39	((lipid OR ldl OR cholesterol) NEAR/2 lowering NEAR/3 (treatment? OR therapy OR therapies)):ti	1268
	40	#23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39	27790
	41	#22 OR #40	128330
	42	'cardiovascular diseases'/exp	3851201
	43	'cardiovascular disease':ti,kw	47681
	44	(coronary NEAR/2 disease*):ti,kw	88379
	45	(vascular NEAR/2 disease*):ti,kw	18571
	46	#43 OR #44 OR #45	151356
	47	#42 OR #46	3858526
	48	'primary prevention'/de	35329
	49	(primary NEAR/5 prevention):ab,ti,kw	35873
	50	'primary prevention':kw	2634
	51	((individuals OR persons OR people OR adults) NEAR/1 without NEAR/1 prior):ab,ti,kw	186
	52	((individuals OR persons OR people OR adults) NEAR/3 'low risk'):ab,ti,kw	1049
	53	#48 OR #49 OR #50 OR #51 OR #52	57749
	54	#47 AND #53	26600
	55	(statins NEAR/3 primary NEAR/3 prevent*):ab,ti,kw	567
	56	#41 OR #54 OR #55	149665
	57	#21 AND #56	14918
	58	#57 NOT ([conference abstract]/lim OR [conference paper]/lim OR [conference review]/lim OR [editorial]/lim OR [letter]/lim OR [note]/lim)	10329
	59	#58 NOT [medline]/lim	2933

	60 #59 AND [2013-2018]/py	**986**
Note		

Table 57 – Summary results of search strategy

Database	
CRD EED	28
Medline@OVID	808
Embase	986
Total (incl. duplicates)	**1822**
Duplicates	93
Total (excl. duplicates)	**1729**

Appendix 3.2.1. Selection criteria used in both systematic reviews

Reviews and primary studies were similarly assessed for eligibility against inclusion/exclusion criteria. All retrieved references were assessed against pre-defined selection criteria, in terms of population, intervention, comparator, and design (Table 58).

Table 58 – Economic evaluation selection criteria

Selection criteria	Inclusion criteria	Exclusion criteria
Population	• For reviews and primary studies: patients: o with no history of cardiovascular events (primary prevention) o with hypercholesterolemia (high-risk, medium-risk, low-risk patients) o including individuals with type1/type2 diabetes, chronic kidney disease (CKD), and family hypercholesterolemia. o In Europe, North America or Australia	• Patients with previous CVD, cardiac events (secondary prevention) • In Asia, Africa, or South America
Intervention	• For reviews and primary studies: treatment with statins for the prevention of cardiovascular events.	• Other interventions (e.g. aspirin, Ezetimib, polypills or PCSK9…) were not considered if they were not combined with a statin.
Comparator	• No treatment • For reviews and primary studies, other interventions were considered only if they were compared to or combined with statins therapy: o Other statins o Statins in combination with other treatment	

	o Aspirin o Polypills o PCSK9 o Usual care o Lifestyle interventions such as smoking cessation, alcohol cessation, increased physical activity and healthy diet	
Outcomes	• For primary studies: incremental cost-effectiveness ratio	
Study design	• For reviews of economic evaluation: papers published since 2008 • For primary studies: o papers published since 2013 o CMA, CUA, CEA and CBA	• For primary studies: o Cost comparisons (not considering health outcomes) o Cost-outcome descriptions (not considering an alternative treatment) o Other designs such as cost calculations Narrative reviews • For reviews and primary studies: o Observational studies o Letters o Editorials o Notes o Abstracts

Note: Cost-minimization analyses (CMA), cost-utility analyses (CUA), cost-effectiveness analyses (CEA) and cost-benefit analyses (CBA).

Appendix 3.2.2. Selection process of reviews of economic evaluations

In March 2018, a search was performed to identify economic systematic reviews regarding statins therapy in primary prevention of cardiovascular events. Medine, Embase, and CRD HTA were searched. The electronic searches returned 347 economic systematic reviews in total (191 in Medline(OVID), 126 in Embase and 30 in CRD HTA). After exclusion of 12 duplicates and removing references published in other language than English and French, 335 references remained. 3 others papers were included from websites HTA institutes, reference lists and hand searching. The flow chart of the selection process is presented below (Figure 30). Based on title and abstract 317 references were excluded. Of the remaining 21 references, 2 references[14, 97] were included based on full-text evaluation (see Table 59) and 18 references were excluded (Table 60).

Among the both reviews, not all of the studies already included in these reviews fit our inclusion criteria (see Table 63). Therefore, we proceeded to a selection of the already included articles (all reasons of exclusion can be found in Table 61 and Table 62).

Figure 30 – Study flow of reviews selection

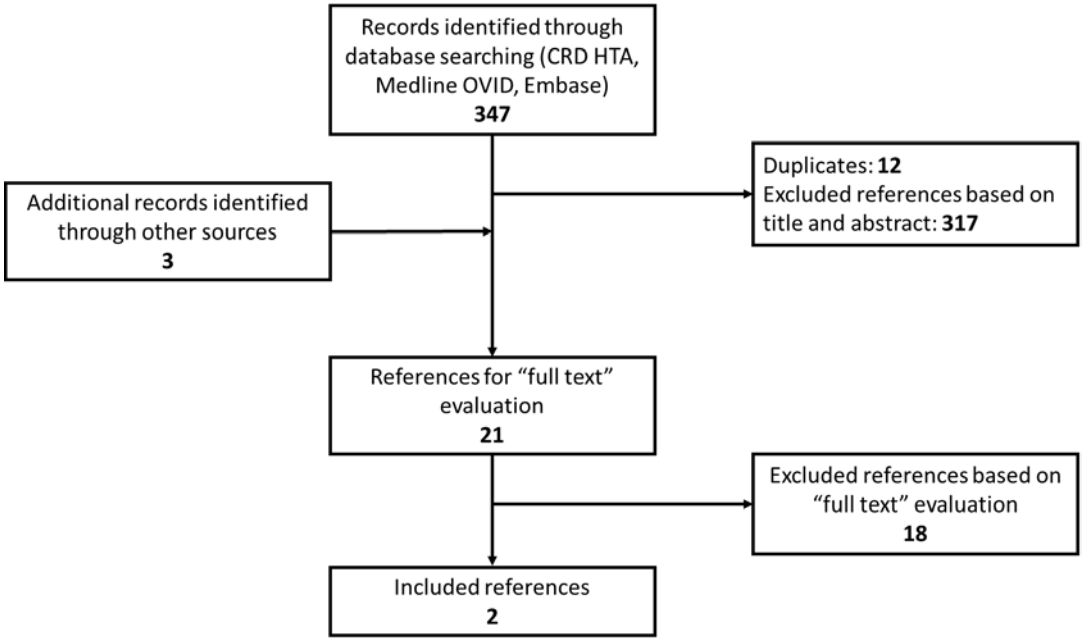


Table 59 – Included references – Economic reviews (full text evaluation)

Reference	
KCE report 52B 2007[97]	De Laet C, Neyt M, Van Brabandt H, Ramaekers D. Rapid Assessment: Prévention cardiovasculaire primaire dans la pratique du médecin généraliste en Belgique. Good Clinical Practice (GCP). Bruxelles: Centre fédéral d'expertise des soins de santé (KCE); 2007. KCE reports 52 B (D/2007/10.273/04).
NICE clinical guideline CG181 2014[14]	NICE CG181 Lipid modification - Cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease. Clinical Guideline. Methods, evidence and recommendations. July 2014.

Table 60 – Excluded references – Economic reviews (full text evaluation)

Reference		Reason for exclusion
Rosian 2006[123]	Rosian I, Pichlbauer E, Stuerzlinger H. The use of statins in primary prevention. Report. Cologne: German Agency for Health Technology Assessment at the German Institute for Medical Documentation and Information (DAHTA@ DIMDI); 2006. Available from: http://www.dimdi.de	**Exclusion: other (not enough information about the search strategy)**
Zechmeister 2006[124]	Zechmeister I, Wild C. Statins and their prognosed as well as real impact on hospital services in Austria. Report. Vienna: Institute of Technology Assessment (ITA); 2006. Available from: http://eprints.hta.lbg.ac.at/588/	**Exclusion: language**
NICE 2006[125]	National IfH, Clinical E. Statins for the prevention of cardiovascular events. Report. London: National Institute for Health and Clinical Excellence (NICE); 2006. Available from: http://www.nice.org.uk/page.aspx?o=289446	**Exclusion: updated by NICE clinical guideline CG181 2014[14]**
Zechmeister 2008[126]	Zechmeister I, Stollenwerk B, Langley T. Have statins met our expectations? A comparison of expected health gains from statins with epidemiological trends in Austria (Part III of the project 'Statins: a comparison between predicted and actual effects on population health in Austria'). Report. Vienna: Ludwig Boltzmann Institut fuer Health Technology Assessment (LBI-HTA); 2008. Available from: http://eprints.hta.lbg.ac.at/804/	**Exclusion: population (secondary prevention)**
Wisloff 2008[127]	Wisloff T, Norheim OF, Halvorsen S, Selmer RM, Kristiansen IS. Health Economic Evaluation of Primary Prevention Strategies Against Cardiovascular Disease. Knowledge Centre for the Health Services at The Norwegian Institute of Public Health (NIPH). 2008;NIPH Systematic Reviews:Executive Summaries.	**Exclusion: language**
Taylor 2009[128]	Taylor F, Ward K, Moore THM, Burke M, Smith GD, Ebrahim S. Statins for the primary prevention of cardiovascular disease. Cochrane Database of Systematic Reviews. 2009(1).	**Exclusion: updated by Taylor 2013[7]**
Colantonio 2010[129]	Colantonio LD, Marti SG, Rubinstein AL. Economic evaluations on cardiovascular preventive interventions in Argentina. Expert Review of Pharmacoeconomics & Outcomes Research. 2010;10(4):465-73.	**Exclusion: intervention**
Center for Drug Evaluation (CDE)[130]	A systematic review of the comparative efficacy and cost-effectiveness of current listed statins in Taiwan. Report. Taipei: Center for Drug Evaluation (CDE).	**Exclusion: full text not found**
Taylor 2011[131]	Taylor F, Ward K, Moore TH, Burke M, Davey Smith G, Casas JP, et al. Statins for the primary prevention of cardiovascular disease. Cochrane Database of Systematic Reviews. 2011(1):CD004816.	**Exclusion: updated by Taylor 2013[7]**
Stevanovic 2012[132]	Stevanovic J, Postma MJ, Pechlivanoglou P. A systematic review on the application of cardiovascular risk prediction models in pharmacoeconomics, with a focus on primary prevention. European Journal of Preventive Cardiology. 2012;19(2 Suppl):42-53.	**Exclusion: intervention**
Mitchell 2012[133]	Mitchell AP, Simpson RJ. Statin cost effectiveness in primary prevention: a systematic review of the recent cost-effectiveness literature in the United States. BMC Research Notes. 2012;5:373.	**Exclusion: other (systematic review restricted to US settings)**

Lim 2012[134]	Lim GB. Vascular disease: Even low-risk individuals can benefit from statin therapy. Nature Reviews Cardiology. 2012;9(7):371.	**Exclusion: study design**
CTT 2012[6]	Cholesterol Treatment Trialists (CTT) Collaborators M, B.; Emberson, J.; Blackwell, L.; Keech, A.; Simes, J.; Barnes, EH.; Voysey, M.; Gray, A.; Collins, R.; Baigent, C.;. The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised trials. Lancet. 2012:380(9841):581-90.	**Exclusion: study design**
Catala-Lopez 2013[121]	Catala-Lopez F, Sanfelix-Gimeno G, Ridao M, et al. 2013 PLoS ONE [Electronic Resource] 8(7):e69462 - When are statins cost-effective in cardiovascular prevention? A systematic review of sponsorship bias and conclusions in economic evaluations of statins	**Exclusion: other (no conclusions about the cost-effectiveness of statins)**
Reiner 2013[135]	Reiner Z. Statins in the primary prevention of cardiovascular disease. Nature Reviews Cardiology. 2013;10(8):453-64.	**Exclusion: study design**
Taylor 2013[7]	Taylor F, 2013 Cochrane Database of Systematic Reviews - Statins for the primary prevention of cardiovascular disease	**Exclusion: study design**
Boehler 2016[136]	Boehler CE, Lord J. Mind the Gap! A Multilevel Analysis of Factors Related to Variation in Published Cost-Effectiveness Estimates within and between Countries. Medical Decision Making. 2016;36(1):31-47.	**Exclusion: other (no conclusions about the cost-effectiveness of statins)**
Wei 2017[137]	Wei CY, Quek RG, Villa G, Gandra SR, Forbes CA, Ryder S, et al. A Systematic Review of Cardiovascular Outcomes-Based Cost-Effectiveness Analyses of Lipid-Lowering Therapies. Pharmacoeconomics. 2017;35(3):297-318.	**Exclusion: other (no conclusions about the cost-effectiveness of statins)**
Ortendahl 2017[138]	Ortendahl JD, Harmon AL, Bentley TGK, Broder MS. A systematic literature review of methods of incorporating mortality in cost-effectiveness analyses of lipid-lowering therapies. Journal of Medical Economics. 2017;20(7):767-75.	**Exclusion: other (no conclusions about the cost-effectiveness of statins)**

