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Federal Department of Home Affairs
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Section Health Technology Assessment

Health Technology Assessment (HTA)

Scoping Report

Title	Statins for primary prevention of cardiovascular events and mortality in Switzerland
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Executive Summary:

In addition to lifestyle optimization, statins are the first-choice treatment to reduce high blood cholesterol and consequently prevent cardiovascular disease (CVD) events. The Federal Office of Public Health (FOPH) is reviewing the public reimbursement of statin therapy in adults without established CVD, because its cost-effectiveness compared to no treatment and/or lifestyle adaptations has been questioned. The aim of this scoping report was to determine the feasibility of conducting a health technology assessment (HTA) for this decision problem.

Systematic literature searches were performed in PubMed (MEDLINE), Embase.com, and other complementary databases to identify relevant published efficacy, effectiveness, safety, and cost-effectiveness evidence. Additional literature was searched for information on potential relevant social, legal, ethical, and organisational aspects related to the topic.

Two high quality systematic reviews (SRs) of randomised controlled trials (RCTs) reported the efficacy and safety of statin therapy for primary prevention of CVD. An update of their literature searches identified two non-randomised studies, but no additional RCTs met the predefined inclusion criteria. Eighteen economic evaluations of statin therapy versus no statin therapy for primary prevention of CVD were included. Preliminary data extraction and quality appraisal were performed for the included studies. Several potentially relevant social, legal, ethical, and organisational aspects related to statin therapy for primary prevention were identified.

All but one of the identified economic evaluations concluded that statin use for primary prevention of CVD was cost-effective. However, the cost-effectiveness results were difficult to compare between studies, because of varying risk scoring systems and/or patient populations. In general, statin treatment for primary prevention of CVD was more cost-effective among higher CVD risk groups. In addition, incremental cost-effectiveness ratios were lower in older age groups and in men compared to women. Multiple studies concluded that treatment adherence had a major impact on cost-effectiveness results of statin use in primary prevention. As such, real-world adherence scenarios

resulted in higher incremental cost-effectiveness ratios compared to full adherence scenarios. Finally, the chosen time horizons had a large impact on the cost-effectiveness results, where longer time horizons resulted in an increased likelihood of cost-effectiveness of statins. Additionally, only two studies conducted a budget impact analysis.

The published economic evaluations did not provide sufficient evidence on the cost-effectiveness of statin therapy in Switzerland. The only economic evaluation performed in Switzerland was a model-based study with many assumptions that were not adequately substantiated. In addition, the study did not consider adverse events of statin therapy, disutility of taking a pill every day or treatment adherence.

A de-novo economic model may be required if a full HTA report is commissioned, to determine the cost-effectiveness of statin therapy compared with no statin therapy in adults without established CVD and with low, medium, and (very) high cardiovascular risks in Switzerland. However, the underlying conceptual model of this de-novo economic model can be based on the published economic models included in the systematic literature search reported in this scoping report.

Based on the findings in this scoping report, conducting a full HTA for the situation in Switzerland is feasible.

Zusammenfassung:

Statine sind, zusammen mit einer Optimierung des Lebensstils, die Behandlung erster Wahl, um einen hohen Cholesterinspiegel im Blut zu senken und somit Herz-Kreislauf-Erkrankungen (HKE) zu verhindern. Das Bundesamt für Gesundheit (BAG) überprüft die Kostenerstattung von Statintherapien für Erwachsene ohne etablierte kardiovaskuläre Erkrankung (Primärprävention), da die Kosteneffizienz im Vergleich zu keiner Behandlung und / oder Lebensstilanpassung in Frage gestellt wurde. Ziel des vorliegenden Scoping-Berichts war es, die Machbarkeit der Durchführung eines HTA Berichtes zu diesem Thema zu ermitteln.

Dafür wurden systematische Literaturrecherchen in PubMed (MEDLINE), Embase.com durchgeführt sowie in weiteren Datenbanken nach relevanter Evidenz für die Wirksamkeit, Effektivität, Sicherheit und Kosteneffizienz von Statinen in der Primärprävention gesucht. Ebenfalls wurde Literatur über potentiell relevante soziale, rechtliche, ethische und organisatorische Aspekte im Zusammenhang mit dem Thema gesucht.

Zwei qualitativ hochstehende systematische Reviews (SRs) mit randomisierten kontrollierten Studien (RCTs) beschrieben die Wirksamkeit und Sicherheit der Statintherapie in der Primärprävention kardiovaskulärer Erkrankungen. Eine aktualisierte Literatursuche auf Grundlage der Literaturstrategie dieser beiden SRs identifizierte zwei nicht randomisierte Studien, ergab jedoch keine weiteren RCTs, welche die vorab definierten Einschlusskriterien erfüllten.

Achtzehn ökonomische Evaluationen, welche Statin-Therapie gegenüber keiner Statin-Therapie zur

Primärprävention von kardiovaskulären Erkrankungen verglichen, wurden eingeschlossen. Für diese wurden eine erste Datenextraktion und eine Qualitätsbewertung durchgeführt. Es wurden mehrere potenziell relevante soziale, rechtliche, ethische und organisatorische Aspekte im Zusammenhang mit der Statin-Therapie zur Primärprävention identifiziert.

Alle bis auf eine der identifizierten ökonomischen Studien kamen zum Schluss, dass der Einsatz von Statinen zur Primärprävention von kardiovaskulären Erkrankungen kosteneffektiv war. Jedoch konnten die Ergebnisse der Kosteneffekitvität wegen der unterschiedlichen Risiko-Scoringsysteme und / oder der unterschiedlichen Patientenpopulationen nur schwer miteinander verglichen werden.

Im Allgemeinen wurde die Behandlung mit Statinen zur Primärprävention von HKE bei Patienten mit einem höheren kardiovaskulären Risiko als kosteneffektiver beschrieben. Für ältere Patienten und für Männer im Vergleich zu Frauen wurden niedrigere inkrementelle Kosten-Effektivitätsverhältnisse gefunden.

Mehrere Studien kamen zu dem Schluss, dass die Therapietreue (Compliance) einen grossen Einfluss auf die Kosteneffektivität der Statin-Anwendung in der Primärprävention hat. Real-World Adhärenz-Szenarien führten daher zu höheren inkrementellen Kosten-Effektivitäts-Verhältnissen im Vergleich zu Szenarien mit vollständiger Adhärenz, welche in randomisierten und kontrollierten Studien oftmals erzielt wird. Des Weiteren zeigten die Studienergebnisse, dass auch der gewählte Zeithorizont einen grossen Einfluss auf die Kosten-Effektivitätsergebnisse hat. Längere Zeithorizonte erhöhten die Wahrscheinlichkeit der Kosten-Effektivität der Statintherapien. Nur in zwei Studien wurden die Auswirkungen von Statintherapien in der Primärpräventionauf das Budget (Budget impact) analysiert.

Die publizierten gesundheitsökonomischen Studien lieferten keine ausreichende Evidenz über die Kosten-Effektivität von Statintherapien in der Schweiz. Die einzige in der Schweiz durchgeführte ökonomische Studie war eine modellbasierte Studie mit Annahmen, die nicht ausreichend begründet waren. Darüber hinaus wurden in der Studie keine unerwünschten Wirkungen (UAWs) der Statintherapie, wie zum Beispiel, der tägliche Aufwand eine Pille einzunehmen, oder die Therapietreue (Compliance), berücksichtigt.

Für einen vollständigen HTA-Bericht wird daher ein de-novo-ökonomisches Modell erforderlich sein, um die Kosten-Effektivität der Statintherapie im Vergleich zu keiner Statintherapie bei Erwachsenen ohne bestehende kardiovaskuläre Erkrankung sowie niedrigem, mittlerem und (sehr) hohem kardiovaskulären Risiko für die Schweiz zu bestimmen. Das einem solchen de-novo-ökonomischen Modell zugrunde liegende konzeptionelle Modell kann jedoch auf den veröffentlichten ökonomischen Modellen basieren, die in der systematischen Literaturrecherche in diesem Scoping-Bericht aufgeführt sind.

Basierend auf den Ergebnissen dieses Scoping-Berichts ist die Durchführung eines vollständigen HTA-Berichtsfür die Situation in der Schweiz machbar.

Résumé:

En complément de l'optimisation du mode de vie, les statines sont le traitement de premier choix pour réduire l'hypercholestérolémie et ainsi prévenir les maladies cardiovasculaires (MCV). L'Office fédéral de la santé publique examine le remboursement public du traitement par statines chez les adultes sans MCV établie, car son rapport coût-efficacité comparé à l'absence de traitement et/ou à une adaptation du mode de vie a été remis en question. L'objectif de ce rapport de *scoping* était de déterminer la faisabilité de la conduite d'une évaluation des technologies de la santé (ETS) relative à ce problème décisionnel.

Des recherches documentaires systématiques ont été effectuées dans PubMed (MEDLINE), Embase.com et d'autres bases de données complémentaires pour identifier les sources scientifiques pertinentes en matière d'efficacité (en campagnes d'essais ou d'observations réelles), d'innocuité et de rapport coût-efficacité. Une revue supplémentaire de littérature a été conduite afin d'obtenir de potentielles informations pertinentes sur les aspects sociaux, légaux, éthiques et organisationnels liés à ce sujet.

Deux revues systématiques (SR) de haute qualité des essais randomisés contrôlés (ERC) ont présenté l'efficacité et l'innocuité du traitement par statines pour la prévention primaire des MCV. Une mise à jour de ces recherches documentaires a identifié deux études non randomisées, mais aucun ECR supplémentaire n'a répondu aux critères d'inclusion prédéfinis. Dix-huit évaluations économiques du traitement par statines comparé à l'absence de traitement par statines pour la prévention primaire des MCV ont été incluses. Une extraction préliminaire des données et une évaluation de la qualité ont été effectuées pour les études incluses. Des aspects sociaux, légaux, éthiques et organisationnels potentiellement pertinents et liés au traitement par statines pour la prévention primaire ont été identifiés.

Toutes les évaluations économiques identifiées, sauf une, ont conclu que l'utilisation de statines pour la prévention primaire des MCV était rentable. Cependant, les résultats sont difficiles à comparer entre les études, en raison des différents systèmes de notation des risques et/ou des différentes populations de patients. En général, le traitement par statines pour la prévention primaire des MCV était plus rentable parmi les groupes à haut risque de MCV. De plus, les rapports coût-efficacité différentiels étaient plus faibles chez les groupes plus âgés et chez les hommes, par opposition aux femmes. Plusieurs études ont conclu que l'adhésion au traitement avait un impact majeur sur le rapport coût-efficacité de l'utilisation des statines en prévention primaire. Ainsi, les scénarios simulant l'adhésion des patients en conditions réelles ont généré des rapports coût-efficacité différentiels plus élevés que les scénarios simulant une adhésion totale. Enfin, les horizons temporels choisis ont eu un impact important sur les résultats concernant la rentabilité, des horizons plus longs entraînant une probabilité accrue de rentabilité des statines. De plus, seules deux études ont mené une analyse d'impact budgétaire. Les évaluations économiques publiées n'ont pas fourni de preuves suffisantes sur le rapport coût-efficacité du traitement par statines en Suisse. La seule évaluation économique réalisée en Suisse est basée sur un modèle et repose sur de nombreuses hypothèses qui ne sont

pas suffisamment étayées. De plus, l'étude n'a pas inclus les événements indésirables liés au traitement par statines, la perte d'utilité relative à la prise quotidienne d'un médicament ou l'observance du traitement.