Table 61 – Articles already included in both economic reviews

Study	Search strategy	Databases	Population	Intervention	Included studies
KCE report 52B 2007 [97xx]	2001-February 2007 for all databases	Medline, Embase, CRD (NHS EED, DARE, NHS HTA).	Primary prevention	Different strategies: statins, aspirin, …	• Among the 19 included articles, 11 studies fit our inclusion criteria o 2 studies are systematic reviews (Franco et al. 2005[122], Ward et al. 2005[139yy]) o 8 studies are primary studies and compared statins with no treatment [113, 125, 140-145] o 1 primary study compared aspirin plus statin versus aspirin[112] • 8 articles did not fit our inclusion criteria (see Table 62 for reasons of exclusion) • 1 model was developed
NICE CG 181 2014[14]	Up to November 2013 for CRD (EED and HTA) and HEED databases. From 2010 to November 2013 for Medline and Embase.	Medline, Embase, NHS EED, NHS HTA, HEED.	Primary and secondary prevention	Different strategies: statins, aspirin, …	• Among the 4 included studies, 3 articles fit our inclusion criteria o 1 study is a systematic review (Ward et al. 2007[109]) o 2 studies are full economic evaluations comparing statins with placebo[110, 111] and one is specific to adult with CKD • 1 article did not fit our inclusion criteria (see Table 63 for reason of exclusion) • 1 model was developed

xx This report was also published in 2009 as Neyt M, De Laet C, Van Brabandt H, Franco O, Ramaekers D. Cost-effectiveness of statins in the primary prevention of cardiovascular disease: a systematic review and economic analysis for Belgium. Acta Cardiologica. 2009;64(1):1-10.[96]

yy Also published in 2007 as Ward S, Lloyd Jones M, Pandor A, Holmes M, Ara R, Ryan A, et al. A systematic review and economic evaluation of statins for the prevention of coronary events. Health Technol Assess. 2007;2007 Apr;11(14):1-160.[109]

Table 62 – Included studies from KCE report 52B 2007[zz]

Author	Publication Years	Title	Remark
Included studies			
Johannesson M.[140]	2001	At what coronary risk level is it cost-effective to initiate cholesterol lowering drug treatment in primary prevention? Eur Heart J. 2001;22(11):919-25.	**Fit the inclusion criteria.** Also included in Ward 2007.
Lim SS, Vos T, Peeters A, Liew D, McNeil JJ.[141]	2001	Cost-effectiveness of prescribing statins according to Pharmaceutical Benefits Scheme criteria. Medical Journal of Australia. 2001;175(9):459-64.	**Fit the inclusion criteria.** Also included in Ward 2007 and in Catala-Lopez 2013.
Grover SA, Ho V, Lavoie F, Coupal L, Zowall H, Pilote L.[142]	2003	The importance of indirect costs in primary cardiovascular disease prevention: can we save lives and money with statins? Archives of Internal Medicine. 2003;163(3):333-9.	**Fit the inclusion criteria.**
Spaans JN, Coyle D, Fodor G, Nair R, Vaillancourt R, Grover SA, Coupal L.[143]	2003	Application of the 1998 Canadian cholesterol guidelines to a military population: health benefits and cost-effectiveness of improved cholesterol management. Can J Cardiol. 2003;19(7):790-6.	**Fit the inclusion criteria.**
Franco OH, Peeters A, Looman CWN, Bonneux L.[122]	2005	Cost-effectiveness of statins in coronary heart disease. J Epidemiol Community Health. 2005;59(11):927-33.	**Fit the inclusion criteria.** Type of study: systematic review.
Nagata-Kobayashi S, Shimbo T, Matsui K, Fukui T.[144]	2005	Cost-effectiveness of pravastatin for primary prevention of coronary artery disease in Japan. International Journal of Cardiology. 2005;104(2):213-23.	**Fit the inclusion criteria.** Also included in Catala-Lopez 2013.
Ward S, Lloyd J, Pandor A, Holmes M, Ara R, Ryan A, Yeo W, Payne N.[aaa 139]	2005	Statins for the Prevention of Coronary Events. Technology assessment report commissioned by the HTA Programme on behalf of the National Institute for Clinical Excellence. Sheffield: ScHARR The University of Sheffield; 2005 January 2005.	**Fit the inclusion criteria.** Also included in NICE clinical guideline CG181 2014 and in Catala-Lopez 2013.
National Institute for Health and Clinical Excellence (NICE)[125bbb]	2006	Statins for the prevention of cardiovascular events. London (UK): National Institute for Health and Clinical Excellence (NICE). Technology appraisal guideline, no.94; 2006, 45 pages.	**Fit the inclusion criteria.** Updated by NICE clinical guideline CG181 2014[14]

zz This report was also published in 2009 as Neyt M, De Laet C, Van Brabandt H, Franco O, Ramaekers D. Cost-effectiveness of statins in the primary prevention of cardiovascular disease: a systematic review and economic analysis for Belgium. Acta Cardiologica. 2009;64(1):1-10.[96]

aaa Also published in 2007 as Ward S, Lloyd Jones M, Pandor A, Holmes M, Ara R, Ryan A, et al. A systematic review and economic evaluation of statins for the prevention of coronary events. Health Technol Assess. 2007;2007 Apr;11(14):1-160.[109]

bbb This guidance has been updated and replaced by NICE clinical guideline CG181 2014[14].

Walshe V, Nash A, Barry M.[145]	2006	Cost-effectiveness of statin therapy for the primary prevention of coronary heart disease. Irish Medical Journal. 2006;100(1):144-5.	**Fit the inclusion criteria.** Also included in Catala-Lopez 2013.
Pignone M, Earnshaw S, Tice JA, Pletcher MJ.[112]	2006	Aspirin, statins, or both drugs for the primary prevention of coronary heart disease events in men: a cost-utility analysis. Annals of Internal Medicine. 2006;144(5):326-36	**Fit the inclusion criteria.**
Franco OH, der Kinderen AJ, De Laet C, Peeters A, Bonneux L.[113]	2007	Primary prevention of cardiovascular disease: Cost-effectiveness comparison. Int J Techn Assessment in Health Care. 2007;23(1):71-9.	**Fit the inclusion criteria.**
Excluded studies			
Malik IS, Bhatia VK, Kooner JS.	2001	Cost-effectiveness of ramipril treatment for cardiovascular risk reduction. Heart. 2001;85(5):539-43.	**Exclusion: intervention (antihypertensives versus no treatment)**
Lindgren P, Fahlstadius P, Hellenius M-L, Jonsson B, de Faireexcl U.	2003	Cost-effectiveness of primary prevention of coronary heart disease through risk factor intervention in 60-year-old men from the county of Stockholm--a stochastic model of exercise and dietary advice. Preventive Medicine. 2003;36(4):403-9.	**Exclusion: intervention (Diet and/or exercise)**
Lundkvist J, Ekman M, Kartman B, Carlsson J, Jonsson L, Lithell H.	2005	The cost-effectiveness of candesartan-based antihypertensive treatment for the prevention of nonfatal stroke: Results from the Study on COgnition and Prognosis in the Elderly. Journal of Human Hypertension. 2005;19(7):569-76.	**Exclusion: intervention (antihypertensives versus no treatment)**
Hay JW, Sterling KL.	2005	Cost-effectiveness of treating low HDL-cholesterol in the primary prevention of coronary heart disease. PharmacoEconomics. 2005;23(2):133-41.	**Exclusion: intervention (fibrates versus no treatment)**
Annemans L, Lamotte M, Kubin M, Evers T, Verheugt FWA.	2006	Which patients should receive aspirin for primary prevention of cardiovascular disease? An economic evaluation. International Journal of Clinical Practice. 2006;60(9):1129-37.	**Exclusion: intervention (aspirin versus no treatment)**
Lamotte M, Annemans L, Evers T, Kubin M.	2006	A multi-country economic evaluation of low-dose aspirin in the primary prevention of cardiovascular disease. Pharmacoeconomics. 2006;24(2):155-69.	**Exclusion: intervention (aspirin versus no treatment)**
Pignone M, Earnshaw S, Pletcher MJ, Tice JA.	2007	Aspirin for the primary prevention of cardiovascular disease in women: a cost-utility analysis. Arch Intern Med. 2007;167(3):290-5.	**Exclusion: intervention (aspirin versus no treatment)**
Tsutani K, Igarashi A, Fujikawa K, Evers T, Kubin M, Lamotte M, Annemans L.	2007	A health economic evaluation of aspirin in the primary prevention of cardiovascular disease in Japan. Intern Med. 2007;46(4):157-62.	**Exclusion: intervention (aspirin versus no treatment)**

Table 63 – Included studies from NICE clinical guideline CG181 2014

Author	Publication Years	Title	Remark
Included studies			
Ward S, Lloyd Jones M, Pandor A, Holmes M, Ara R, Ryan A, et al.[109ccc]	2007	A systematic review and economic evaluation of statins for the prevention of coronary events. Health Technol Assess 2007;11(14).	**Fit the inclusion criteria.** Also included in KCE report 52B 2007 and in Catala-Lopez 2013.
Erickson KF, Japa S, Owens DK, Chertow GM, Garber AM, Goldhaber-Fiebert JD.[111]	2013	Cost-effectiveness of statins for primary cardiovascular prevention in chronic kidney disease. Journal of the American College of Cardiology. United States 2013; 61(12):1250-1258	**Fit the inclusion criteria.**
McConnachie A, Walker A, Robertson M, Marchbank L, Peacock J, Packard CJ et al.[110]	2013	Long-term impact on healthcare resource utilization of statin treatment, and its cost effectiveness in the primary prevention of cardiovascular disease: a record linkage study. European Heart Journal. United Kingdom 2014; 35(5):290-298	**Fit the inclusion criteria.**
Excluded studies			
Choudhry NK, Patrick AR, Glynn RJ, Avorn J.[146]	2011	The cost-effectiveness of C-reactive protein testing and rosuvastatin treatment for patients with normal cholesterol levels. Journal of the American College of Cardiology. 2011; 57(7):784-791	**Exclusion: intervention (rosuvastatin 20mg for those with high-sensitivity C-reactive protein≥2.0 mg/litre versus usual care);** Also included in Catala-Lopez 2013.

Table 64 – Summary of included studies from reviews

Database	
KCE report 52B 2007[97] – primary studies	11
KCE model	1
NICE clinical guideline CG181 2014[14] – primary studies	3
NICE model	1
Total (incl. duplicates)	**16**
Duplicates	1 (Ward 2007[109])
Total (excl. duplicates, inc. model)	**15**

ccc Also published in 2005 as Ward SLJ, M.; Pandor, A.; Holt, J. M.; Ara, R.; Ryan, A.; et al.;. Statins for the Prevention of Coronary Events: Technology assessment report commissioned by the HTA Programme on behalf of the National Institute for Clinical Excellence. National Institute for Health and Clinical Excellence; 2005[139]

Appendix 3.3. Selection process of economic evaluations

In March 2018, a search was performed to identify full economic evaluations regarding the use of statins in primary prevention of cardiovascular events since the last published review in 2014 (NICE clinical guideline CG181 2014[14]). The electronic searches returned 1822 full economic evaluations in total (808 in Medline(OVID), 986 in Embase and 28 in CRD EED). After exclusion of 93 duplicates and removing references published in other language than English and French, 1729 references remained. The flow chart of the selection process is presented below (Figure 31). Based on title and abstract 1705 references were excluded. Of the remaining 24 references, 10 references([99-108]) were included based on full-text evaluation (see Table 65) and 14 references were excluded (see Table 66).