Un modèle économique *de novo* pourrait être nécessaire si un rapport d'ETS complet est commandé, afin de déterminer la rentabilité du traitement par statines par rapport à l'absence de traitement par statines chez les adultes sans MCV établie et avec des risques cardiovasculaires faibles, moyens et élevés en Suisse. Cependant, le modèle conceptuel sous-jacent à ce modèle économique *de novo* pourrait être basé sur les modèles économiques publiés inclus dans la recherche systématique de ce rapport de *scoping*.

Compte tenu des résultats présentés dans ce rapport, la conduite d'une étude ETS en Suisse s'avère possible.

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Abbreviations and acronyms

ACC/AHA	American College of Cardiology/American Heart Association
AGLA	Austrian Atherosclerosis Society and the Working Group on Lipids and Atherosclerosis
AMSTAR	A MeaSurement Tool to Assess systematic Reviews
CADTH	Canadian Agency for Drugs and Technologies in Health
CE	Cost-Effectiveness
CHD	Coronary Heart Disease
CHEC	Consensus Health Economic Criteria
CHF	Swiss Franc
CTT	Cholesterol Treatment Trialists
CVD	Cardiovascular Disease
e.g.	Exempli gratia (for example)
FOPH	Federal Office of Public Health
FRS	Framingham Risk Score
GRADE	Grading of Recommendations, Assessment, Development and Evaluations
HAS	Haute Autorité de Santé (French National Authority for Health)
HMG CoA	Hydroxymethyl glutaryl coenzyme A reductase
HRQoL	Health-Related Quality of Life
hs-CRP	High sensitive C-reactive protein
HTA	Health Technology Assessment
ICER	Incremental Cost-Effectiveness Ratio
i.e.	Id est (that is)
LDL-C	Low Density Lipoprotein Cholesterol
MESH	Medical Subject Headings
MI	Myocardial Infarction
NA	Not Applicable
NHS	National Health Service
NHS/EED	National Health Service Economic Evaluation Database
NICE	National Institute for Health and Care Excellence
NR	Not Reported
OTC	Over The Counter
PICO	Patients, Intervention, Comparator, Outcome

PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROCAM	Prospective Cardiovascular Münster Model
QALYs	Quality-Adjusted Life Years
QoL	Quality of Life
QRISK	Prediction algorithm for cardiovascular disease
RCT/RCTs	Randomised Controlled Trial/Randomised controlled trials
SCORE	Systematic Coronary Risk Evaluation
SD	Standard Deviation
SR/SRs	Systematic Review/ Systematic Reviews
WHO	World Health Organisation
ZiN	Zorginstituut Nederland (National Health Care Institute)

Objective of the HTA scoping report

The Federal Office of Public Health (FOPH) is reviewing the public reimbursement of statin therapy in adults without established cardiovascular disease (CVD) and with low, medium, and (very) high cardiovascular risks, because its cost-effectiveness compared to no treatment and/or lifestyle adaptations has been questioned.

In the scoping phase, the necessity and feasibility of conducting a full HTA on the efficacy, effectiveness, safety, and cost-effectiveness of using statins for primary prevention of CVD is examined and a central research question is presented based on a systematic literature search. In addition, operational key questions are formulated, in order to determine the full scope of a potential HTA report. The target population, the appropriate comparator, and the relevant health outcomes and costs are defined.

Based on the quantity and quality of the identified evidence, the feasibility of a full HTA is assessed by the FOPH, and it will be decided whether a full HTA report is going to be commissioned for this topic or not.

1. Policy question and context

Cardiovascular disease (CVD) is ranked as the number one cause of mortality and is a major cause of morbidity worldwide. High blood cholesterol is linked to CVD events. Statins, cholesterol lowering drugs, are the first-choice treatments to reduce high blood cholesterol.

There is strong evidence of the effectiveness of statins in people who experienced a cardiovascular event (secondary prevention)[1] and people at high risk of cardiovascular disease (primary prevention)[1], but the evidence on cost-effectiveness of statin use in people at low or medium risk of CVD is limited.[2] Therefore, cost-effectiveness of primary/secondary prevention of CVD using statins in low or medium risk populations is not known. As the size of these lower risk groups is large, prescribing statins to all these people may have a large impact on the national healthcare budget.

The overall aim of the HTA theme brought forward by the applicant Curafutura therefore is to investigate the clinical effectiveness, safety, and cost-effectiveness (WZW) of cholesterol-lowering substances especially statins in primary prevention of CVD in order to determine whether the reimbursement of statins for primary prevention of CVD can or should be restricted in Switzerland.

2. Medical background

CVDs are a group of disorders of the heart and blood vessels and comprise a wide range of diseases. According to the definition of the World Health Organisation (WHO), CVDs include the following.[3]

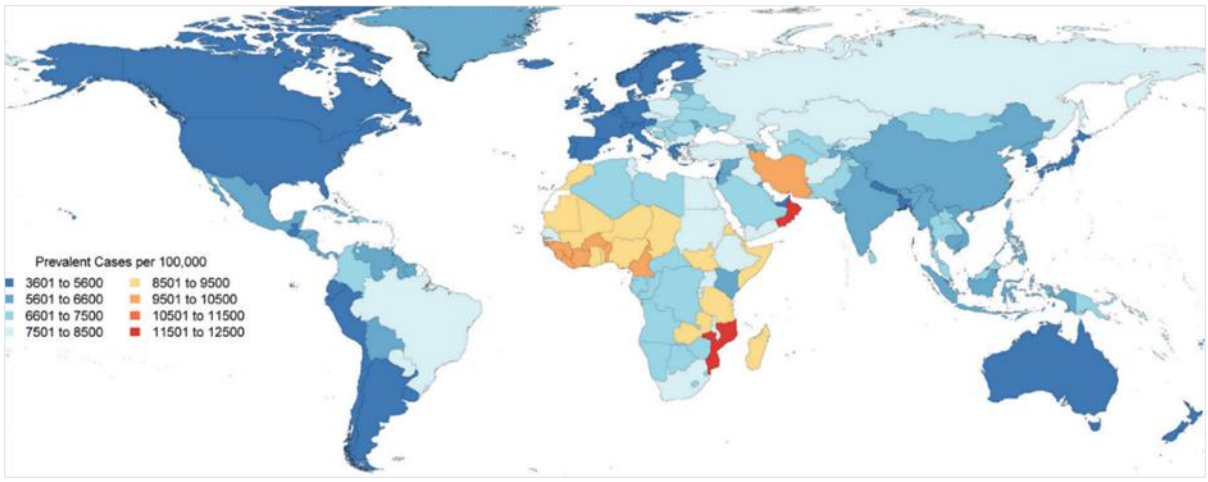
- Coronary heart disease (disease of the blood vessels supplying the heart muscle), including myocardial infarction (MI), heart attack, and angina.
- Cerebrovascular disease (disease of the blood vessels supplying the brain), including ischaemic and haemorrhagic stroke.
- Peripheral arterial disease (disease of blood vessels supplying the arms and legs).
- Rheumatic heart disease (damage to the heart muscle and heart valves from rheumatic fever, caused by streptococcal bacteria).
- Congenital heart disease (malformations of heart structure existing at birth).
- Deep vein thrombosis and pulmonary embolism (blood clots in the leg veins, which can dislodge and move to the heart and lungs).

There are often no symptoms of the underlying disease of the blood vessels; a heart attack or stroke may be the first sign of underlying disease. Symptoms of a heart attack include pain or discomfort in the centre of the chest, in the arms, left shoulder, elbows, jaw, or back. Stroke is mostly associated with sudden weakness of the face, arm, or leg; mostly on one side of the body. Symptoms of rheumatic heart disease include shortness of breath, fatigue, irregular heartbeats, chest pain, and fainting.[4]

CVDs place a high social burden on developed countries, including impaired quality of life, reduced economic activity, and large use of health service resources.[2] Furthermore, CVDs remain the leading cause of morbidity and mortality for both women and men in Western countries, such as Switzerland.[5] Globally, there were about 423 million prevalent CVD cases in 2015. The age-standardised prevalence of CVD varied by country; in Switzerland the number of prevalent cases per 100,000 was in the range of 3,601 to 5,600, as in most neighbour countries (Figure 1).[6]

In 2016, approximately 17.6 million deaths were attributed to CVD globally, which represents an increase of 14.5% from 2006. In Switzerland the age-adjusted death rate for CVD was 112.1 per 100,000 in males and 44.7 per 100,000 in women.[7]

Figure 1. Global map of age-standardised prevalence of CVD in 2015[6]



Although genetic factors play an important role, the main other causes of CVD are behavioural risk factors such as tobacco use, unhealthy diets, physical inactivity, and harmful use of alcohol. The effects of these behaviours may appear in individuals as raised blood pressure, raised blood glucose, raised blood lipids, overweight, and obesity.[4] As documented by genetic, pathology, observational, and intervention studies, dyslipidaemia and especially hypercholesterolaemia plays a crucial role in the development of CVD. Most cholesterol is normally carried in the blood in low-density lipoprotein cholesterol (LDL-C). There is a strong positive association between LDL-C and CVD risk: reducing the plasma LDL-C concentration by 1.0 mmol/L causes a corresponding 20% to 25% risk reduction in CVD mortality and non-fatal MI.[8] This correlation exists in both men and women and in those with and without established CVD. The reduction of LDL-C is therefore of prime concern in the prevention of CVD.[9] LDL-C consists of several subclasses of particles with different sizes and densities, which have different atherogenic potential. For example small dense LDL-C has a greater atherogenic potential, therefore the small dense LDL-C proportion is a better marker for prediction of CVD than total LDL-C.[10]

Smoking cessation, healthy diets, and regular physical activity can lower the risk of CVD. In addition, drug treatment may be necessary to reduce the plasma LDL-C concentration and as a result lower the cardiovascular risk.[4] Statins, or 3-hydroxy-3-methylglutaryl co-enzyme A reductase inhibitors, are a class of lipid-lowering drugs and are first choice agents for reducing plasma LDL-C.[2 11] Statins may be used for the primary or secondary prevention of CVD: primary prevention comprises treating people

without established CVD (but who may be at risk of future CVD events), whereas secondary prevention involves treating persons with established CVD.[11]

It is important for clinicians to be able to assess CVD risk rapidly and accurately, so that they can make the right management decisions. Prevention of CVD should be adapted to an individual's total CVD risk: the higher the risk, the more intense the action should be.[9] Several scoring systems, with various advantages and disadvantages, exist to assess CVD risk, such as the Prospective Cardiovascular Münster Model/Arbeitsgruppe Lipide und Atherosklerose from the Swiss Atherosclerosis Association (PROCAM/AGLA[a]), Systemic Coronary Risk Estimation (SCORE[b]), QRISK[c] (a prediction algorithm for cardiovascular disease), American College of Cardiology/American Heart Association (ACC/AHA[d]) pooled cohort equation, and the Framingham Risk Score (FRS[e]).

3. Technology

3.1 Technology description

Statins, or hydroxymethyl glutaryl coenzyme A (HMG CoA) reductase inhibitors, are one of the most widely prescribed groups of drugs in the world since their introduction to the market more than twenty years ago.[12] Currently, six statin (mono-)drugs are available on the Swiss market, these include pitavastatin (Livazo®), atorvastatin (Sortis® and generics), rosuvastatin (Crestor® and generics), pravastatin (Selipran® and generics), simvastatin (Zocor® and generics), and fluvastatin (Lescol® and generics).

Statins block the HMG CoA reductase enzymes in the liver which play a key role in cholesterol synthesis.[13] [14] Generally, statins are tolerated well by patients. However, some adverse events associated with the intake of statins, e.g. liver dysfunction and myopathy, have been shown to occur.[12]

Typically, statins are administered in the form of tablets, which are to be taken once daily.[15] Often, statin therapy is taken for life, as ceasing statin therapy will result in higher cholesterol levels within a few weeks.

The evidence on the beneficial effects of statin therapy has led to the promotion of their use on a global scale, particularly in the developed world. The overwhelming body of evidence supporting statin therapy, resulted in recommendations in the guidelines of the American Heart Association[16], the European

[a] https://www.agla.ch/risikoberechnung/agla-risikorechner

[b] https://www.escardio.org/Education/Practice-Tools/CVD-prevention-toolbox/SCORE-Risk-Charts

[c] https://qrisk.org/

[d] http://tools.acc.org/ASCVD-Risk-Estimator-Plus/#!/calculate/estimate/

[e] https://www.mdcalc.com/framingham-risk-score-hard-coronary-heart-disease

Society of Cardiology[17], and Schweizer Arbeitsgruppe Lipide und Atherosklerose (AGLA).[18] Consequently, statins are currently seen as the first-choice drugs for LDL cholesterol reduction.[19]

3.2 Alternative technologies

Lifestyle changes are often advised before, or in conjunction with statin therapy, as these can (further) reduce the cholesterol level and CVD risk. Lifestyle changes that reduce the CVD risk include: 1) healthy and Mediterranean diet, 2) regular exercising, 3) maintaining a healthy weight, and 4) smoking reduction or smoking cessation.[15]

Since the focus of the current project is on the cost-effectiveness of statins, other cholesterol lowering drugs such as PCSK9 inhibitors and ezetimibe are outside the scope of this project.

4. Central research question

In this chapter, the central research questions on which the systematic literature search is based are detailed. The central research question is divided into two sub questions (A and B). Furthermore, the Patient group, Intervention, Comparator and Outcomes (PICO) are discussed and an overview of the PICO is provided in Table 1.

4.1 Central research question and sub questions

Central research question of systematic literature search

What are the efficacy[f], effectiveness[g], and safety[h], as well as the costs (cost-effectiveness) and budget impact of statin therapy in adults (and for different age groups) without established CVD and with low, medium, and (very) high cardiovascular risks (i.e. primary prevention) compared to placebo, or no treatment, and/or adaption of lifestyle?

Research sub question of efficacy, effectiveness, and safety systematic literature search

A. What is the efficacy, effectiveness, and safety of statin therapy for prevention of cardiovascular events and mortality in adults without established CVD and with low, medium, and (very) high cardiovascular risks (i.e. primary prevention) compared to placebo, or no treatment, and/or adaption of lifestyle?

Research sub question of costs, budget impact, and cost-effectiveness

B. What is the cost-effectiveness of statin therapy for prevention of cardiovascular events and mortality in patients without established CVD and with low, medium, and (very) high cardiovascular risk (i.e. primary prevention) compared to placebo, or no treatment, and/or adaption of lifestyle?

4.2 Patients

The population for whom statins are indicated consists of adult patients (i.e. ≥18 years) without established CVD and with low, medium and (very) high cardiovascular risk. This includes patients with and without familial hypercholesterolemia, but these subgroups are not investigated separately in this study. Cardiovascular diseases are defined in Chapter 2 of this report. The cardiovascular risk of individuals

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[f] *Efficacy is the extent to which a specific health technology produces a beneficial, reproducible result under study conditions compared with alternative technologies (i.e. internal validity).*

[g] *Effectiveness is the extent to which a specific health technology, when applied in real world circumstances in the target group, does what it is intended to do for a diagnostic or therapeutic purpose regarding the benefits compared with alternative technologies (i.e. external validity).*

[h] *Safety is a judgement of the harmful effects and their severity using the health technology. Relevant adverse events are those that result in death, are life-threatening, require inpatient hospitalisation or cause prolongation of existing hospitalisation (i.e. serious adverse events) and those that occur repetitively and the most frequent (highest rate).*

can be estimated by clinicians with scoring systems, such as the PROCAM/AGLA tool, SCORE, QRISK, the ACC/AHA pooled cohort equation, or the Framingham risk score.

4.3 Intervention

The technology of interest are the statins included on the Spezialitätenliste (i.e. the list with drugs for which reimbursement by health insurances is mandatory) in Switzerland (pitavastatin (Livazo®), atorvastatin (Sortis® and generics), rosuvastatin (Crestor® and generics), pravastatin (Selipran® and generics), simvastatin (Zocor® and generics), and fluvastatin (Lescol® and generics)).

4.4 Comparator

The technology chosen as the comparator is treatment with placebo medication, no treatment, and/or adaptation for lifestyle. Adaptation for lifestyle is defined as reduction in smoking or smoking cessation, diet adaptation, or increasing physical activity.

4.5 Outcomes

For the scoping phase, the patient-relevant outcomes of interest are presented in Table 1.

4.6 PICO-Box

Table 1 displays the PICO box used during the systematic literature search. In the table, the outcomes are split for the efficacy, effectiveness, and safety review and the cost-effectiveness review.

Table 1. PICO box

P:	Adults (i.e. all ages and according to defined age groups) without established CVD with low, medium, and (very) high cardiovascular risk (according to PROCAM/AGLA Tool or other prominent scoring systems used in European/Western health systems, e.g. SCORE, QRISK, ACC/AHA pooled cohort equation, Framingham risk score)
I:	Statins licensed in Switzerland*: atorvastatin (Sortis® and generics), fluvastatin (Lescol® and generics), pitavastatin (Livazo®), pravastatin (Selipran®, Mevalotin® and generics), rosuvastatin (Crestor® and generics), and simvastatin (Zocor® and generics)
C:	Placebo, or no treatment, and/or adaption for lifestyle (i.e. reduction in smoking or smoking cessation, diet adaptation, or increasing physical activity)
O (clinical):	1. All-cause mortality 2. CV mortality (i.e. mortality related to cardiovascular diseases as defined in the included studies). 3. Fatal and non-fatal CV events (i.e. mortality related to a specific event): a. Fatal CVD not further specified (i.e. fatal CVD in general or multiple diagnoses of fatal CVD grouped together without stratification of the data for the specific diagnosis) b. Non-fatal CVD not further specified (i.e. non-fatal CVD in general or multiple diagnoses of non-fatal CVD grouped together without stratification of the data for the specific diagnosis)

	c. Specific fatal CVD events (i.e. a fatal event of a specific diagnosis of CVD, such as fatal stroke) d. Specific non-fatal CVD events (i.e. a non-fatal event of a specific diagnosis of CVD, such as non-fatal stroke) e. Fatal CHD not further specified (i.e. fatal CHD in general or multiple diagnoses of CHD grouped together without stratification of the data for the specific diagnosis) f. Non-fatal CHD not further specified (i.e. non-fatal CHD in general or multiple diagnoses of CHD grouped together without stratification of the data for the specific diagnosis) g. Specific fatal CHD events (i.e. a fatal event of a specific diagnosis of CHD, such as fatal MI) h. Specific non-fatal CHD events (i.e. a non-fatal event of a specific diagnosis of CHD, such as non-fatal MI) 4. Combined endpoints (e.g. fatal CVD, non-fatal CVD, fatal CHD, and non-fatal CHD combined) 5. Change in blood cholesterol concentration: a. Change in total blood cholesterol concentration b. Change in LDL-C blood cholesterol concentration 6. Treatment-associated adverse events (i.e. myopathy, muscle pain, cognitive loss, incident diabetes, hepatic dysfunction, cancer, haemorrhagic stroke, liver enzyme elevations, renal dysfunction, arthritis, nausea & headache) 7. Revascularisation 8. Stop/compliance/adherence of/to statin medication 9. Quality of life 10. Life expectancy
O (health economic):	1. Health-care costs (total and incremental) within a specific time period a. Prevention related: costs of statins, control visits, and treatment of adverse events/side effects b. CVD related: costs of treatment of cardiovascular events, follow-up, medication etc. c. Future unrelated healthcare costs: costs in life years gained due to treatment 2. Non-health related care costs within a specific time period † a. Productivity (loss) costs b. Travel costs c. Caregiver costs 3. Incremental cost effectiveness ratio (ICER) and incremental and total costs, QALYs and life years within a specific time period. 4. Budget impact

* Lovastatin (Mevacor® and generics) is excluded, because it is not licensed in Switzerland; † Non-health related care costs will not be used in the model, but will be collected in the data extraction sheet to provide insight in interpreting the cost-effectiveness results of the published studies.

5. Systematic search strategy

In the scoping phase, a systematic literature search was done based on the methodology of systematic literature reviews (SRs). A SR is a method to collect, critically appraise, and summarise the best available evidence in a transparent and systematic way using generally accepted evidence-based principles.

The methodology of SRs follows international standards, such as the Cochrane Collaboration guidelines for performing SRs and PRISMA guidelines.[20 21]

The SR process consists of the following fundamental steps:

1. Formulation of the research questions
2. Comprehensive information search, including defining data sources and search strategy
3. Selection procedure, applying pre-determined clear inclusion and exclusion criteria
4. Critical appraisal (quality and risk of bias assessment)
5. Data extraction
6. Quality control

The applied systematic literature search follows the same fundamental steps described above. As the scoping phase comprised of a systematic literature search to inform the decision on whether a full HTA can be conducted, a preliminary critical appraisal and preliminary data extraction of included literature was conducted in the scoping phase. In the Outlook (Chapter 10) the SR process that may be conducted for the full HTA is further detailed.

The following describes the search strategy for the applied systematic literature search of both the efficacy, effectiveness, and safety (5.1) and the cost-effectiveness (5.2) of statins in primary prevention of CVD is described in detail.

5.1 Efficacy, effectiveness, and safety

Since a large amount of studies is published on statin therapy for the prevention of CVD events and mortality in adults without established CVD, we implemented a stepwise approach for the efficacy, effectiveness, and safety systematic literature search:

I. Search for SRs and meta-analyses.
II. Update search for RCTs based on the most relevant/recent included SRs on statin therapy for primary prevention of CVD events and mortality.
III. Search for long-term outcomes in non-randomised studies (i.e. non-randomised controlled trials, cohort studies, case-control studies).