Figure 31 – Study flow of primary studies

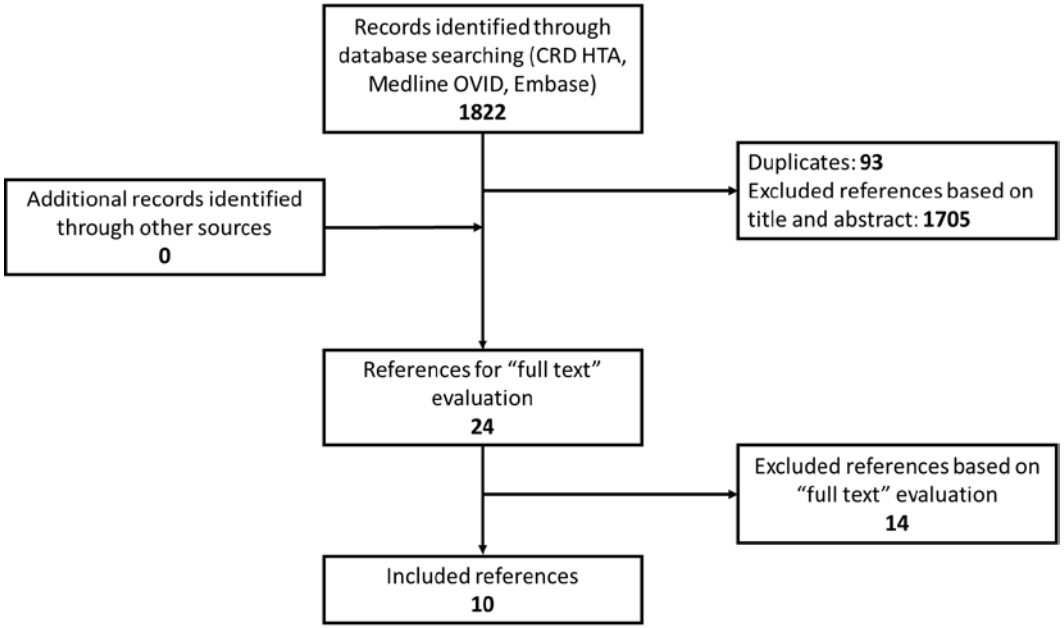


Table 65 – Included references – primary studies (full text evaluation)

Reference	
De Vries 2014[99]	de Vries FM, Denig P, Visser ST, Hak E, Postma MJ. Cost-effectiveness of statins for primary prevention in patients newly diagnosed with type 2 diabetes in the Netherlands. Value in Health. 2014;17(2):223-30.
Aarnio 2015[107]	Aarnio E, Korhonen MJ, Huupponen R, Martikainen J. Cost-effectiveness of statin treatment for primary prevention in conditions of real-world adherence - Estimates from the Finnish prescription register. Atherosclerosis. 2015;239(1):240-7.
Odden 2015[106]	Odden MC, Pletcher MJ, Coxson PG, Thekkethala D, Guzman D, Heller D, et al. Cost-effectiveness and population impact of statins for primary prevention in adults aged 75 years or older in the United States.[Summary for patients in Ann Intern Med. 2015 Apr 21;162(8):I-28; PMID: 25894041]. Annals of Internal Medicine. 2015;162(8):533-41.
Pandya 2015[105]	Pandya A, Sy S, Cho S, Weinstein MC, Gaziano TA. Cost-effectiveness of 10-Year Risk Thresholds for Initiation of Statin Therapy for Primary Prevention of Cardiovascular Disease. JAMA. 2015;314(2):142-50.
Mihaylova 2016[104]	Mihaylova B, Schlackow I, Herrington W, Lozano-Kuhne J, Kent S, Emberson J, et al. Cost-effectiveness of Simvastatin plus Ezetimibe for Cardiovascular Prevention in CKD: Results of the Study of Heart and Renal Protection (SHARP). American Journal of Kidney Diseases. 2016;67(4):576-84.
Shiffman 2016[102]	Shiffman D, Arellano AR, Caulfield MP, Louie JZ, Bare LA, Devlin JJ, et al. Use of low density lipoprotein particle number levels as an aid in statin treatment decisions for intermediate risk patients: a cost-effectiveness analysis. BMC Cardiovascular Disorders. 2016;16(1):251.
Ferket 2017[100]	Ferket BS, Hunink MG, Khanji M, Agarwal I, Fleischmann KE, Petersen SE. Cost-effectiveness of the polypill versus risk assessment for prevention of cardiovascular disease. Heart. 2017;103(7):483-91.
Heller 2017[103]	Heller DJ, Coxson PG, Penko J, Pletcher MJ, Goldman L, Odden MC, et al. Evaluating the Impact and Cost-Effectiveness of Statin Use Guidelines for Primary Prevention of Coronary Heart Disease and Stroke. Circulation. 2017;136(12):1087-98.
Jowett 2017[101]	Jowett S, Barton P, Roalfe A, Fletcher K, Hobbs FDR, McManus RJ, et al. Cost-effectiveness analysis of use of a polypill versus usual care or best practice for primary prevention in people at high risk of cardiovascular disease. PLoS ONE [Electronic Resource]. 2017;12(9):e0182625
Romanens 2017[108]	Romanens M, Sudano I, Szucs T, Adams A. Medical costs per QALY of statins based on Swiss Medical Board assumptions. Kardiovaskulare Med. 2017;20(4):96-100.

Table 66 – Excluded references – primary studies (full text evaluation)

Reference		Reason for exclusion
Mearns 2013[147]	Mearns BM. Public health: cost-effectiveness of various strategies for preventing RHD. Nature Reviews Cardiology. 2013;10(7):366.	**Exclusion: study design**
Gulliford 2014[148]	Gulliford M.C, Bhattarai N, Charlton J, Rudisill C. Cost-effectiveness of a universal strategy of brief dietary intervention for primary prevention in primary care: Population-based cohort study and Markov model. Cost Eff. Resour. Allocat. 2014;12(1).	**Exclusion: intervention**
Smith 2014[149]	Smith T, Elwood P, Keating C, Rothwell P, Detering E, Freedman A, et al. The Aspirin Foundation Scientific Conference: The history, the present state and the future of aspirin prophylaxis. ecancermedicalscience. 2014;8(1).	**Exclusion: study design**
Van Boven 2014[150]	Van Boven J.F.M, Postma M.J. Cost-effectiveness in primary prevention, cost savings in secondary prevention: Promoting therapy adherence to antilipemic agents is cost effective. Pharm. Weekbl. 2014;149(35):30-1.	**Exclusion: study design**
Laires 2015[151]	Laires PA, Ejzykowicz F, Hsu TY, Ambegaonkar B, Davies G. Cost-effectiveness of adding ezetimibe to atorvastatin vs switching to rosuvastatin therapy in Portugal. Journal of Medical Economics. 2015;18(8):565-72.	**Exclusion: population**
Durand-Zaleski 2016[152]	Durand-Zaleski I. Cost-effectiveness studies: Wrong ideas methodology insights. Arch. Cardiovasc. Dis. 2016;8(2):157-60.	**Exclusion: study design**
Wald 2016[153]	Wald NJ, Luteijn JM, Morris JK, Taylor D, Oppenheimer P. Cost-benefit analysis of the polypill in the primary prevention of myocardial infarction and stroke. European Journal of Epidemiology. 2016;31(4):415-26.	**Exclusion: study design**
Arrieta 2017[154]	Arrieta A, Page TF, Veledar E, Nasir K. Economic Evaluation of PCSK9 Inhibitors in Reducing Cardiovascular Risk from Health System and Private Payer Perspectives. PLoS ONE [Electronic Resource]. 2017;12(1):e0169761.	**Exclusion: intervention**
Danese 2017[155]	Danese M.D, Gleeson M, Griffiths R.I, Catterick D, Kutikova L. Methods for estimating costs in patients with hyperlipidemia experiencing their first cardiovascular event in the United Kingdom. J. Med. Econ. 2017;20(9):931-7.	**Exclusion: study design**
Davies 2017[156]	Davies GM, Vyas A, Baxter CA. Economic evaluation of ezetimibe treatment in combination with statin therapy in the United States. Journal of Medical Economics. 2017;20(7):723-31.	**Exclusion: population**
Kazi 2017[157]	Kazi DS, Penko J, Coxson PG, Moran AE, Ollendorf DA, Tice JA, et al. Updated Cost-effectiveness Analysis of PCSK9 Inhibitors Based on the Results of the FOURIER Trial. JAMA. 2017;318(8):748-50.	**Exclusion: population**
Mortensen 2017[158]	Mortensen MB, Falk E, Schmidt M. Twenty-Year Nationwide Trends in Statin Utilization and Expenditure in Denmark. Circulation. Cardiovascular Quality & Outcomes. 2017;10(7).	**Exclusion: study design**
Stam-Slob 2017[159]	Stam-Slob MC, van der Graaf Y, Greving JP, Dorresteijn JA, Visseren FL. Cost-Effectiveness of Intensifying Lipid-Lowering Therapy With Statins Based on Individual Absolute Benefit in Coronary Artery Disease Patients. Journal of the American Heart Association. 2017;6(2):18.	**Exclusion: population**
Stam-Slob 2018[160]	Stam-Slob MC, van der Graaf Y, de Boer A, Greving JP, Visseren FLJ. Cost-effectiveness of PCSK9 inhibition in addition to standard lipid-lowering therapy in patients at high risk for vascular disease. International Journal of Cardiology. 2018;253:148-54.	**Exclusion: population**

Appendix 3.4. Results from reviews of economic evaluations

Appendix 3.4.1. KCE report 52B

Table 67 – An overview of study results of economic evaluations included in KCE report 52B

Author & year of publication	Conflict of interest	Intervention	Cost-effectiveness	Conclusion
Statins versus no treatment				
Johannesson et al. 2001[140]	No conflict of interest declared.	Cholesterol lowering drug treatment versus no treatment.	Statin treatment is cost-effective if the 5-year risk of CHD exceeds the following per cent risk: (in function of the CE threshold: results presented for threshold of $40,000/QALY (the authors also used $60,000 and $100,000 thresholds)): Age 35 40 45 50 55 60 65 70 Men 3.34 4.06 5.09 6.50 8.27 11.59 17.33 21.36 Women 2.95 3.17 3.93 5.07 6.80 10.08 15.82 20.30 96	*"In primary prevention, cholesterol lowering treatment is unlikely to be cost-effective for all patients with elevated cholesterol levels, and so it is crucial to determine in which patient populations treatment should be initiated."*[140] *"The results can serve as a basis for treatment guidelines based on cost-effectiveness."* [140]
Lim et al. 2001[141]	No conflict of interest declared.	Pravastatin (40 mg/day for 20 years) versus no treatment	Cost (AUD) per LYG of treatment according to the Australian Pharmaceutical Benefits Scheme (PBS) criteria against treatment criteria based on 15-year risk of CHD mortality according to MRFIT criteria PBS criteria / >2.5% 15-year risk CHD mortality / >5% 15-year risk CHD mortality Men 110,000 31,000 23,000 80% uncertainty (96,000-150,000) (27,000-4,000) (20,000-29,000) Women 87,000 39,000 37,000 80% uncertainty (80,000-130,000) (33,000-53,000) (32,000-51,000) 96	*"While PBS criteria do target patients at risk of CHD, there is room for improvement in identifying those most at risk of CHD, and treatment according to PBS criteria is not likely to be the most cost-effective. For optimal cost-effectiveness, targeting of therapy for primary CHD prevention needs to be based on population-specific, multivariable risk."*[141]

Grover et al. 2003[142]	Potential conflict of interest[ddd].	Atorvastatin calcium (10 mg/day) versus no treatment	Cost (CAD) per LYG of atorvastatin according to risk level and age. Low-risk persons are non-smokers with a blood pressure of 120/80 mmHg and high-risk persons are smokers with a blood pressure of 160/100 mmHg. Direct costs considered / Direct and indirect costs included. Low risk age: 40: 11,816 (Men), 19,866 (Women); 50: 7,885 (Men), 10,747 (Women); 60: 5,365 (Men), 4,275 (Women) High risk: 40: 5,124 (Men), 7,580 (Women); 50: 4,161 (Men), 4,982 (Women); 60: 3,846 (Men), 3,756 (Women) Direct and indirect costs included: 40: 6,625 cost savings; 50: cost savings (Men), cost savings (Women); 60: cost savings (Men), cost savings (Women) 96eee	*"Lipid therapy with statins can reduce CVD morbidity and mortality as demonstrated in a number of clinical trials. Adding the indirect CVD costs associated with productivity losses at work and home can result in forecasted cost savings to society as a whole such that lipid therapy could potentially save lives and money."* [142]
Spaans et al. 2003[143]	No conflict of interest declared.	Statin therapy versus no treatment	Cost-effectiveness (CAD/LYG) according to risk level. Risk factors were age (men > 45 y, women > 55 y), diabetes, smoking, premature heart disease in a first-degree relative (i.e., CAD before 55 y in men or 65 y in women), hypertension (systolic blood pressure > 140 mmHg, or diastolic blood pressure > 90 mmHg) or taking antihypertensive medication. Risk levels: low: < 1 risk factor; moderate: 2 risk factors; high: 3 risk factors; and very high: > 4 risk factors or CAD. Undiscounted: 9,500 (Low), 7,700 (Moderate), 7,400 (High), 7,400 (Very high), 8,000 (Total) Discounted: 11,800 (Low), 9,200 (Moderate), 8,400 (High), 7,700 (Very high), 9,300 (Total) 96fff	*"The health benefits of statin therapy in this population are substantial and the cost effectiveness is acceptable. Statin therapy warrants greater attention as a preventive strategy for coronary artery disease."* [143]
Franco et al. 2005[122]	No conflict of interest declared.	Statins versus no treatment	The ratios reported ranged over an enormous range: from savings to $556,700/LYG. Distribution of ICERs ($ per LYG) by category of annual absolute risk of CHD: < 1%: 24,505 / 48,559 / 255,893 1%-< 2%: 10,205 / 26,933 / 73,124 2%-< 3%: 12,951 / 23,060 / 46,273 3%-< 4%: 7,987 / 15,048 / 48,701 > 4%: 5,449 / 10,607 / 21,545 (Centile 10 / Median / Centile 90) 96	*"In conclusion, this review confirms how the cost effectiveness of statins treatment in the prevention of CHD is related to the absolute risk of CHD, but shows that within risk strata there still exists large variability in cost effectiveness estimates. Nearly all studies agree that treatment at high levels of risk is cost effective and at low levels is expensive. But in practice, it is not difficult to find CERs that fit any decision for the population at large with intermediate*

ddd Dr Grover has received honoraria as a consultant or speaker for the following companies: Pfizer Canada Inc, Kirkland; Merck Frosst Inc, Pointe-Claire/Dorval, Quebec; Bristol-Myers Squibb, Wallingford, Conn; and AstraZeneca Canada Inc, Mississauga, Ontario. Dr Grover also owns shares of Pfizer Inc, New York, NY, and Merck Inc, Whitehouse Station, NJ. Additional financial support was provided by an unrestricted grant from Pfizer Canada Inc, Kirkland, Quebec.