In search step I a systematic literature search was conducted to find relevant SRs on our review objectives. Other new RCTs might have been published after the closing search date of the included SRs. Therefore, we conducted update searches in a second review step to fill the gap for recently published RCTs. RCTs do not report on effectiveness outcomes and mostly not on long-term safety outcomes; to close the gap on these specific outcomes a third search step to identify non-randomised studies was incorporated. This project also aims to closes the gap to the HTA published in 2013 in the report ‘Statine zur Primärprävention kardiovaskulärer Erkrankungen’ by the Swiss Medical Board.[22]

Search strategy

PubMed (MEDLINE) and Embase.com databases were searched for peer-reviewed scientific literature. The searches were built using the PICO-framework (see PICO box in Table 1). Since there is large overlap in studies included in other literature databases (such as Cochrane Library) for the efficacy, effectiveness, and safety search it was decided to search in these two main databases. Given the various outcomes of interest, it was decided to keep the search broad. Only search strings on 'Patient' (i.e. CVD) and 'Intervention' (i.e. primary prevention with statins) were applied in combination with a search string for study designs. The applied search filters were publication period (2013-2019 for the reviews and non-randomised studies search; and 2012-2019 for the RCT search, based on the search strategies of the included SRs of Yebyo et al. 2019[23] and Taylor et al. 2013[2]) and the language of the publications (English, Dutch, French, and German). Furthermore, animal studies, case reports, and non-pertinent publication types (e.g. editorials, letter, and comments) were excluded with additional search strings. Also, SRs were excluded with a search string in review step II and III. The details of the search strategies are included in Appendix 1. The search for SRs was conducted on 22 May 2019, and the search for RCTs and non-randomised studies was conducted on 9 July 2019. The literature database output, including all indexed fields per record (e.g. title, authors, and abstract) was exported to Endnote version X7.8. Duplicates in Endnote were automatically removed and further manually deleted.

Selection procedure

From the articles retrieved from PubMed (MEDLINE) and Embase.com the relevant references were selected by a two-step selection procedure, based on:

1. Screening of title and abstract: this step yielded the articles that were assessed in full text. The major topics of the articles were assessed on relevancy for the objectives by the title and abstract. In this step, articles that seemed to contain relevant data for the objectives were selected for full-text screening, while articles that did not seem to contain relevant data were not selected for full-text assessment. In case of doubt, the study was assessed in full text.
2. Screening of full article: the articles selected during the first phase were assessed in full text. Articles were included if the reported information was relevant and of sufficient quality, based on the inclusion and exclusion criteria (see below).

The process of selection and inclusion and exclusion of articles was registered in an Endnote library by one of the researchers. The exclusion criteria applied during the full-text screening phase are reported in PRISMA flow charts (see Section 5.4.1).

Inclusion and exclusion criteria

The inclusion and exclusion criteria applied during the selection processes of the three search steps are presented in Table 2.

Table 2. Inclusion and exclusion criteria efficacy, effectiveness and safety systematic literature search

	Inclusion	Exclusion
Period publication	• 1st step: 2013-22 May 2019 (search in English) • 2nd step: - 2018-9 July 2019 for outcomes reported in Yebyo, 2019 (search in 4 languages); - 2012-9 July 2019 for outcomes reported in Taylor, 2013 (search in 4 languages); - 2012-31 December 2017 for outcomes reported in Yebyo, 2019 not covered with their search in English (search in French, German, Dutch) • 3rd step: 2013-9 July 2019 (search in 4 languages)	
Language of publication	English, French, German, Dutch	All other languages
Country of study	Western countries*	All other countries
Study design/ type	• 1st step: SR/meta-analysis • 2nd step: RCTs • 3rd step: non-randomised studies (i.e. non-RCT, cohort study, case-control study)	• Narrative review, without transparent and systematic reporting of the study results • RCTs which were already reported in the SRs included in the scoping report • Meta-analysis including primary and secondary prevention trials • Cross-sectional studies • Case reports • Non-pertinent publication types (e.g. expert opinion, letter to editor, editorial, comment)
Study quality	• Sufficient methodological quality	• Insufficient methodological quality (both inherent methodology as well as insufficient description of inherent methodology provided)
Study population	• Patients ≥18 years who received statins for **CVD indications** • 1st step: - Reviews on CVD in general in patients ≥18 years without established CVD with low, medium, or (very) high cardiovascular risk - Reviews in populations with mixed cardiovascular risks (i.e. not aimed at a specific risk group or age group) • 2nd/3rd step: - Studies on CVD in general or a specific CVD disease (e.g. stroke) in patients ≥18 years without established CVD with low, medium, or (very) high cardiovascular risk - Studies in multiple populations or a specific risk group (e.g. diabetes mellitus)	• Patients <18 years • Patients with chronic diseases who received statins for **non-CVD indications** (e.g. Alzheimer's disease, rheumatoid arthritis, renal disease or aortic stenosis) • Subpopulations of patients (e.g. with cancer, lung diseases or hepatic diseases)
Study intervention	• Statins licensed in Switzerland† • Treatment duration ≥12 months • Length of follow-up of outcomes ≥6 months	• All other interventions • Treatment duration <12 months • Length of follow-up of outcomes <6 months

Study comparison	• Placebo • No treatment • Adaption for lifestyle (smoking reduction or stop, diet adaptation, physical activity)	• Statin vs. statin • Statin vs. other cholesterol-lowering drug (e.g. ezetimibe) • Statin vs. lipid-lowering agents (e.g. fibrates) • Different doses of statins • No comparison
Study outcomes	See PICO-Box†	• Other outcomes

* Austria, Australia, Belgium, Bulgaria, Canada, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Japan, Latvia, Lithuania, Luxembourg, Malta, the Netherlands, New Zealand, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, Switzerland, United Kingdom, United States of America (reference: https://www.un.org/development/desa/dpad/wp-content/uploads/sites/45/WESP2019_BOOK-web.pdf); † See Section 4.6 PICO-Box; Abbreviations: RCT = Randomised controlled trial, PICO = Patient population - Intervention – Comparator – Outcome

Quality control

The following quality control measures were applied during the selection process:

- The first 30% of titles and abstracts from the peer-reviewed literature were screened in duplicate by two independent researchers. The results were compared and discussed before the remaining references were assessed by one researcher. During screening there was less than 5% discrepancy between the two researchers.
- The first 10% of the full-text articles from the peer-reviewed literature were assessed for relevancy and critically appraised in duplicate by two independent researchers. The remaining full-text selection was done by one researcher in close collaboration with a second reviewer; any doubts were discussed in detail. During screening there was less than 5% discrepancy between the two researchers. In case of discrepancy or disagreements during the selection phase, a third researcher was consulted. The study was discussed until consensus was reached.

Preliminary critical appraisal

The quality of the included SRs was assessed with the AMSTAR-2 checklist.[24] Based on the key risk of bias criteria used in the GRADE (Grading of Recommendations, Assessment, Development and Evaluations) approach, a first estimation was made of the risk of bias of the studies included during the full-text selection.[25] When there are major methodological flaws, this can lead to exclusion of an article. During the full review in the HTA phase a more extensive critical appraisal will be applied. No RCTs were included in the scoping phase. For the quality assessment of the individual RCTs included in the two selected SRs of Yebyo et al. 2019[23] and Taylor et al. 2013[2], we will build on the applied assessments in these SRs (i.e. the Cochrane criteria) and we will not redo their critical appraisal with GRADE criteria. For non-randomised studies, the following limitations were initially judged:

- Failure to develop and apply appropriate eligibility criteria (inclusion of control population).
- Flawed measurement of both exposure and outcome.
- Failure to adequately control confounding.
- Incomplete or inadequately short follow-up.

5.2 Cost-effectiveness

In line with the efficacy, effectiveness, and safety review, a systematic literature search of existing SRs on the cost-effectiveness of statin therapy for primary prevention of CVD events was performed as a first step when writing the scoping protocol. However, several factors rendered all identified SRs unfit to be used as a 'base study' to be updated in our scoping phase (focus on specific countries.[26-28], focus on male populations[29], limited clinical search terms[30], or limited cost-effectiveness search terms[31]). Therefore, instead of updating an existing SR, a new systematic literature search was conducted. The methods of this systematic literature search will be discussed in this section. The cost-effectiveness review followed the same systematic literature search principles as outlined in the efficacy, effectiveness and safety protocol (5.1).

Search strategy

PubMed (MEDLINE), Embase.com, and NHS EED databases were searched for peer-reviewed scientific literature. The PICO method was used to specify the research questions. Table 1 outlines the utilised PICO for the cost-effectiveness review. Based on expert opinion, a review period of 10 years (2009-2019) was adopted. The most important reason for limiting the search to this time period, was because it was expected that recent studies included more mature data due to longer follow-up and would therefore be deemed of higher quality. However, even within this relatively recent time period, it is important to be aware of recent changes in statin prices and the influence of inflation and discount rates on the cost-effectiveness outcomes.

Publications in English, Dutch, French, and German were included.

The search terms of the efficacy, effectiveness, and safety literature search were combined with search terms to find economic evaluations. The search terms for economic evaluations were developed together with an information specialist of the Erasmus University Medical Centre and validated extensively with other search terms for economic evaluations and previous SRs of the cost-effectiveness of primary prevention of CVD events with statins.

The search for economic evaluations of primary prevention of CVD with statins was executed on 11 July 2019. The literature database output, including all indexed fields per record (e.g. title, authors, and abstract) was exported to Endnote version X7.8. Duplicates in Endnote were automatically removed and further manually deleted.

Inclusion and exclusion criteria

The list of inclusion and exclusion criteria is presented in Table 3.

Table 3. Inclusion and exclusion criteria for cost effectiveness systematic literature search

	Inclusion	Exclusion

Period publication	• 2009-2019 (10 years; based on expert opinion)	
Study language	• English • Dutch • German • French	All other languages
Country of study	• Western countries*	
Study design/type	Economic evaluations • Cost-utility • Cost-effectiveness • Cost-minimisation • Cost-benefit Resource use measurement	Costing studies
Study quality		• Small sample size (n<20; this criterion is not applicable for model based studies)
Study population	• Patients without previous cardiovascular events	• Population with previous cardiovascular events
Study intervention	Statins licensed in Switzerland: Atorvastatin (Sortis® and generics), Fluvastatin (Lescol® and generics), Pitavastatin (Livazo®), Pravastatin (Selipran® and generics), Rosuvastatin (Crestor® and generics), Simvastatin (Zocor® and generics)	
Study comparison	Placebo or no treatment and/or adaption for lifestyle (smoking reduction or stop, diet adaptation, physical activity)	Studies comparing statins with other statins or with other cholesterol lowering drugs
Study outcomes	• See outcomes in PICO table	

* Austria, Australia, Belgium, Bulgaria, Canada, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Japan, Latvia, Lithuania, Luxembourg, Malta, the Netherlands, New Zealand, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, Switzerland, United Kingdom, United States of America (reference: https://www.un.org/development/desa/dpad/wp-content/uploads/sites/45/WESP2019_BOOK-web.pdf);

Quality control

The same quality control measures were put in place in the cost-effectiveness literature search as for the effectiveness, efficacy, and safety literature search.

- The first 30% of titles and abstracts from the peer-reviewed literature were screened in duplicate by two independent researchers from iMTA. The results were compared and discussed before the remaining references were assessed by one researcher. During screening there was more than 5% discrepancy between the two researchers, therefore all titles and abstracts were screened in duplicate. Any conflicts were discussed and amended accordingly.
- The first 10% of the full-text articles from the peer-reviewed literature were assessed for relevancy and critically appraised in duplicate by two independent researchers from iMTA. Again, during screening there was more than 5% discrepancy between the two researchers, therefore all full-text articles were screened in duplicate. Any conflicts were discussed and amended accordingly.

Preliminary critical appraisal

The Consensus Health Economics Checklist (CHEC) checklist was used for the appraisal of the methodological quality of the economic evaluations.[32] The CHEC was preferred over the Drummond checklist, because of the decreasing use of the Drummond checklist in the field[33] and the experienced feasibility of completing the checklists. The CHEC is one of the two most often used checklists in recent studies, the other checklist is CHEERS.[33] The CHEC was chosen over the CHEERS checklist as the CHEC can be used to assess the methodological quality of economic evaluations, while the CHEERS checklist was primarily intended for use as a reporting checklist.

The CHEC is a 19-item checklist[32] with clear questions about the economic evaluation that will give us insight into the general quality of the study for a preliminary critical appraisal of the quality of the included studies. In addition to the CHEC, it was assessed whether statin-specific outcomes were included in the economic evaluations (e.g. treatment adherence and disutility for taking pills every day).

5.3 Other sources

Hand search of reference lists SRs

During the full-text screening phase of both the efficacy, effectiveness, and safety review and cost-effectiveness, reference lists of SRs were checked to find any other studies or SRs that were not captured with our literature search. For the efficacy, effectiveness, and safety review, three SRs were included by this process and assessed in full-text in the scoping phase. For the cost-effectiveness review, no additional studies were identified.

HTA websites

Clinical guidelines and technology assessments from the major national HTA agency websites (e.g. EUnetHTA for Europe[i], NICE[j] from the UK, IQWIG[k] from Germany, HAS[l] from France, ZiN[m] from the Netherlands, CADTH[n] from Canada and PBAC[o] from Australia) were searched for documents addressing primary prevention of CVD with statin therapy (i.e. search terms ‘statins’ in relevant language). This

[i] www.eunethta.eu/
[j] www.nice.org.uk
[k] www.iqwig.de/
[l] www.has-sante.fr/
[m] www.zorginstituutnederland.nl/
[n] www.cadth.ca/
[o] www.pbs.gov.au/

search aimed to check if the published cost-effectiveness studies and guidelines (see other HTA domains) possibly missed relevant evidence on the efficacy, safety, and economic aspects. The initial search yielded the NICE clinical guideline on cardiovascular disease[p] and three SRs on the CADTH webpage.[q,r,s] No missed studies/articles were identified in these guidelines/reviews.

Other HTA Domains

For legal aspects, a search in the Swiss legislation database[t] (in English, French, German languages; for all legal product types; for both national and international law documents; for both in force and not in force legislations) was conducted to find any relevant legislation documents associated with statin therapy, from 1848 until 2019. The terms "statins" and "cardiovascular disease", and their French and German translations were entered. In the full HTA, a search filter for legal evidence may be added to the 'Patient population' and 'Intervention' search terms that were used in the effectiveness, efficacy, and safety search and cost-effectiveness search in PubMed (MEDLINE) and/or Embase.com.

For ethical and social aspects, information was retrieved from the economic evaluations identified in the cost-effectiveness search.

For the organisational aspects, a search for studies published since 2009 listed under the MESH subheadings of "Hydroxymethylglutaryl-CoA Reductase Inhibitors/organisation and administration" or "Hydroxymethylglutaryl-CoA Reductase Inhibitors/supply and distribution" on the PubMed (MEDLINE) website was conducted.

5.4 PRISMA flow diagrams

5.4.1 *Efficacy, effectiveness, and safety systematic literature search*

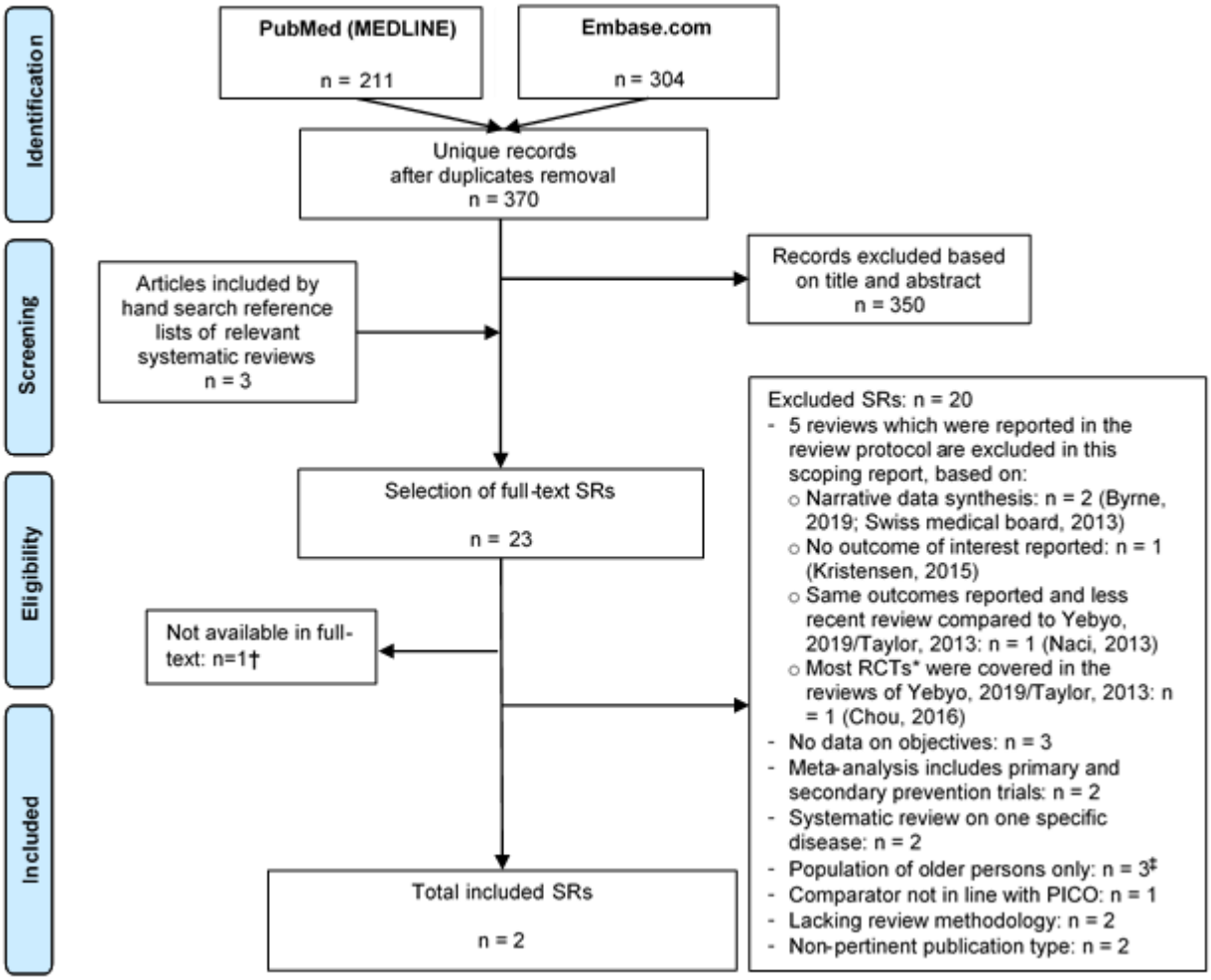
Search step I: Search for SRs

In the first search step, 370 unique records were identified in PubMed (MEDLINE) and Embase.com. The PRISMA flowchart is presented in Figure 2. Of those, 350 records were excluded based on their title and abstract. Three SRs were included as a result of the hand-search, resulting in 23 SRs which were screened in full-text. For the first search step, SRs were selected with a broad focus on CVD in

[p] https://www.nice.org.uk/guidance/cg181
[q] https://www.cadth.ca/discontinuation-statin-therapy-primary-prevention-patients-who-have-achieved-normal-lipid-levels
[r] https://www.cadth.ca/lipid-lowering-agents-stroke-prevention-review-clinical-evidence-safety-and-guidelines
[s] https://www.cadth.ca/clinical-and-economic-review-hmg-coa-reductase-inhibitors-coronary-heart-disease-0
[t] https://www.admin.ch/opc/search/search.php?lang=en

populations with mixed cardiovascular risks (i.e. not aimed at one specific CVD disease such as stroke, or a specific risk group such as patients with diabetes mellitus or a population of older persons). The reasons for exclusion were no data on objectives (n=3), meta-analysis included primary and secondary prevention (n=2), SR on one specific disease (n=2), population of older persons only (n=3), comparator not in line with our PICO (n=1), lacking review methodology (n=2), and non-pertinent publication type (n=2). One review was not available in full text (see reference below). Initially, in the scoping report protocol seven SRs were selected on statin therapy for the prevention of CVD events. After more detailed full-text assessment and between-study comparison of the quality and reported outcomes in these SRs, five SRs were eventually excluded (see description of the exclusion reasons in Figure 2) and two SRs (Yebyo et al. 2019[23] and Taylor et al. 2013[2]) were included. The results of two excluded relevant but less recent SRs, Chou et al. 2016[34] and Naci et al. 2013[35], were compared with the results of the SR of Yebyo et al. 2019[23] (see Table II and Table III in Appendix 2). We conclude that their review results and conclusions are in line with the included SR of Yebyo et al.[23] and the exclusion of the less recent SRs is justified. The SR of Yebyo et al., 2019 did not include all predefined outcomes of interest, including the relevant outcomes on blood cholesterol. Therefore, the older SR of Taylor et al. was included to complement Yebyo et al., after expert consultation with a cardiologist. The applied search strategy in these two SRs was used for an update search on recently published RCTs. This search was also used to develop a search strategy for long-term outcomes in non-randomised studies. The latter search was also built on the search conducted by the Swiss Medical Board[22]; i.e. starting the search in 2013.