eee Low risk population is defined as non-smokers with a blood pressure of 120/80 mm Hg and high risk population is defined as smokers with a blood pressure of 160/100 mm Hg.

fff Risk level were defined according to the number of risk factors (smoking, hypertension, diabetes, coronary artery disease, family history): low risk

				annual risk of CHD (1% to 4%). The most probable explanation for these differences is different methodology in the CEA, and the impact of funding source suggests the potential for some estimates to be biased." [122]
Nagata-Kobayashi et al. 2005[144]	No conflict of interest declared.	Lifetime pravastatin (10 or 20 mg/day) versus no treatment	Cost-effectiveness (million Yen/QALY) in men treated with pravastatin 20 mg/day (in the original study results for women and 10 mg/day are also presented). Eight distinctive groups were defined on the basis of these cardiac risk factors: (1) persons who meet the criteria for hypercholesterolaemia and age; (2) smoking; (3) hypertension; (4) hyperglycaemia; (5) smoking and hypertension; (6) smoking and hyperglycaemia; (7) hypertension and hyperglycaemia; and (8) smoking, hypertension, and hyperglycaemia. Age 1 2 3 4 5 6 7 8 45 76 63 31 48 26 40 19 16 50 56 47 22 35 18 29 14 11 55 53 44 20 32 17 27 12 10 60 44 36 16 27 13 22 9.3 7.5 65 64 53 22 38 17 30 12 9.4 70 120 91 31 61 24 47 15 11 [96]	*"The cost-effectiveness of pravastatin therapy for primary prevention of MI varies widely depending on the combination of cardiac risks. Treating hyperlipidemia with pravastatin is not cost-effective in persons at low cardiac risk in Japan."* [144]

Ward et al. 2005[ggg] [139]	Potential conflict of interest[hhh]	Statins (all statins as a single class) versus no treatment	Discounted cost/QALY (in £1,000) in function of annual CHD risk and age: (undiscounted results were also presented in the original paper) age 45 55 65 75 85 45 55 65 75 85 CHD risk Men Women 3.0% 9.5 12.6 16.8 26.2 36.8 13.7 15.9 19.3 31.5 47.4 2.5% 10 13.5 18.5 29.4 41.5 14 16.6 21 35 52.4 2.0% 10.8 14.9 21 34.1 48.1 14.9 18 23.7 40.2 59.3 1.5% 12.2 17.2 25.1 41.5 58 16.6 20.6 28.2 48.5 69.1 1.0% 14.9 21.5 32.5 54.7 74.1 20.3 25.9 37 63.7 84.3 0.5% 20.9 31.1 49.5 84.8 105 30.5 40 59.3 98.9 111 [96iii]	*"In the base case primary prevention analyses the ICERs vary according to risk level and age. The estimated average ICER by risk level increases from £20k to £28k from men between 3% and 0.5% CHD risk and between £21 k and £57 k for women. There is however significant variation within risk levels by age. At an annual CHD risk of 3%, the estimated cost per QALY ranges from £9.5 k to £36.8 k for males and from £13.7 k to £47.4 k for females between the ages of 45 and 85. At aged 85 the estimated cost per QALY rises from £36.8 k (£47.4 k) for males (females) at 3% CHD risk, to around £105.2 k (£110.6 k) for males (females) at 0.5% CHD risk."* [139]
National Institute for Health and Clinical	No conflict of interest declared[kkk] .	Statins versus no treatment	The ranges of cost per QALY gained (in £1,000) at an annual risk of a CHD event ranging from 3% to 0.5%: Age 45 55 65 75 85 10 - 31 13 - 40 17 - 59 26 - 99 37 - 111 People with diabetes and at an annual risk of CHD ranging from 3% to 0.5% 6.2 - 22 27 - 96 [96]	*"Statin therapy is recommended as part of the management strategy for the primary prevention of CVD for adults who have a 20% or greater 10-year risk of developing CVD. This level of CVD risk should be estimated using an appropriate risk calculator, or by clinical assessment for people for whom an appropriate risk*

ggg Also published in 2007 as Ward S, Lloyd Jones M, Pandor A, Holmes M, Ara R, Ryan A, et al. A systematic review and economic evaluation of statins for the prevention of coronary events. Health Technol Assess. 2007;2007 Apr;11(14):1-160.[109]

hhh *"Dr Wilf Yeo has received speaker fees from Novartis, Pfizer, MSD and AstraZeneca for talks to GPs and prescribing advisors on the National Service Framework for CHD, which includes the use of statins. However, for the duration of his involvement with the preparation of this report, he has declined to comment on statins nor attend any advisory boards where statins may have been discussed. His department has received research funding for the Anglo-Scandinavian Cardiac Outcomes Trail, an investigator-led multi-centre study in high-risk hypertension patients of older versus more modern BP lowering drugs, with statin therapy in a factorial design. This study used atorvastatin and was part funded by Pfizer".*[139]

iii In this review, three scenario analyses are reported: the base case CHD analysis, a first scenario of CHD analysis with CVD outcomes and a second scenario of CVD analysis. Due to the large number of results presented in the original report, only the base case CHD analysis is presented here.

kkk Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

Excellence (NICE) 2006[jjj] [125]				*calculator is not available (for example, older people, people with diabetes or people in high-risk ethnic groups).”* [125]
Walshe et al. 2006[145]	No conflict of interest declared.	Statins versus no treatment	Cost-effectiveness of statins (€/LYG) under the GMS and DP schemes (the GMS scheme (abbreviation not specified in original study) included the dispensing fee whilst the drugs payment scheme (DP) included the 50% mark up on drug acquisition cost in addition to the dispensing fee) Drugs | Atorva-statin | Rosuva-statin | Fluva-statin | Generic simvastatin | Simva-statin | Generic pravastatin | Prava-statin GMS | 17,900 | 18,500 | 18,700 | 20,910 | 27,300 | 26,752 | 33,800 DP | 24,500 | 25,500 | 25,800 | 29,999 | 38,700 | 38,999 | 48,500 [96]	*“All the statins could be considered cost effective ie. threshold below €50,000/LYG however atorvastatin proved the most cost effective statin in this pharmacoeconomic study.”*
Aspirin plus statin versus aspirin				
Pignone et al. 2006[112]	Potential conflict of interest	Low-dose aspirin, a statin, both drugs as combination therapy, or no therapy. 6 levels (2.5%, 5%, 7.5%, 10%, 15%, and 25%) of 10-year risk of CHD (Framingham risk equation)	Cost per QALY gained (in $) for 6 levels of 10-year risk of CHD: Base-case analysis: Aspirin vs. no therapy | Aspirin + statin vs. aspirin Alternative model: Aspirin vs. no therapy | Aspirin + statin vs. aspirin 2.5% | 9,800 | 164,700 | dominated | / 5% | dominant | 97,900 | dominated | / 7.5% | dominant | 56,200 | dominant | 57,100 10% | dominant | 42,500 | dominant | 43,100 15% | dominant | 33,600 | dominant | 33,900 25% | dominant | 15,300 | dominant | 15,500 [96]	*“Compared with no treatment, aspirin is less costly and more effective for preventing CHD events in middle-aged men whose 10-year risk for CHD is 7.5% or higher. The addition of a statin to aspirin therapy becomes more cost-effective when the patient’s 10-year CHD risk before treatment is higher than 10%.”*[112]

[jjj] This guidance has been updated and replaced by NICE clinical guideline CG181 2014[14].

Statin versus other risk-lowering interventions				
Franco et al. 2007[113]	No conflict of interest declared.	Four risk-lowering interventions (smoking cessation, antihypertensives, aspirin, and statins) Anderson risk equation	ICERs (€/LYG) of interventions on the efficiency frontier (ICERs of treatment options versus no treatment were also published in the original paper). Subgroups based on their level of 10-year absolute risk of CHD (moderate: 10-20%; high: 20-30%) Moderate risk: age 50 / 60 SC nicotine substitutes: Cost saving / Cost saving SC bupropion: 8,033 / 6,107 SC GP advice: Dominated / Dominated Aspirin: 36,207 / 15,799 Antihypertensive drugs: Dominated / Dominated Statins: 488,460 / 287,608 High risk: age 50 / 60 SC nicotine substitutes: Cost saving / Cost saving SC bupropion: 2,188 / 2,355 SC GP advice: Dominated / Dominated Aspirin: 9,336 / 7,213 Antihypertensive drugs: Dominated / Dominated Statins: 287,496 / 171,670 96	*"A cost-effective strategy should offer smoking cessation for smokers and aspirin for moderate and high levels of risk among men 45 years of age and older. Statin therapy is the most expensive option in primary prevention at levels of 10-year coronary heart disease risk below 30 percent and should not constitute the first choice of treatment in these populations."*[113]

Table 68 – Evidence tables of model developed in KCE report 52B

Author & year of publication	Conflict of interest	Intervention	Cost-effectiveness	Conclusion
KCE report 52B 2007[97] (model)	No conflict of interest declared.	Four risk-lowering interventions (smoking cessation, antihypertensives, aspirin, and statins).	**Table 7: ICERs (cost per year of life saved) of interventions on the efficiency frontier** Risk group: Moderate (50, 60); High (50, 60) Intervention / Age SC GP advice: dominated by SC nicotine substitutes SC nicotine substitutes: Cost saving; Dominated by SC bupropion SC bupropion: 2 792 / 2 287; Cost saving Aspirin: 30 504 / 13 038; 6 892 / 4 749 Statins[a]: 87 259 / 50 649; 49 810 / 29 350 SC: smoking cessation; GP: general practitioner. [a]: a very optimistic price scenario is applied, i.e. the lowest price when administering a low dose (pravastatin Teva® 20mg). 97 Remark: *"Antihypertensives were not taken into account since this intervention was dominated by aspirin treatment."*[97]	*"The results show that smoking cessation is an intervention which should be encouraged both from a health impact and from an economic point of view. For smokers, low-dose aspirin treatment could be considered for a high-risk population (Framingham 20-30%) or for older people with moderate risk (Framingham 10-20%). For non-smokers, i.e. comparing low-dose aspirin treatment with placebo (table 6), aspirin treatment is cost effective in all subgroups. The results for statin treatment are not very cost-effective. Only for the high risk group aged 60, the intervention could be considered borderline cost-effectiveness (€29 350/YLS)."*[97]

6.9.1.1 NICE clinical guideline CG181

Table 69 – An overview of study results of economic evaluations included in NICE clinical guideline CG181

Author & year of publication	Conflict of interest	Intervention	Cost-effectiveness	Conclusion
Statins versus no treatment				
Ward et al. 2007[109]	Potential conflict of interest[III]	Intervention 1: no treatment Intervention 2: statin therapy (all statins as a single class)	*TABLE 82 Primary prevention: cost-effectiveness results for a cohort of 1000 patients at varying annual risks for the scenario CVD; discounted cost per QALY (£,000)* 109mmm	*"The results for the CVD analysis in primary prevention show lower ICERs than for the CHD analysis. In the CHD analysis men aged 45 years at 3% CHD risk have an estimated ICER of £10,200. In the CVD analysis the corresponding ICER is £5200. The most marked difference between the results is for older age groups. For instance, in the base-case CHD analysis a female cohort aged 85 years at 0.5% annual CHD risk produced an estimated cost per QALY of £110,600, compared with £45,600 in the CVD analysis".* [109] *"The potential targeting of statins at low-risk populations is however associated with major uncertainties, particularly the likely uptake and long-term compliance to lifelong medication by asymptomatic younger patients."* [109]