Figure 2. PRISMA flowchart of the efficacy, effectiveness, and safety systematic literature search – Step I



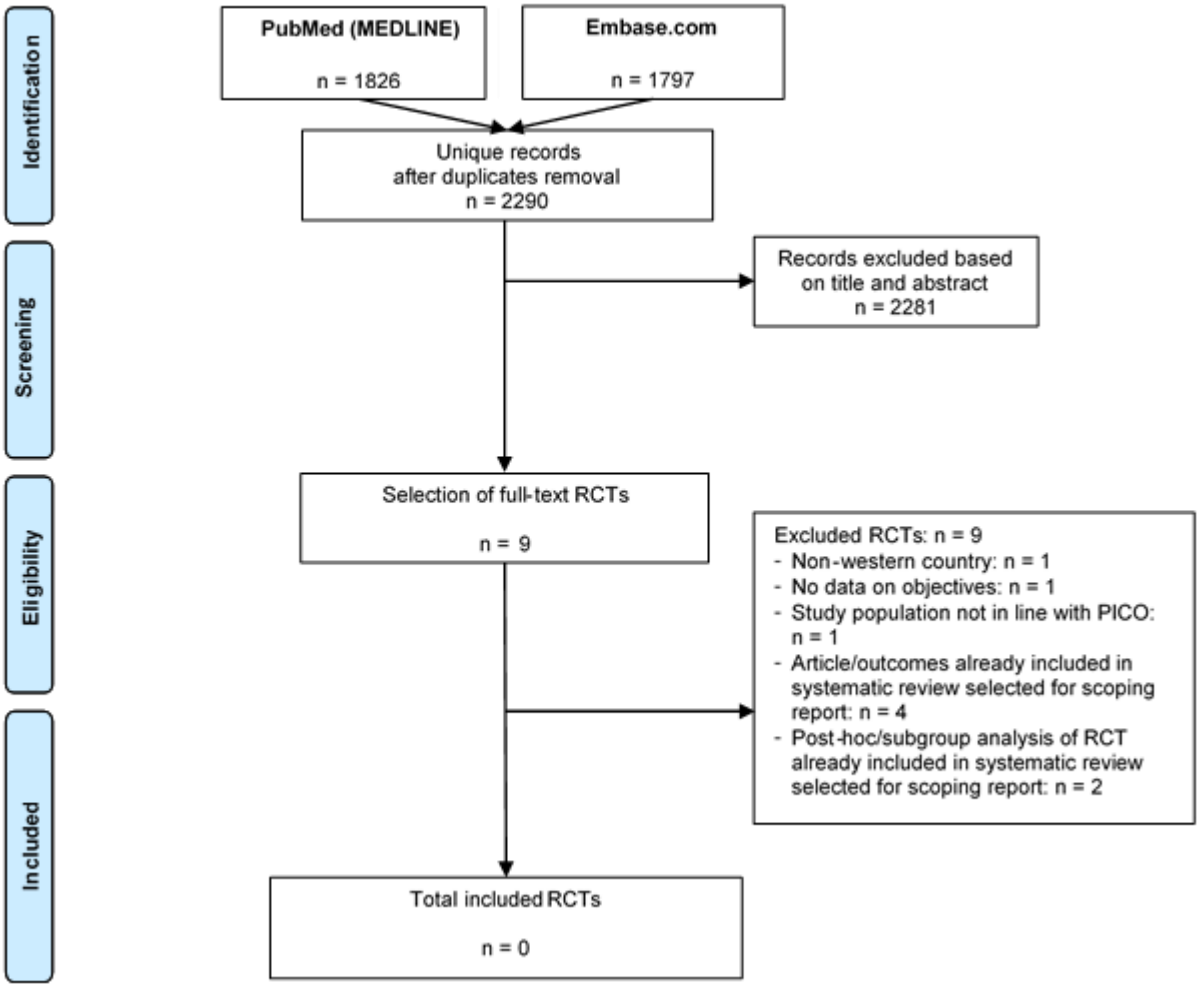
* 18 of the 19 RCTs included in the Chou, 2016 review were included in Yebyo, 2019 or Taylor, 2013; one RCT was not covered and will be excluded by our criterion for the inclusion of Western countries only: Heljić B, Velija-Asimi Z, Kulić M. The statins in prevention of coronary heart diseases in type 2 diabetics. Bosn J Basic Med Sci. 2009;9(1):71-76; † Kim BH, Cho KI, Jang JS, Park YH, Je HG. Efficacy and safety of statins for primary prevention of cardiovascular events in women and men: Systemic review and up-to-date meta-analysis. Experimental and Clinical Cardiology. 2014;20(1):1222-7. ‡ Three reviews in older populations (Ponce, 2019; Teng, 2015; Savarese, 2013) were excluded after a detailed check. There is almost complete overlap in the included RCTs in these three reviews and all RCTs, except one less recent RCT published in 2003, are covered in the included reviews of Yebyo, 2019 and Taylor, 2013.

Search step II: Update search for RCTs based on the included SRs

In total, 2,290 unique records were identified in PubMed (MEDLINE) and Embase.com for the second search step (Figure 3). Of those, 2,281 records were excluded based on their title and abstract, resulting in nine RCTs selected to be screened in full text. After applying the inclusion and exclusion criteria, all nine RCTs were excluded, because of the following reasons: non-western country (n=1), no data on objectives (n=1), study population not in line with our PICO (n=1), the RCT or outcomes reported in the RCT were already reported in the SRs included in our scoping report (i.e. in Yebyo et al. (2019)[23] or Taylor et al. (2013)[2]) (n=4), and post-hoc or subgroup analysis of an RCT already included in the two SRs included in our scoping report (n=2).

Figure 3. PRISMA flowchart of the efficacy, effectiveness and safety systematic literature search:

Search step II update RCTs

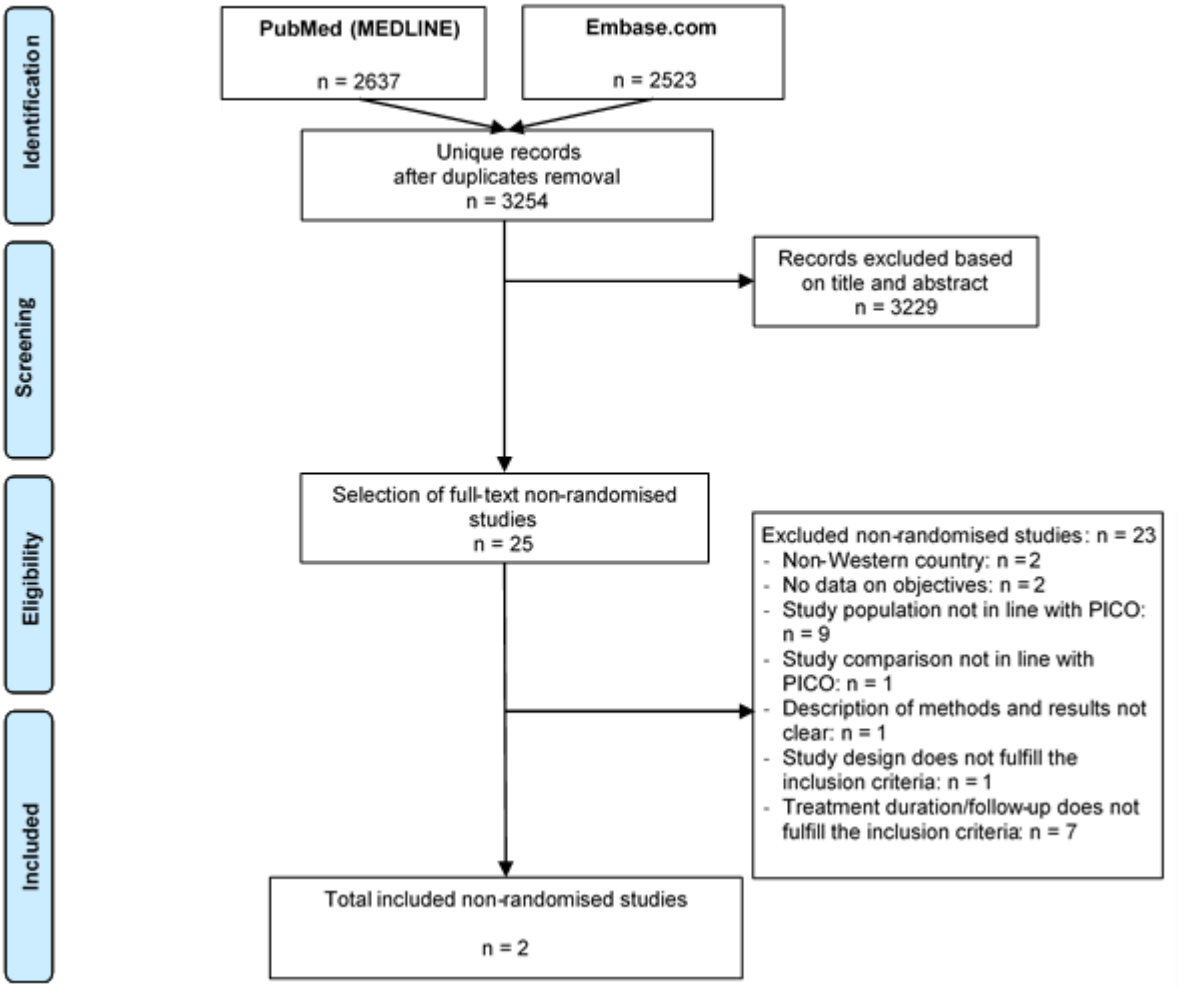


Search step III: Search for long-term outcomes in non-randomised studies

For the third search step 3,254 unique records were identified in PubMed (MEDLINE) and Embase.com (Figure 4). Of those, 3,229 records were excluded based on their title and abstract, resulting in 25 non-randomised studies selected to be screened in full-text, and two non-randomised studies were finally included. The main reasons for exclusion were study population not in line with our PICO (n=9 studies), and treatment duration or follow-up did not fulfil our inclusion criteria (n=7 studies). A complete overview of the reasons for exclusion is enclosed in the PRISMA flow chart.

Figure 4. PRISMA flowchart of the efficacy, effectiveness and safety systematic literature search:

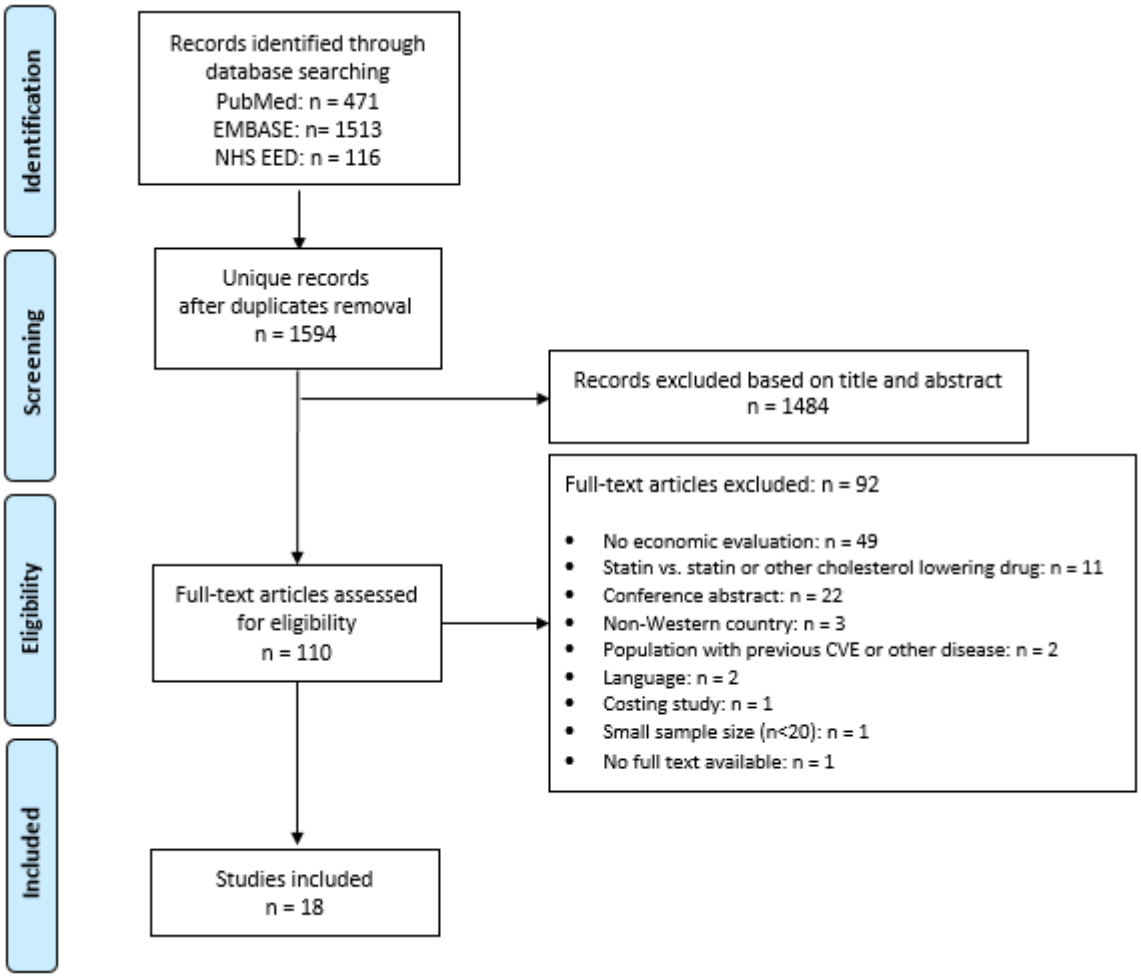
Search step III non-randomised studies



5.4.2 *Cost-effectiveness systematic literature search*

In the cost-effectiveness systematic literature search, 1,594 unique records were identified in PubMed (MEDLINE), Embase.com, and NHS EED (Figure 5). Of those, 1,484 records were excluded based on their title and abstract, resulting in 110 articles selected to be screened in full-text, and 18 economic evaluations were finally included. The reasons for exclusion are provided in the PRISMA flow chart (Figure 5).

Figure 5. PRISMA flowchart of the cost-effectiveness systematic literature search



6. Synthesis of evidence base

6.1 Evidence base pertaining to efficacy, effectiveness, and safety

Study characteristics

In the first search step, two high quality SRs were included, which used meta-analyses for the data synthesis.[2 23] The study characteristics of these SR reviews are outlined in Table 4. The most recent SR of Yebyo et al., 2019 is conducted by the University of Zürich and searched for existing SRs and individual RCTs that compared statins with a placebo or another statin, which were published until January 2018. The SR of Taylor et al., 2013 is an update review of the Cochrane Collaboration, which searched for scientific literature up to January 2012 on the effects of statins in people with no history of CVD. In Yebyo et al. 40 RCTs (of which n=33 placebo-controlled trials) and in Taylor et al. 18 RCTs comparing statins with placebo or usual care were included, which provide data on the efficacy and safety outcomes. None of the RCTs compared statin therapy with lifestyle advice only. The RCTs that

were included in these reviews are outlined in Table 5. With our update search for RCTs based on the search strategies of the SRs of Yebyo et al., 2019 and Taylor et al., 2013, no new RCTs were included on statin therapy for primary prevention of CVD events and mortality.

In our third search step to search for long-term outcomes in non-randomised studies, two studies were included that provide additional data on the effectiveness and safety outcomes.[36 37] An overview of the study characteristics is included in Table 6. Ramos et al. (2018) conducted a retrospective cohort study in Spain with data collected from the database of the Catalan primary care system.[36] In 46,864 people aged 75 years or more without clinically recognised atherosclerotic CVD and with and without type 2 diabetes they assessed whether statin treatment was associated with a reduction in atherosclerotic CVD and mortality. Izzo et al. (2013) evaluated the risk of incident diabetes in relation to statin prescription in an Italian cohort study including 4,750 hypertensive non-diabetic outpatients, of which 676 patients used statins.[37] The preliminary risk of bias was assessed for the studies: the study of Izzo et al. had a low risk of bias and Ramos et al. a moderate risk of bias. In the full HTA, the risk of bias will be assessed in more detail.

Table 4. Study characteristics of the selected SRs on primary prevention in CVD

Reference, quality review	Review objective	Data sources, search period, language, data synthesis	Exclusion criteria	Study population	Intervention	Comparator	Included studies on primary prevention
Yebyo, 2019 High quality review	To estimate the effectiveness and safety of statins as a class and of individual statins for primary prevention of CVD	- SRs and update search individual RCTs - PubMed SRs published between Jan 2013-Nov 2016; update search to Jan 2018 English Meta-analysis	- RCTs without an outcome of interest - RCTs including participants with clinically different risk profile from that of a primary prevention population (e.g. with renal insufficiency) - RCTs comparing a statin with another active drug or a statin combined with an active drug - Proportion participants with history of CVD ≥10% of total sample size - If cases were disbalanced between statin and placebo arms when the proportion of participants with history of CVD was <10% of total sample size	Persons without a history of any CVD events at baseline *Age (median; IQR):* 58.3 y; 46-76 y *Sex (% male, median; IQR):* 61%; 48-77% *Ethnicity (% Caucasian, median; IQR):* 92%; 83-95% *Risk groups (median %; IQR)* - Type 2 diabetes: 14%; 3-95% - Hypertension: 42%; 27-84% - Smoker: 28%; 17-45%	Statins (simvastatin, lovastatin, fluvastatin, atorvastatin, pravastatin, rosuvastatin)	- Placebo - Another statin	- n=40 RCTs (of which n=33 placebo-controlled trials) - n=94,283 participants Included trials available from Jan 1, 1985 to Nov 30, 2016 15 RCTs were of good, 9 of fair, 16 of poor quality (but most RCTs of poor quality were small, which contributed little to the overall effect)
Taylor, 2013 (Cochrane review) High quality review	To assess the effects, both harms and benefits, of statins in people with no history of CVD	- Built on previous SRs of Bartlett 2005, Ebrahim 1999, Ward 2007 (searches conducted in 2007 were updated) - Cochrane Central Register of Controlled Trials (2011, Issue 4) - MEDLINE OVID (1950-Dec 2011) - EMBASE OVID (1980-Jan 2012) - To Jan 2012 - All languages - Meta-analysis	- No RCT - Treatment duration <1 year - Follow-up <6 months - RCTs in which statins were used to treat or control chronic conditions - >10% had a history of CVD (including previous angina, myocardial infarction and/or stroke)	Adults ≥18 years with no restrictions on total, LDL or HDL cholesterol levels *Age* (*mean; range*): 57 y; 28-97 y *Sex (% male, mean):* 60.3% *Ethnicity (% Caucasian, mean)*: 85.9% *Risk groups* - Excluding 4 RCTs that solely recruited participants with diabetes, 1-20% of the participants had diabetes - Excluding 2 RCTs that solely recruited participants with hyper-tension, 15-67% of the participants had hypertension - Smoker: range 10-45%	Statins (pravastatin, atorvastatin, fluvastatin, lovastatin, rosuvastatin, simvastatin, cerivastatin)	- Placebo - Usual care	- n=18 RCTs - n=19 trial arms - n=56,934 participants Included trials dated from 1994 to 2008 In general, risk of bias of the included RCTs was low

Abbreviations: CHD = coronary heart disease, CVD = cardiovascular disease, HDL = high density lipoprotein, LDL = low density lipoprotein, MI = myocardial infarction, QALY = Quality-adjusted life year, RCT = randomised controlled trial, y = years. * The following concomitant interventions were accepted in the RCTs: 1. drug treatments and other interventions were accepted if they were given to both arms of the intervention groups; 2, adjuvant treatments with one additional drug were accepted where a patient developed excessively high lipids during the trial.

Table 5. RCTs included in the selected SRs

	Yebyo, 2019	Taylor, 2013
ACAPS	✓	✓
AFCAPS/TexCAPS	✓	✓
ALLHAT-LLT	✓	
ANDROMEDA	✓	
ARIES	✓	
ASCOT-LLA	✓	
ASCOT-LLA_post	✓	
ASPEN	✓	✓
ASTRONOMER	✓	
Bak, J Intern Med, 1998	✓	
Bays, Clinical Ther, 2004	✓	
BCAPS	✓	
Bone, J Clin Endocrinol Metab, 2007	✓	✓
CAIUS	✓	✓
CARDS	✓	✓
CELL A/CELL B		✓
CERDIA		✓
COMETS	✓	
CORALL	✓	
Derosa, Clinical Ther, 2003		✓
DISCOVERY	✓	
Gentile, Diabetes, Obes Metab, 2000	✓	
Heljić, Bosinian J Basic Med Sci, 2009	✓	
HOPE-3	✓	
HYRIM	✓	✓
Jacobsen, Arch Intern Med, 1995	✓	
JUPITER	✓	✓
KAPS	✓	✓
Kerzner, Am J Cardiol, 2003	✓	
Lewis, Hepatology, 2007	✓	
MEGA	✓	✓
Melani, Eur Heart J, 2003	✓	
METEOR	✓	✓
Mohler, Circulation, 2003	✓	
MRC/BHF Heart Protection		✓
Muldoon, Am J Med, 2004	✓	
PHYLLIS	✓	✓
PMSG-Diabetes	✓	
PREVEND-IT	✓	✓
RCASS	✓	
QLMG	✓	
URANUS	✓	
WOSCOPS	✓	✓