Age (years)		Annual risk					
CHD risk		3.0%	2.5%	2.0%	1.5%	1.0%	0.5%
CVD risk <54 years		3.8%	3.2%	2.6%	2.0%	1.3%	0.7%
CVD risk >54 years		4.3%	3.7%	3.0%	2.4%	1.8%	1.1%
Men	45	£5.2	£5.5	£6.0	£6.8	£8.2	£11.0
	55	£5.9	£6.4	£7.1	£8.1	£9.9	£13.4
	65	£7.5	£8.3	£9.4	£11.2	£14.1	£19.9
	75	£10.9	£12.3	£14.3	£17.4	£22.4	£32.4
	85	£17.1	£19.5	£22.7	£27.6	£35.3	£49.8
CHD risk		3.0%	2.5%	2.0%	1.5%	1.0%	0.5%
CVD risk <54 years		4.0%	3.4%	2.7%	2.1%	1.5%	0.8%
CVD risk >54 years		4.7%	4.0%	3.3%	2.5%	1.8%	1.1%
Women	45	£5.4	£5.6	£6.0	£6.8	£8.3	£11.9
	55	£5.5	£5.8	£6.4	£7.4	£9.4	£13.7
	65	£6.4	£7.0	£8.0	£9.6	£12.6	£19.2
	75	£9.1	£10.2	£12.0	£14.7	£19.5	£30.0
	85	£14.5	£16.5	£19.5	£23.8	£31.1	£45.6

III *"Dr Wilf Yeo has received speaker fees from Novartis, Pfizer, MSD and AstraZeneca for talks to GPs and prescribing advisors on the National Service Framework for CHD, which includes the use of statins. However, for the duration of his involvement with the preparation of this report, he has declined to comment on statins nor attend any advisory boards where statins may have been discussed. His department has received research funding for the Anglo-Scandinavian Cardiac Outcomes Trail, an investigator-led multi-centre study in high-risk hypertension patients of older versus more modern BP lowering drugs, with statin therapy in a factorial design. This study used atorvastatin and was part funded by Pfizer".* [109]

mmm In this review, three scenario analyses are reported: the base case CHD analysis, a first scenario of CHD analysis with CVD outcomes and a second scenario of CVD analysis. Based on NICE clinical guideline's conclusions, we decided to present only the scenario 2.

McConnachie et al. 2013[110]	Potential conflict of interest[nnn]	Intervention 1: no statins during trial (4.9 years); after 5 years additional follow up 35.2% taking lipid-lowering therapy Intervention 2: pravastatin 40 mg daily during trial (4.9 years); after 5 years additional follow up 38.7% taking lipid-lowering therapy ASSIGN baseline risk	**Table 6** Cumulative mean costs (per 1000 people treated) and quality-adjusted life years after 15 years, in those originally randomized to receive pravastatin or placebo, with mean, 95% confidence interval, and *P* value for the difference between randomized groups (pravastatin − placebo) 110	*"Five years' primary prevention treatment of middle-aged men with a statin significantly reduces healthcare resource utilization, is cost saving, and increases QALYs. Treatment of even younger, lower risk individuals is likely to be cost-effective".*[110]

	Placebo	Pravastatin	Difference (Prava − Plac)	Interaction *P* value
Cardiovascular disease costs (£million/1000 people)				
All	3.55	2.84	−0.71 (−1.09 to −0.32), *P* < 0.001	
Low risk	2.11	1.27	−0.84 (−1.27 to −0.42), *P* < 0.001	0.85
Intermediate risk	3.47	2.89	−0.58 (−1.27 to 0.08), *P* = 0.086	
High risk	5.04	4.36	−0.68 (−1.49 to 0.11), *P* = 0.088	
QALYs (per 1000 people)				
All	11 057	11 193	136 (25 to 247), *P* = 0.017	
Low risk	11 905	12 016	111 (−12 to 238), *P* = 0.079	0.95
Intermediate risk	11 075	11 207	131 (−51 to 309), *P* = 0.17	
High risk	10 220	10 371	151 (−72 to 376), *P* = 0.18	
Non-Cardiovascular disease costs (£million/1000 people))				
All	6.00	6.03	0.03 (−0.44 to 0.52), *P* = 0.87	
Low risk	4.42	4.33	−0.09 (−0.81 to 0.66), *P* = 0.83	0.65
Intermediate risk	5.84	6.20	0.36 (−0.44 to 1.18), *P* = 0.37	
High risk	7.68	7.55	−0.13 (−1.00 to 0.75), *P* = 0.78	

Costs shown are for all cardiovascular admissions and incremental costs of events, plus treatment and monitoring costs, and for non-cardiovascular disease admission costs. Costs and quality-adjusted life years shown for all randomized subjects, and separately by thirds of cardiovascular risk. Interaction *P* values test whether between-treatment differences are equal across cardiovascular risk groups. All costs and quality-adjusted life year decrements are discounted annually at 3.5%. Costs are given in units of £1 million.

People with chronic kidney disease (CKD)

nnn The original trial was funded by Bristol-Myers Squibb (manufacturer of pravastatin) and the first 5 years of follow-up was supported by Bristol-Myers Squibb and the Sankyo Company. The current research was supported by unrestricted grants from the Wellcome Trust (Scottish Health Informatics Programme) and Celera Diagnostics and none of these 2 organisations has had any involvement in the design, conduct, or analysis of the reported research or in the writing or review of this manuscript.

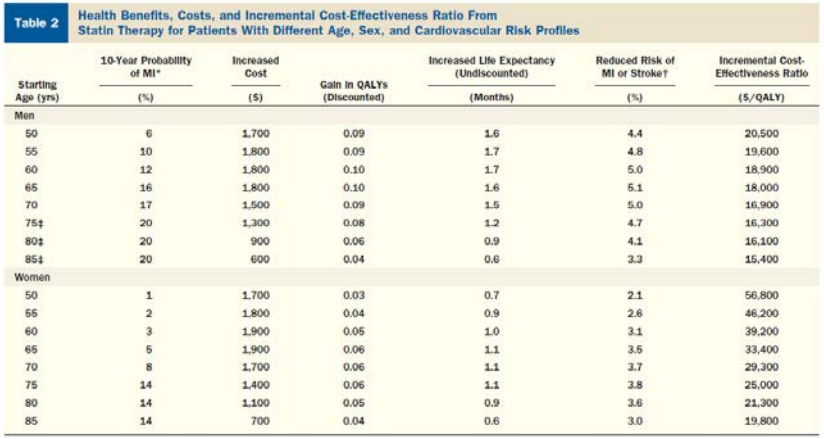
Erickson et al. 2013[111]	NA	People with mild-to-moderate CKD and moderate hypertension (base case) Intervention 1: no treatment Intervention 2: statins as a single class Framingham risk calculator		*"Although statins reduce absolute CVD risk in patients with CKD, the increased risk of rhabdomyolysis, and competing risks associated with progressive CKD, partly offset these gains. Low-cost generic statins appear cost-effective for primary prevention of CVD in patients with mild-to-moderate CKD and hypertension."* [111]

Table 2 Health Benefits, Costs, and Incremental Cost-Effectiveness Ratio From Statin Therapy for Patients With Different Age, Sex, and Cardiovascular Risk Profiles

Starting Age (yrs)	10-Year Probability of MI* (%)	Increased Cost ($)	Gain in QALYs (Discounted)	Increased Life Expectancy (Undiscounted) (Months)	Reduced Risk of MI or Stroke† (%)	Incremental Cost-Effectiveness Ratio ($/QALY)
Men						
50	6	1,700	0.09	1.6	4.4	20,500
55	10	1,800	0.09	1.7	4.8	19,600
60	12	1,800	0.10	1.7	5.0	18,900
65	16	1,800	0.10	1.6	5.1	18,000
70	17	1,500	0.09	1.5	5.0	16,900
75‡	20	1,300	0.08	1.2	4.7	16,300
80‡	20	900	0.06	0.9	4.1	16,100
85‡	20	600	0.04	0.6	3.3	15,400
Women						
50	1	1,700	0.03	0.7	2.1	56,800
55	2	1,800	0.04	0.9	2.6	46,200
60	3	1,900	0.05	1.0	3.1	39,200
65	5	1,900	0.06	1.1	3.5	33,400
70	8	1,700	0.06	1.1	3.7	29,300
75	14	1,400	0.06	1.1	3.8	25,000
80	14	1,100	0.05	0.9	3.6	21,300
85	14	700	0.04	0.6	3.0	19,800

For more detailed results see Online Table S10. Because costs are rounded to the nearest $100, incremental cost-effectiveness ratios may be slightly different than the incremental costs and QALYs in the table suggest. *Determined on the basis of a Framingham risk score (19). †Combined reduction in myocardial infarction (MI) and stroke before development of end-stage renal disease. ‡ATPIII currently recommends that individuals with risk level of 20% or more should be treated with statins. All other groups of CKD patients in the table would not have statin therapy currently recommended if they had no other CV risk equivalents.

Abbreviations as in Table 1.

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Table 70 – Evidence tables of model developed in NICE clinical guideline CG181

<table>
<tr><th>Author & year of publication</th><th>Conflict of interest</th><th>Intervention</th><th>Cost-effectiveness</th><th>Conclusion</th></tr>
<tr><td colspan="5">Statins versus no treatment or other statins</td></tr>
<tr><td>NICE clinical guideline CG181 2014[14] (model)</td><td>No conflict of interest declared.</td><td>Statins versus placebo or no treatment.

Statins were divided into 3 intensity groups[ooo] (low-, medium- and high-intensity statins).
(QRISK2 assessment tool)</td><td>For atorvastatin 20 mg as high-intensity statin
• Men (Age 60 at start and QRISK2 10%)
<table><tr><th>Intervention</th><th>Costs</th><th>QALY</th><th>ICER</th></tr><tr><td>None</td><td>£3 042</td><td>11.438</td><td>-</td></tr><tr><td>Low</td><td>£4 377</td><td>11.639</td><td>Dominated</td></tr><tr><td>Medium</td><td>£4 216</td><td>11.714</td><td>Extended dominance</td></tr><tr><td>High (20mg)</td><td>£4 291</td><td>11.737</td><td>£4 177/QALY (probabilistic: £4 125/QALY)</td></tr></table>• Women (Age 60 at start and QRISK2 10%)
<table><tr><th>Intervention</th><th>Costs</th><th>QALY</th><th>ICER</th></tr><tr><td>None</td><td>£2 979</td><td>12.062</td><td>-</td></tr><tr><td>Low</td><td>£4 381</td><td>12.277</td><td>Dominated</td></tr><tr><td>Medium</td><td>£4 202</td><td>12.371</td><td>Extended dominance</td></tr><tr><td>High (20)</td><td>£4 269</td><td>12.402</td><td>Not reported (+/- £2 161/QALY)</td></tr></table>For atorvastatin 80 mg as high-intensity statin
• Men (Age 60 at start and QRISK2 10%)
<table><tr><th>Intervention</th><th>Costs</th><th>QALY</th><th>ICER</th></tr></table></td><td>“The analysis found that high-intensity statin treatment using atorvastatin 20 mg is cost effective compared to medium-intensity statin treatment using simvastatin 20 mg at a cost-effectiveness threshold of £20,000 per QALY gained for men aged 60 who do not have CVD and who have a QRISK2 CV risk score above 6.8%. Atorvastatin 80 mg is cost effective compared to medium-intensity statins for those men aged 60 who have a QRISK2 score above 8.7%. Medium-intensity treatment is cost effective or dominant compared to no treatment or low-intensity treatment at all risk levels of interest. The results for atorvastatin 20 mg versus simvastatin 20 mg at a QRISK2 score of 10% were robust for all age and sex subgroups and almost all sensitivity analyses. These results do not include the potential effects of adverse events other an increase in cases of type 2 diabetes. A scenario analysis was therefore carried out considering the impact if a greater rate of adverse events in high-intensity treatment caused some people to cease taking statins or to change to a lower intensity. This found that high-intensity treatment would still be cost effective compared to medium-intensity treatment if 10% of people taking high-intensity statins</td></tr>
</table>

[ooo] **Low-intensity statins group** (21-29% reduction in LDL cholesterol) is composed by fluvastatin 20mg/day, fluvastatin 40mg/day, pravastatin 10mg/day, pravastatin 20mg/day, pravastatin 40mg/day and simvastatin 10mg/day. **Medium-intensity statins group** (32-38% reduction in LDL cholesterol) is composed by fluvastatin 80mg/day, simvastatin 20mg/day, simvastatin 40mg/day, atorvastatin 10mg/day and rosuvastatin 5mg/day. **High-intensity statins group** (42-55% reduction in LDL) is composed by simvastatin 80mg/day, atorvastatin 20mg/day, atorvastatin 40mg/day, atorvastatin 80mg/day, rosuvastatin 10mg/day, rosuvastatin 20mg/day and rosuvastatin 40mg/day.

None	£3 042	11.438	-
Low	£4 377	11.639	Dominated
Medium	£4 216	11.714	Not reported (+/- £4 254 / QALY)
High (80)	£4 522	11.737	£13 253/QALY

- Women (Age 60 at start and QRISK2 10%)

Intervention	Costs	QALY	ICER
None	£2 979	12.062	-
Low	£4 381	12.277	Dominated
Medium	£4 202	12.371	Not reported (+/- £3 958/QALY)
High (80)	£4 515	12.402	£9 881 /QALY

ceased treatment and another 10% switched to a medium-intensity statin, demonstrating that the results are insensitive to the rates of adverse events over a very wide range of possible rates."[14]

Table 104: Risk thresholds using QRISK2 at which high-intensity primary prevention treatme cost effective compared to medium-intensity treatment (simvastatin 20 mg) for different cost-effectiveness thresholds

	Risk threshold above which high-intensity statins are cost effective					
	£20,000 per QALY gained			£30,000 per QALY gained		
	A20	A40	A80	A20	A40	A
Men age 40	3.1%	3.3%	4.0%	2.9%	3.0%	3.
Men age 50	5.0%	5.3%	6.3%	4.8%	5.0%	5.
Men age 60	6.8%	7.1%	8.7%	6.4%	6.7%	7.
Men age 70	6.8%	7.5%	10.1%	6.4%	6.8%	8.
Women age 40	2.4%	2.6%	3.4%	2.2%	2.3%	2.
Women age 50	3.5%	3.8%	4.8%	3.3%	3.5%	4.
Women age 60	5.2%	5.6%	7.2%	4.8%	5.1%	6.
Women age 70	7.3%	8.1%	11.6%	6.7%	7.3%	9.

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People with type 2 diabetes

NICE clinical guideline CG181 2014[14] (model)

No conflict of interest declared.

Statins versus placebo or no treatment. Statins were divided into 3 intensity groups[ppp] (low-, medium- and high-intensity statins).

(United Kingdom Prospective Diabetes Study (UKPDS tool)

For atorvastatin 20 mg as high-intensity statin

- Men aged 60year at start and with UKPDS 10-year risk of 10% (Total CV risk = 26.9%)

Intervention	Costs	QALY	ICER
None	£4 359	10.940	-
Low	£5 419	11.191	Dominated
Medium	£5 154	11.309	Dominated
High (20mg)	£5 136	11.367	£1 822/QALY

- Women aged 60year at start and with UKPDS 10-year risk of 10% (Total CV risk = 29.0%)

Intervention	Costs	QALY	ICER
None	£4 308	11.512	-
Low	£5 422	11.787	Dominated
Medium	£5 142	11.930	Dominated
High (20mg)	£5 135	11.995	Not reported (+/- £1 712/QALY)

For atorvastatin 80 mg as high-intensity statin

- Men aged 60year at start and with UKPDS 10-year risk of 10% (Total CV risk = 26.9%)

Intervention	Costs	QALY	ICER
None	£4 359	10.940	-
Low	£5 419	11.191	Dominated
Medium	£5 154	11.309	Not reported (+/- £2 154/QALY)

"The analysis found that high-intensity statin treatment using atorvastatin 20 mg is cost effective compared to medium-intensity statin treatment at a cost-effectiveness threshold of £20,000 per QALY gained for people who have type 2 diabetes but do not have CVD and who have a UKPDS CV risk score above 3.9%. Atorvastatin 80 mg is cost effective compared to medium-intensity statins for those who have a UKPDS score above 5.0%. Medium-intensitytreatment is cost effective or dominant compared to no treatment or low-intensity treatment at all risk levels of interest. At a UKPDS risk score of 10% atorvastatin 20 mg dominated simvastatin 20 mg and atorvastatin 80 mg had an ICER of £3445 per QAly gained compared with simvastatin 20 mg."[14]

ppp Low-intensity statins group (21-29% reduction in LDL cholesterol) is composed by fluvastatin 20mg/day, fluvastatin 40mg/day, pravastatin 10mg/day, pravastatin 20mg/day, pravastatin 40mg/day and simvastatin 10mg/day. Medium-intensity statins group (32-38% reduction in LDL cholesterol) is composed by fluvastatin 80mg/day, simvastatin 20mg/day, simvastatin 40mg/day, atorvastatin 10mg/day and rosuvastatin 5mg/day. High-intensity statins group (42-55% reduction in LDL) is composed by simvastatin 80mg/day, atorvastatin 20mg/day, atorvastatin 40mg/day, atorvastatin 80mg/day, rosuvastatin 10mg/day, rosuvastatin 20mg/day and rosuvastatin 40mg/day.

High (80mg)	£5 351	11.367	£3 445/QALY

- Women aged 60year at start and with UKPDS 10-year risk of 10% (Total CV risk = 29.0%)

Intervention	Costs	QALY	
None	£4 308	11.512	-
Low	£5 422	11.787	Dominated
Medium	£5 142	11.930	Not reported (+/- £1 995/QALY)
High (80mg)	£5 363	11.995	£3 416/QALY

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Appendix 3.5. Results from selected primary studies

Appendix 3.5.1. Evidence tables - Comparison of various CVD risk and age thresholds

Table 71 – Statins therapy: Baseline population

	Aarnio 2015[107]	Odden 2015[106]	Pandaya 2015[105]	Shiffman 2016[102]	Heller 2017[103]	Romanens 2017[108]
Country	Finland	US	US	US	US	Switzerland
Age and Gender	Adults aged 45, 50, 55, 60 and 65 years old	Adults aged 75–94 years old	Adults aged 40–75 years old	Adults aged 40–75 years old	Men aged 45 to 74 years old Women aged 55 to 74 years old	Adults aged 40–65 years
Risk	Various level of risks estimated by the **FINRISK risk function** (take into account factors such as age, smoking, cholesterol, systolic blood pressure, HDL-C, diabetes, parents' infraction)	Based on the density lipoprotein cholesterol level + **ACC/AHA** ASCVD Risk Calculator	Various level of risks based on the **ACC/AHA** ASCVD Risk Calculator (ASCVD risk treatment threshold) from 1% to 30% and more)	**Intermediate risk of CVD (ACC/AHA** ASCVD Risk Calculator): with an estimated 10-year CVD risk between 5% and 7.5% (average of 6.25%)	Various level of risks and use of two different algorithms: **ATP III algorithm**: • Have LDL-C >130 mg/dL, ≥2 CHD risk factors and a Framingham 10-year CHD risk >10%; or • Have LDL-C >160 mg/dL, ≥2 CHD risk factors, and a Framingham 10-year CHD risk <10%; or • Have LDL-C 190 mg/dL and <2 CHD risk factors **ACC/AHA algorithm**: • Have LDL-C >190 mg/dL regardless of other risk factors • Have LDL-C <190 mg/dL but have an ACC/AHA 10-year CHD risk >7.5%	Various level of risks defined with the use of **SCORE** for low risk population (2.5%, 5% and 7.5%)
Other	Primary prevention Diabetic patients included in the risk formula.	Primary prevention Diabetic patients included.	Primary prevention Diabetic patients (14.7%) included.	Primary prevention Without diabetes With LDL-C: 70–189 mg/dL	Primary prevention Without diabetes	Primary prevention Without diabetes

Note: LDL-C: low-density lipoprotein cholesterol; ASCVD: Atherosclerotic Cardiovascular Disease; ACC/AHA: American College of Cardiology and American Heart Association; SCORE: Systematic COronary Risk Evaluation; CVD: Cardiovascular disease; CHD: coronary heart disease

Table 72 – Statins therapy: Study characteristics

	Aarnio 2015[107]	Odden 2015[106]	Pandaya 2015[105]	Shiffman 2016[102]	Heller 2017[103]	Romanens 2017[108]
CoI & industry funded	Potential conflict of interest. Partially funded by industry.	Conflict of interest: not clear. Not funded by industry.	No conflict of interest. Funding: NA.	Potential conflict of interest. Funding: NA.	No conflict of interest declared. Not funded by industry.	No conflict of interest declared. Not funded by industry.
Model	Markov model	Markov model	Individual-based (microsimulation) model	Markov model	Markov model	No model. Calculations based on the assumptions that all events occur uniformly after 50% of the time period[qqq]
Perspective	Societal	Health care system	Societal	Payer	Not specified (seems health care system)	Not specified
Time horizon	10-year horizon	10-year horizon	Life time	5-year horizon	10-year horizon	10 years (a five-year period was also calculated but is not reported here).
Discount rate	3% for costs and outcomes	3% for costs and outcomes	3% for costs and outcomes	3% for costs and outcomes	3% for costs and outcomes	No discount rate

Note: CoI: Conflict of interest

[qqq] For a 10-year period, all non-fatal events occurred at year 5. The number of fatal events corresponded to the assumed risk at 10 years (with the Score interment) and a ratio of 1/4.5 was assumed for non-fatal events.

Table 73 – Statins therapy: Intervention and comparators

Aarnio 2015[107]	Odden 2015[106]	Pandaya 2015[105]	Shiffman 2016[102]	Heller 2017[103]	Romanens 2017[108]
• **No treatment** • **Statin** (with various risk thresholds) (+ 2 scenarios on adherence: real world vs full adherence)	• **No ASCVD threshold** (eligible for statins through other criteria e.g. diabetes or elevated LDL-C) • **Secondary prevention** (100%) only • **Primary prevention**: o LDL-C ≥4.91 mmol/L (**190 mg/dL**) o LDL-C ≥4.14 mmol/L (**160 mg/dL**) o LDL-C ≥3.36 mmol/L (**130 mg/dL**) o Diabetes o 10-year risk score ≥7.5% (i.e. **all adults aged 75 and older**)	• **No** ASCVD risk–based treatment strategies • **12** variations of the ACC/AHA guidelines ASCVD **risk treatment thresholds**: ≥30%, ≥20%, ≥15%, ≥10%, ≥7.5%, ≥5%, ≥4%, ≥3%, ≥2%, and ≥1%, • **Treating all patients**	• **No Statin** • Moderate-intensity statin therapy (MST) for all patients (**MST – all**) • MST for patients in the top decile of LDL-P levels (**MST Test+**) • High-intensity statin therapy (HST) for patients in the top decile of LDL-P levels and MST for others (**HST test +**) • HST for all patients (**HST all**) NB: for patients with intermediate risk of CVD	• Current levels of statin use (**Status Quo**) • Statin for patients eligible by the **ATP III** algorithm* • Statin for patients eligible by the **ACC/AHA** algorithm** • **Universal** use of statins (All men aged 45 to 74 years old / Women aged 55 to 74) + In each scenario, universal use of high-intensity statins among those with CVD or diabetes mellitus.	• **No treatment** • **Statin** (with various risk thresholds)

*Note: LDL-C: Low-Density Lipoprotein Cholesterol; ASCVD: Atherosclerotic Cardiovascular Disease; ACC/AHA: American College of Cardiology and American Heart Association; LDL-P: Low-Density Lipoprotein Particle; CVD: Cardiovascular disease; * **ATP III algorithm:** (i) Have LDL-C >130 mg/dL, ≥2 CHD risk factors and a Framingham 10-year CHD risk >10%; or (ii) Have LDL-C >160 mg/dL, ≥2 CHD risk factors, and a Framingham 10-year CHD risk <10%; or (iii) Have LDL-C 190 mg/dL and <2 CHD risk factors; ** **ACC/AHA algorithm**: (i) Have LDL-C >190 mg/dL regardless of other risk factors; or (ii) Have LDL-C <190 mg/dL but have an ACC/AHA 10-year CHD risk >7.5%*

Table 74 – Statins therapy: Outcomes data (part 1)

	Aarnio 2015[107]	Odden 2015[106]	Pandaya 2015[105]	Shiffman 2016[102]	Heller 2017[103]	Romanens 2017[108]
Cardiovascular events considered	CHD (acute myocardial infarction). Stroke not considered	CVD = CHD (cardiac arrest, angina, myocardial infarction (MI)) + ischemic stroke	CVD = CHD (cardiac arrest, angina, myocardial infarction (MI)) and stroke	CVD = myocardial infarction + revascularisation (percutaneous intervention or coronary artery bypass surgery) and stroke	CVD = CHD and stroke.	CVD = CHD (myocardial infarction+ coronary revascularisation) and stroke
Adverse events (AE) considered	No adverse event taken into account	Myopathy, haemorrhagic stroke, functional limitation due to muscle pain and weakness, and mild cognitive impairment	Mild AE (myalgia or myopathy) and major AE (rhabdomyolysis) and type 2 diabetes.	Mild AE (myalgia), severe AE (rhabdomyolysis) and statin-induced diabetes	Myopathy, haemorrhagic (not ischemic) stroke, and diabetes mellitus	Not taken into account
Adherence	Scenario 1: full adherence (100%) => same RR as above Scenario 2 (real world data): patients classified to have: • Good aherence (proportion of days covered (PDC) ≥ 80%) => same RR as with 100% adherence. Proportion of patients in this category not specified (but seems equal to 54.6%) • Moderate adherence (40% ≤ PDC < 80%) => half of the RR • Low adherence (PDC < 40%) = > same risk as without treatment Adherence was assumed to remain stable after year 4.	Not taken into account	67% in the first year; 53% in the second year and 50% in the following years (based on real-world data)	25.4 % of patients were assumed to discontinue statin therapy in the first year (range: 0-44.4%)	Not taken into account	Not taken into account

Note: CHD = Coronary heart disease; CVD = Cardiovascular disease; PDC = proportion of days covered; RR = Risk ratio; AE: Adverse event.

Table 75 – Statins therapy: Outcomes data (part 2)

	Aarnio 2015[107]	Odden 2015[106]	Pandaya 2015[105]	Shiffman 2016[102]	Heller 2017[103]	Romanens 2017[108]
Effectiveness of statin intervention	• Risk ratio of: 0.73 (0.67-0.80) for CHD events (but 1.00 in the first year) (Taylor et al.[7].	Decrease of LDL-C level from statins: 34% (20.4-47.6). Beta coefficient per mg/dL of LDL-C: • 0.004 (SD 0.0006) for 75-84 years; • 0.003 for 85-94 years (Mihaylova et al.[161]: RR 0.83 (0.78 − 0.87 for 70+))	Risk ratio of: • 0.75 for CHD events • 0.81 for stroke (Baigent et al.[162]) Another scenario was tested in the sensitivity analysis: • Decrease of LDL-C level from statins: 29% • Relative risk reductions of 0.23 for CHD (RR 0.77) and 0.17 for stroke (RR 0.83) for each mmol/L LDL reduced.	Hazard ratio for High-intensity statin (Ridker et al.[76] and Choudry et al.[146]): • 0.46 (0.30-0.70) for MI • 0.54 (0.41-0.72) for Revascularization • 0.52 (0.34-0.79) for stroke Hazard ratio for Moderate-intensity statin (Pandya et al.[105]): • 0.75 (0.71-0.78) for Coronary artery disease • 0.83 (0.76-0.87) for stroke	Decrease of LDL-C level: • 40% (36-44%) for moderate-intensity statin • 54.77% (50.77-58.77) for high-intensity statin (Mihaylova et al.[161] and Stone et al.[163]) Risk ratio per 1-mmol/L reduction in LDL-C from statins regardless of baseline LDL-C: • 0.79 (0.76-0.81) for any major coronary event • 0.82 (0.75-0.90) for stroke (Mihaylova et al.[161] for CHD and Framingham heart study cohort 2015 for stroke[rrr])	2 scenarios: • RRR = 0.30 => RR = 0.7 • RRR = 0.22 => RR = 0.78 (Based on Mihaylova et al.[6]) Assumption: all events occur uniformly after 50% of the time period. The number of fatal events corresponded to the assumed risk at 10 years (with the Score interment) and a ratio of 1/4.5 was assumed for non-fatal events).
QALYs	Disutility for taking a statin pill every day not included	Disutility for taking a statin pill every day (pill burden) not included in the base case (only in the sensitivity analysis)	Disutility for taking a statin pill every day included	Disutility for taking a statin pill every day included	Disutility for taking a statin pill every day (pill burden) not included in the base case (only in the sensitivity analysis)	Disutility for taking a statin pill every day not included. Assumed disutility (no sources reported => authors opinion): • -1 for fatal events; • -0.2 for non-fatal events

Note: CHD: Coronary heart disease; SD: Standard deviation; LDL: Low-Density Lipoprotein; MI: Myocardial infarction; RRR: Relative risk reduction; RR: Risk ratio

[rrr] https://biolincc.nhlbi.nih.gov/studies/framcohort/

Table 76 – Statins therapy: Cost data

	Aarnio 2015[107]	Odden 2015[106]	Pandaya 2015[105]	Shiffman 2016[102]	Heller 2017[103]	Romanens 2017[108]
Currency / year	2011 Finnish Euro	2014 US $	2013 US $	2014 US $	2016 US $	Not reported
Cost input considered	Direct health care costs and indirect costs (productivity losses)	Direct health care costs	Direct and indirect health care and non-health care costs (Travel time and costs, wait times and productivity losses included)	Direct health care costs	Not clear	Not reported. Assumption done by the authors (no sources): • For fatal events: CHF 8500 • For non-fatal events: CHF 25 000 the first year and 8000 the following 4 years (assumed that all events occurred at year 5 for a 10 year period)
Annual Statin costs	€52 in full adherence => weighted by the PDC in cases of no full adherence. Average annual statin cost in the Finnish population.	$60.84 (48.67-365). Average of 4 moderate dose generic statins: atorvastatin 10 mg, simvastatin 20 mg, pravastatin 40 mg, and lovastatin 40mg.	$267 ($68 in a "generic price only" scenario). Average of generic 20mg simvastatin (38.5%), generic 20mg atorvastatin (52.5%) and branded 20mg rosuvastatin (9.0%).	• Low/Moderate-intensity statin: $48.0 (±20%), statin not specified. • High-intensity statin: $91.0 (±20%), statin not specified.	• Moderate-intensity statin: $48.67 ($10.57–$438.00) (e.g. pravastatin 40 mg) • High-intensity statin: $148.30 ($31.71–$1217.00) (e.g. atorvastatin 80 mg)	• CHF470 (including monitoring)
Annual cost of monitoring patients receiving statins in primary prevention	€147.9	$35.75	$110 (69-150)	-	$7.30 ($3.65-$10.95) + $19 ($9.5-$28.5) in the ATP III and ACC/AHA scenarios Total $26.3 ($13.15-$39.45)	See above.
Total costs	€199.90	$96.59 ($84.42-$400.75)	$377 ($336-$417) Generic price scenario: $178 ($137-$218)	Low/Moderate-intensity statin: $48.0 ($38.4-$57.6) High-intensity statin: $91.0 ($72.8-$109.2)	Moderate-intensity statin: $74.97 ($23.72–$477.45) High-intensity statin: $174.6 ($44.86–$1256.45)	CHF470

Note: PDC = Proportion of days covered

Appendix 3.5.2. Evidence tables - 'Patient with diabetes or chronic kidney disease

Table 77 – Diabetes and CKD: Baseline population

	De Vries 2014[99]	Mihaylova 2016[104]
Country	The Netherlands	UK
Age	Adults divided into 3 age groups: • <45 • 45-55 years old • 55-65 years old	Patients aged 40 years or older (average: risk <10%: 52; risk 10%-19%: 61; risk ≥20%: 69)
Risk	The United Kingdom Prospective Diabetes Study (UKPDS) risk engine was used to estimate the patients' 10-year risks for CHD and stroke (based on patient characteristics - age, lipid ratio- and other risk factors such as smoking status). Limitation of the study: there is evidence that the UKPDS risk engine over estimates the risks for CHD and stroke.[164]	Patients are categorised by **5-year cardiovascular risk**: • low <10%; • medium between 10% and <20%; or • high >=20% and **CKD stage**: • 3 • 4 • 5 not on dialysis • on dialysis therapy. The cardiovascular risk was determined using a Cox proportional hazards model based on the following variables: Gender, Ethnicity, Smoking status, diabetes status, Type of renal disease, and Systolic blood pressure, Albumin, Hemoglobin, Total cholesterol, HDL-cholesterol, and Urinary ACR levels.
Other	Primary prevention Diabetes Type 2 patients only.	Primary prevention • Patients with moderate to severe CKD but without known coronary heart disease • Diabetic patients included (23%) Patients were eligible if they were receiving maintenance dialysis or had serum or plasma creatinine levels of at least 150 mmol/L (1.7 mg/dL) in men or 130 mmol/L (1.5 mg/dL) in women.

Note: CHD = Coronary heart disease; UK: United Kingdom; CKD: Chronic kidney disease

Table 78 – Diabetes and CKD: Study characteristics

	De Vries 2014[99]	Mihaylova 2016[104]
CoI & industry funded	Potential conflict of interest. Funded by industry.	No conflict of interest declared. Partially funded by industry.
Model	Markov Model	Performed alongside a RCT, i.e. the SHARP study (Intention–to-treat analysis) + long-term projections
Perspective	Health care payers' perspective	UK National Health Service perspective
Time horizon	10-year horizon	5 years (RCT) + long term projections to estimate survival gain due to avoiding a major atherosclerotic event.
Discount rate	4% for costs and 1.5% for health effect	3.5% for costs and outcomes
Intervention / comparator	Statin (40mg generic simvastatin) vs no treatment	Base-case: simvastatin 20mg plus ezetimibe 10mg versus placebo + scenario analyses on other High-intensity statin regimens (achieving 40% or more reductions in LDL-cholesterol: Rosuvastatin 10mg; Atorvastatin 20mg, 40mg and 80mg; Simvastatin 80mg).

Note: RCT: Randomized controlled trial; SHARP: Study of Heart and Renal Protection.

Table 79 – Diabetes and CKD: Outcomes (part 1)

	De Vries 2014[99]	Mihaylova 2016[104]
Cardiovascular events considered	CVD = (myocardial infarction + CHD) + stroke	Not clear. Seems **major atherosclerotic events** (myocardial infarction or death from coronary heart disease, nonhemorrhagic stroke, or arterial revascularization excluding dialysis access procedures) for the cost-utility analyses and both (i) Atherosclerotic events and (ii) major vascular event (no definition found) for the cost per case avoided (not reported here).
Adverse events (AE) considered	Rhabdomyolysis and Myopathy.	Major adverse events (= if hospitalized)
Adherence	Statin adherence rates were defined as the percentages of pill days covered (PDC). Based on real-world adherence rates: - Mean PDC = 81% in year 1 - Mean PDC = 77% in year 2 - Mean PDC = 75% in year 3 In the base case, statin adherence was assumed to stay constant after year 3.	Based on the actual adherence observed in the SHARP study. If adherence <10%: no cost was attributed to such patients while adherence remained at that level.

Note: CVD: Cardiovascular disease; CHD: coronary heart disease; SHARP: Study of Heart and Renal Protection.

Table 80 – Diabetes and CKD: Outcomes (part 2)

	De Vries 2014[99]	Mihaylova 2016[104]
Effectiveness of statin intervention	**Risk ratio:** • 0.69 for MI • 0.70 for stroke (de Vries et al.[33])	**Simvastatin plus ezetimibe produced a mean reduction of 0.85 mmol/L in LDL cholesterol level, which yielded:** • A 17% proportional reduction (rate ratio [RR], 0.83; 95% CI, 0.72-0.95; P 5 0.007) in all (first and subsequent) major atherosclerotic events corresponding to a 20% proportional reduction (RR, 0.80; 95% CI, 0.68-0.94) per 1-mmol/L LDL cholesterol level reduction. Same estimates were used for dialyses patients. **Simvastatin plus ezetimibe also yielded:** • a 16% proportional reduction (RR, 0.84; 95% CI, 0.74-0.96; P 5 0.01) in atherosclerotic hospital episodes • a 11% reduction (RR, 0.89; 95% CI, 0.79-0.99; P 5 0.04) in nonatherosclerotic vascular episodes • a 15% proportional reduction (RR, 0.85; 95% CI, 0.75-0.97; P 5 0.01) in mean costs of all vascular hospital episodes (corresponding to 17% proportional reduction [RR, 0.83; 95% CI, 0.72-0.96] per 1-mmol/L LDL cholesterol reduction). • no significant effect on renal hospital episodes (RR, 0.97; 95% CI, 0.90-1.03; P 5 0.3) or other nonvascular and nonrenal hospital episodes (RR, 1.03; 95% CI, 0.97-1.09; P 5 0.4). **Scenario on high intensity statins** • Effects were assumed to be in proportion to their relative potency in reducing LDL cholesterol levels (between Rosuvastatin 10mg (43%); Atorvastatin 20mg (44%), 40mg (48%) and 80mg (53%); Simvastatin 80mg (42%)) compared to simvastatin + ezetimibe. **Long term projections:** Gompertz proportional hazards parametric survival models for paticipants not having and having major atherosclorotic events during the SHARP study (matched by their 5-year estimated cardiovascular risk)
QALYs	Disutility for taking a statin pill every day included (-0.001)	Disutility for taking a statin pill every day not included. QALYs during the estimated survival was based on stage of CKD and came from a study that assessed the quality of life for a sample of the population using the time-trade-off technique.

Note: MI: Myocardial infarction; RR: Rate ratio; CI: Confidence intervals; P: p-value; CKD: Chronic kidney disease; QALY: Quality-adjusted life year; SHARP: Study of Heart and Renal Protection.

Table 81 – Diabetes and CKD: Costs

<table>
<tr><th></th><th>De Vries 2014[99]</th><th>Mihaylova 2016[104]</th></tr>
<tr><td>Currency / year</td><td>2012 Dutch Euro</td><td>Treatment costs: £ 2015 UK
Hospital costs: £ 2011 UK</td></tr>
<tr><td>Cost input considered</td><td>Direct health care costs</td><td>Direct health care costs (only inpatient costs; outpatient and primary care costs were not included). In the long term (projection), only the cost of treating end-stage renal disease was considered.</td></tr>
<tr><td>Annual Statin costs</td><td>€7.3 (40mg generic simvastatin)</td><td>Base-case (Simvastatin 20mg + Ezetimibe 10mg): £434.35 (£1.19/day) in case of full adherence (Mean cost per patient during the study period: £1319)
Scenario analysis on high-intensity statin regimens:
£21.9-£401.5 (£0.60-1.10/day)
£18.25 – £401.5 (£0.05-£0.1/day)
<table>
<tr><th></th><th colspan="4">Yearly costs</th></tr>
<tr><td>Dose (mg/day)</td><td>10mg/day</td><td>20mg/day</td><td>40mg/day</td><td>80mg/day</td></tr>
<tr><td>Simvastatin</td><td>-</td><td>-</td><td>-</td><td>£25.55 (£0.07/day)</td></tr>
<tr><td>Atorvastatin</td><td>-</td><td>£18.25 (£0.05/day)</td><td>£21.9 (£0.06/day)</td><td>£36.5 (£0.1/day)</td></tr>
<tr><td>Rosuvastatin</td><td>£233.6 (£0.64/day)</td><td>£339.45 (£0.93/day)</td><td>386.9 (£1.06/day)</td><td>-</td></tr>
<tr><td>Simvastatin 20mg + Ezetimibe 10mg</td><td>-</td><td>£434.35 (£1.19/day)</td><td>-</td><td>-</td></tr>
</table></td></tr>
<tr><td>Annual cost of monitoring patients receiving statins in primary prevention</td><td>€102.8
(Two GP visits (€59.5), annual lipid spectrum testing (€20.3), and four pharmacists' prescription fees (€23))</td><td>Not included (only hospital costs are considered)</td></tr>
<tr><td>Total costs</td><td>€110.1</td><td>See Annual statin costs</td></tr>
</table>

6.9.1.2 *Evidence tables - 'Polypills' compared to plain statins and antihypertensive*

Table 82 – Polypill: Baseline population

	Jowett 2017[101]	Ferket 2017[100]
Age	People aged ≥40 years old	People aged ≥40 years old
Risk	Various levels of risks based on the updated Framingham equation.	Various levels of risks based on the QRISK calculator.
Other	Baseline population: Only people already on treatment (statin or antihypertensive drugs) are considered (people not on medication not considered)	Baseline population: Only people not on medication (statin or antihypertensive drugs) are considered (people already on medication are not considered)

Table 83 – Polypill: Study characteristics

	Jowett 2017[101]	Ferket 2017[100]
CoI & industry funded	No CoI declared. Study financed by the National Institute for Health Research in UK.	No CoI declared. Study financed by the National Institute for Health Research Cardiovascular Biomedical Research Unit at Barts.
Model	Markov Model (1-year cycle)	Individual based state-transition (microsimulation) model
Perspective	NHS and personal social services perspective	NHS health system
Time horizon	10 years	Until 95 years old
Discount rate	3.5%	3.5%
Intervention / comparator	• **Current practice:** statins and/or blood pressure lowering therapies: eight treatments/cardiovascular risks strata for the different subgroups defined according to age and gender • **Optimal guidelines:** optimal treatment according to NICE guidelines, i.e. Simvastatin 40mg if CVD risk ≥ 20% and antihypertensives if blood pressure > 140/90mm/Hg and cardiovascular risk ≥ 20%. Compared to usual care, additional drugs are added to reach a target systolic blood pressure of 140mmHg, up to a maximum of three drugs. • **Polypills:** 40 mg simvastatin + three antihypertensives at half-dose (12.5mg hydrochlorothiazide, 5mg lisinopril, 2.5mg amlodipine), regardless of baseline CVD risk or systolic blood pressure.	• **Current practice:** no systematic prevention programme • **Three guideline strategies:** o Statin from a 10-year CVD risk of 20% (or to all patients aged ≥75 years old) + antihypertensive medication for patients with SBP ≥ 140 mm Hg and a 10-year CVD risk of 20% or with SBP ≥ 150 mm Hg regardless of risk o Statin from a 10-year CVD risk of 10% (or to all patients aged ≥85 years old) o Statin from a 10-year CVD risk of 10% (or to all patients aged ≥85 years old) + antihypertensive medication for patients with SBP ≥ 140 mm Hg and a 10-year CVD risk of 10% or with SBP ≥ 150 mm Hg regardless of risk + Periodic risk assessment: The risk was assessed every 5 years (QRISK score). • **Five age-depended polypill strategies** (20 mg simvastatin + three antihypertensives at half-dose (amlodipine 2.5 mg, losartan 25 mg and hydrochlorothiazide 12.5 mg)): From the age of (1) 40 – (2) 45 – (3) 50 –(4) 55 – (5) 60

Note: CoI: Conflict of interest; CVD: Cardiovascular diseases; NHS: National Health System

Table 84 – Polypill: Outcomes (part 1)

	Jowett 2017[101]	Ferket 2017[100]
Cardiovascular events considered	CVD: CHD (Myocardial infarction, angina, heart failure), stroke or PVD (peripheral vascular disease). The risk of further events once someone had an initial cardiovascular event was not modelled	CVD: Myocardial infarction, angina, stroke, transient ischaemic attack
Adverse events (AE) considered	Not included	Diabetes
Adherence	For Polypill: 84% For Statin: 85%	Based on cohort data (84.6%?)

Note: CVD: Cardiovascular diseases; CHD = Coronary heart disease; PVD: Peripheral vascular disease.

Table 85 – Polypill: Outcomes (part 2)

	Jowett 2017[101]	Ferket 2017[100]
Effectiveness of statin intervention	• Usual care: Baseline calculated 10y CVD risk • RR with statin (Cholesterol Treatment Trialists' Collaboration 2005 [162] and Heart Protection Study Collaborative Group 2002[165]: o Stroke: 0.80 (95% CI 0.73-0.86) o CHD: 0.72 (95% CI 0.69-0.76) o PVD: 0.85 (95% CI 0.75-0.95) Taken into account only if Statin was not given in usual care. • Reduction in CV risk with reduction in **BP** for the **polypill** (dependent on age, sex and risk group, Law et al.[166] and Murabito et al.[167]): o Stroke: 10-52% o CHD: 14-65% o PVD: 13-23% • Reduction in CV risk with reduction in BP for the "**optimal target**" (dependent on age, sex and risk group, Law et al.[166] and Murabito et al.[167]): o Stroke: 15-37% o CHD: 20-47% o PVD: 13-32% • Polypills: effects of the separate drugs was assumed additive.	Current practice: event rates were modelled assuming absence of a systematic prevention programme. RR with statin (Taylor et al. 2013[7]): • Coronary hearth diseases: 0.73 (0.67-0.80) • Cerebrovascular diseases: 0.78 (0.68-0.89) Hazard ratio per 5 mmHg decrease in systolic blood pressure (The Blood Pressure Lowering Treatment Trialists' Collaboration[168]): • Coronary hearth diseases: 0.896 (0.832-0.965) • Cerebrovascular diseases: 0.853 (0.801-0.908) If combined, an absence of interaction between statin and antihypertensive drugs was assumed. For the polypill, calculations of the reductions in blood pressure was done based on the three antihypertensive drugs separately (additive effect).

QALYs	Disutility for taking a pill every day not included.	Based on EQ-5D Disutility for taking a statin pill every day was included.

Note: RR: Risk reduction; CHD = Coronary heart disease; PVD: Peripheral vascular disease; CV: cardiovascular; BP: Best practice; EQ-5D: EuroQol-5D.

Table 86 – Polypill: Cost data

	Jowett 2017[101]	Ferket 2017[100]
Currency / year	2011-2012 UK £	2012-2013 UK £
Cost input considered	Seems direct health care costs	Seems direct health care costs
Annual Statin costs	£15.26 (Simvastatin 40mg)	£16.44 (Atorvastatin 20mg)
Annual antihypertensive drugs (n=3) cost	£12.13 (Amlopidine 5mg) £11.87 (Indapamide 2.5 mg) £18.13 (Ramipril 5mg)	£12.26 (Amlopidine 10mg) £41.40 (Indapamide 1.5 mg) £15.52 (Ramipril 10mg)
Annual Polypill cost	£171	£382.64
Annual cost of monitoring patients	Included (+/- £59.25)	Included (total cost of monitoring not reported)
Total costs	£ 230.25	-

Appendix 3.6. Annual cost in Belgium (2018)

Appendix 3.6.1. Annual cost of statin in Belgium (2018)

Table 87 – Annual statin prices for the cheapest statin of its class in Belgium (2018)

	Small boxes (≤30)	Big boxes (>90)
Atorvastatin 10	€ 112.50	€ 46.48
Atorvastatin 20	€ 137.66	€ 88.38
Atorvastatin 40	€ 135.42	€ 88.38
Atorvastatin 80	€ 137.12	€ 88.38
Simvastatin 20	€ 113.64	€ 57.12
Simvastatin 40	€ 135.42	€ 74.39

Simvastatin 80	-	€ 220.13
Fluvastatin 80	-	€ 102.39
Pravastatin 20	€ 107.81	€ 66.93
Pravastatin 40	€ 228.52	€ 117.99
Rosuvastatin 5	€ 112.54	€ 50.01
Rosuvastatin 10	€ 133.62	€ 84.32
Rosuvastatin 15	€ 135.42	€ 84.97
Rosuvastatin 20	€ 136.22	€ 85.18
Rosuvastatin 30	€ 137.12	€ 86.61
Rosuvastatin 40	€ 136.22	€ 87.00
Ezetimibe 10 + Simvastatin 20	-	€ 592.23 (€ 182.95*)
Acetylsalicylic acid (100 mg) + Atorvastatin (20 mg) + Ramipril (5 mg)	€ 275.97	€ 140.97
Acetylsalicylic acid (100 mg) + Atorvastatin (20 mg) + Ramipril (10 mg)	€ 275.97	€ 177.62

*Note: Data from CBIP – KCE calculation. *Generic medicine will be available in the mid-2019.*

6.9.1.3 Estimation of annual cost of monitoring in Belgium

Table 88 – Estimate of annual cost of monitoring in Belgium

	Nomenclature code	Costs (2018)	Quantity (2017)	Estimation of the weighted average costs	Estimation of annual cost of monitoring
GP fee	101010	€ 15.48	209 719 (0.58%)	€ 25.11	€ 20.59 (according to Table 10, 82% of patients had a prescription from GP)
	101032	€ 21.09	2 233 086 (6.14%)		
	101076	€ 25.43	33 915 790 (93.28%)		
Specialist fee	102255	€ 56,33	53 545 (8.25%)	€ 48.08	€ 8.65 (according to Table 10, 18% of patients had a prescription from a specialist)
	102874	€ 58,97	595 227 (91.75%)		
	102093	€ 31,69	170 372 (11.09%)		
	102594	€ 38,11	1 365 738 (88.91%)		
Lump sum for the clinical biology (non- accredited physician; B<700)	592815	€ 18,78	65 308 (1.57%)	€19.55	€ 19.55
	592852	€ 19,56	4 081 354 (98.43%)		
Dose total cholesterol	540282	€ 0.55 (25% of the fee)		€ 0.55 (25% of the fee)	€ 0.55 (25% of the fee)
Dose HDL-cholesterol	540293	€ 0.78 (25% of the fee)		€ 0.78 (25% of the fee)	€ 0.78 (25% of the fee)
Immunoassay of iso-enzyme creatine kinase	542172	€ 1.95 (25% of the fee)		€ 1.95 (25% of the fee)	€ 0.98 (25% of the fee, hypothesis that only half of patients required this test)
Total costs					**€ 51.09**

Note: Data from CBIP and eCoNoDat – KCE calculation

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