ACAPS = Asymptomatic Carotid Artery Progression Study, **AFCAPS/TexCAPS** = Air Force/Texas Coronary Atherosclerosis Prevention Study, **ALLHAT-LLT** = Antihyper-tensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial, **ANDROMEDA** = A raNdomized, Double-blind study to compare Rosuvastatin and atOrvastatin in patiEnts with type II DiAbetes, **ARIES** = African American Rosuvastatin Investigation of Efficacy and Safety, **ASCOT-LLA** = Anglo-Scandinavian Cardiac Outcomes Trial Lipid Lowering Arm, **ASPEN** = Atorvastatin for Prevention of Coronary Heart Disease Endpoints in Non-Insulin-Dependent Diabetes Mellitus, **ASTRONOMER** = Aortic Stenosis Progression Observation: Measuring Effects of Rosuvastatin, **BCAPS** = Beta-Blocker Cholesterol-Lowering Asymptomatic Plaque Study, **CAIUS** = Carotid Atherosclerosis Italian Ultrasound Study, **CARDS** = Collaborative Atorvastatin Diabetes Study, **CELL** = Cost Effectiveness of Lipid Lowering Study, **CERDIA** = abbreviation not found (RCT on the effect of long-term statin therapy on silent myocardial ischemia in type 2 diabetic patients), **COMETS** = COmparative study with rosuvastatin in subjects with METabolic Syndrome, **CORALL** = COmpare the effect of RSV with Atorvastatin on apoB/apoA1 ratio in patients with type 2 diabetes meLLitus and dyslipidaemia, **DISCOVERY** = Direct Statin Comparison of LDL-C Values: An Evaluation of Rosuva-statin Therapy Compared with Atorvastatin, **HOPE-3** = Heart Outcomes Prevention Evaluation, **HYRIM** = Hypertension High Risk Management, **JUPITER** = Justification for the Use of Statins in Prevention: an Intervention Trial Using Rosuvastatin, **KAPS** = Kuopio Atherosclerosis Prevention Study, **MEGA** = Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese, **METEOR** = Measuring Effects on Intima-Media Thickness: an Evaluation of Rosuvastatin, **MRC/BHF** = Medical Research Council/British Heart Foundation, **PHYLLIS** = Plaque Hypertension Lipid-Lowering Italian Study, **PMSG** = Pravastatin Multinational Study Group for Cardiac Risk Patients, **PREVEND-IT** = Prevention of Renal and Vascular Endstage Disease Intervention Trial, **RCASS** = Regression of Cerebral Artery Stenosis Study, **QLMG** = Quality of Life Multicenter Group, **URANUS** = Use of Rosuvastatin vs. Atorvastatin iN type 2 diabetes mellitUS, **WOSCOPS** = West of Scotland Coronary Prevention Study

Table 6. Study characteristics of the selected non-randomised studies on primary prevention in CVD

Reference, country, risk of bias	Study design, study period, follow-up period	Study population	Intervention group	Comparison group	Sample size
Ramos, 2018 Spain Moderate risk of bias	Retrospective cohort study July 2006-Dec 2015 Follow-up (median; IQR): 7.7 y (7.2-8.0)	People aged ≥75 y registered in the SIDIAP database without clinically recognised atherosclerotic CVD *Age (mean; range)* 77 y; range NR *Sex (% female)* 63%	Statin use (simvastatin, pravastatin, lovastatin, fluvastatin, rosuvastatin, atorvastatin) Persons with at least two invoices for statins during the enrolment period were included	No statin use	*75-84 y without T2DM* Statin new users: n = 4,802 Statin non-users: n = 27,114 *≥85 y without T2DM* Statin new users: n = 743 Statin non-users: n = 6,325 *75-84 y with T2DM* Statin new users: n = 1,756 Statin non-users: n = 4,885 *≥85 y with T2DM* Statin new users: n = 201 Statin non-users: n = 1,038
Izzo, 2013 Italy Low risk of bias	Cohort study (Campania Salute Network) Study period NR Follow-up (mean ± SD): 55.8 ± 42.5 mo	Non-diabetic hypertensive patients *Age (mean; range)* 58.6 ± 9.0 y; range NR *Sex (% female)* 42.3%	Statin use (simvastatin 20 or 40 mg/day, atorvastatin 10 or 20 mg/day, rosuvastatin 10 mg/day) All patients had received the medication over at least one year without any suspension for the entire year before the end of follow-up	No statin use	Statin users: n = 676 Non-users: n = 4,074

Abbreviations: CVD = cardiovascular disease; IQR = interquartile range; NR: not reported; SIDIAP = Spanish Information System for the Development of Research in Primary Care; SD = standard deviation; T2DM = type 2 diabetes mellitus

Study outcomes

In this scoping report an overview is given which outcomes of interest are reported in the selected SRs of Yebyo et al., 2019[23] and Taylor et al., 2013[2], and the two included non-randomised studies[36 37] found with our search for long-term outcomes. The results of the included studies will be extracted in the full review in the HTA report.

The SR of Yebyo et al. does not include all predefined outcomes of interest, therefore, besides the Yebyo et al. SR also the SR of Taylor et al. was included. With the inclusion of these two SRs all predefined outcomes of interest are covered (Table 7). The two non-randomised studies provide additional data on the effectiveness and safety outcomes.

Table 7. PICO outcomes reported in the SR reviews, RCTs and non-randomised studies

	Yebyo et al., 2019	Taylor et al., 2013	Update RCTs (n=0)	Non-randomised studies (n=2)
All-cause mortality	✓	✓*		✓
CVD mortality	✓			
Fatal CVD not further specified		✓		
Non-fatal CVD not further specified	✓	✓*		
Specific fatal CVD events	✓ - Fatal stroke	✓* - Fatal stroke		
Specific non-fatal CVD events	✓ - Non-fatal stroke	✓* - Non-fatal stroke		✓
Fatal CHD not further specified		✓		
Non-fatal CHD not further specified		✓		✓
Specific fatal CHD events	✓ - Fatal MI			
Specific non-fatal CHD events	✓ - Non-fatal MI - Unstable angina - Heart failure			
Combined endpoints		✓ - Combined fatal and non-fatal CVD - Combined fatal and non-fatal CHD - Combined fatal and non-fatal stroke events - Combined fatal and non-fatal CVD, CHD, and stroke events		✓ - Combined fatal and non-fatal CHD - Combined fatal and non-fatal stroke events
Change in total blood cholesterol concentration		✓		
Change in LDL-C blood cholesterol concentration		✓		
Treatment-associated adverse events	✓ - All cancers - Type 2 diabetes - Myopathy - Renal dysfunction - Hepatic dysfunction - Nausea and headache	✓ - Cancer* - Type 2 diabetes* - Haemorrhagic stroke - Liver enzyme elevations* - Renal dysfunction* - Arthritis		✓ - Cancer - Type 2 diabetes - Myopathy - Liver toxicity - Haemorrhagic stroke
Revascularisation		✓		
Stop/compliance/adherence of/to statin medication	✓ - Stop	✓ - Compliance		
HRQoL		✓		

Abbreviations: CHD = coronary heart disease, CVD = cardiovascular disease, HDL = high density lipoprotein, HRQoL = health-related quality of life, LDL = low density lipoprotein, MI = myocardial infarction. * Data on this outcome will not be extracted from the SR of Taylor et al., 2013, because more up-to-date data is reported in the SR of Yebyo et al., 2019

6.2 Evidence base pertaining to costs, budget impact, and cost-effectiveness

Study and model characteristics

The study and model characteristics are presented in Table 8 and Table 9.

The model structure of the included models was similar. All but one model (Stomberg et al.) include patients without CVD who start statin therapy and are at risk of CVD events. In addition, in some models patients are also at risk of adverse events related to statin therapy. If patients experience a CVD event, they transition to CVD events health states in which they may have a higher mortality probability and additional costs for secondary prevention therapy.

The study design of all included studies was a cost-utility analysis, expressing outcomes in quality-adjusted life years (QALY) or disability-adjusted life years (DALY). McConnachie et al. was the only cost-utility analysis study that was based on a trial-based economic evaluation; all other included studies were model-based economic evaluations.[38] The study of McConnachie et al. was performed alongside the West of Scotland Coronary Prevention Study (WOSCOPS), which included 6,595 men with hypercholesterolaemia without a history of myocardial infarction. Most model-based economic evaluations used Markov models (n=13). The other studies were microsimulation models (n=3) or simple calculation models (n=1).

The majority of studies were performed from a healthcare payer perspective (n=15); the other three studies applied a societal perspective. Eight of the studies were performed for the US, seven studies were performed for European countries, two studies for Canada, and one study for Japan. Among the seven European studies, one study was conducted in Switzerland.[39]

The patient populations of interest can be divided into four categories (Table 8 and Table 9): people from the general population without CVD (without further specifications), people from the general population without CVD but with elevated hs-CRP levels, people from the general population without CVD but with hyperlipidaemia or hypercholesterolaemia, and people with type 2 diabetes.

The types of statins used in the intervention arms differed between the studies. Some studies only considered low, moderate or high potency statins, whiles others focused on one specific statin. There seems to be an association between the patient population and the specific statin used in the intervention arm. In all five studies on patients with elevated hs-CRP, the statin used in the intervention arm was rosuvastatin because all studies were based on the JUPITER trial. Further, in two out of the three studies on patients with type 2 diabetes, atorvastatin was the statin used in the intervention arm. Finally, pravastatin was used in both studies on patients with hyperlipidaemia/or hypercholesterolaemia.

The type of comparator(s) used also differed between studies. Eight studies considered ‘no statin treatment’ as comparator. No statin treatment comparator was defined as ‘standard care’, which may or may not include lifestyle advice. A further seven studies evaluated statins versus placebo. One study compared statins with no lipid-regulating treatment (defined as no statins or any other lipid-lowering treatment), one

study compared various CVD risk thresholds for statin therapy, and one study compared over the counter (OTC) statins with prescription statins. None of the studies compared statin therapy with lifestyle advice only.

Eight of the included studies were sponsored by pharmaceutical companies producing statins.[40-47] The authors of one SR of economic evaluations of statin therapy raised the issue of sponsorship bias in economic evaluations.[31] Catala-Lopez et al. demonstrated an important sponsorship bias in the literature on the cost-effectiveness of statin therapy for prevention of CVD events. Pharmaceutical company-sponsored studies were significantly less likely to reach neutral or unfavourable conclusions than non-pharmaceutical company sponsored studies.[31] In fact, all pharmaceutical company sponsored studies concluded that the corresponding statin had a favourable ICER compared to any of the other agents (including competing statins) or placebo.[31]

Input parameters - costs

Table 10 shows which costs were considered in the included studies. In the PICO, three types of healthcare costs were distinguished: prevention-related, CVD-related, and future unrelated healthcare costs.

Regarding prevention-related costs, all studies considered the costs of statins and most studies also considered the costs of monitoring and follow-up of patients using statins for primary prevention of CVD (e.g. laboratory tests and physician visits). The costs of adverse events of statin use were only included in seven studies (Table 10). The reasons for the lack of adverse events caused by statins in the other studies were because these adverse events are considered rare, incidences were unknown, costs were expected to be low, or adverse events would disappear when patients discontinued statins. CVD-related costs of treatment of non-fatal events were included in all studies, 14 studies included long-term healthcare costs of CVD events (such as long-term follow-up or rehabilitation, and less than half of the studies (n=8) considered costs of fatal events (Table 10)). Finally, none of the studies considered the additional healthcare costs (unrelated to statin treatment or CVD) during the life years gained as a result of statin treatment provides an overview of non-health related costs included in the economic evaluations to provide insight in interpreting the cost-effectiveness results. Only three studies considered one or more types of non-healthcare related costs (Table 10). Non-healthcare related costs are not considered in the primary perspective of cost assessments in economic evaluations in Switzerland, therefore it is important to note that in the full HTA future unrelated healthcare costs will not be considered.

Input parameters – effectiveness and CVD events

Table 11 shows which effectiveness measures and utilities were included. Effectiveness of statin treatment was based on relative risks or hazard ratios of CVD events with statin therapy compared to no statin therapy or placebo derived from meta-analyses or clinical trials (sources provided in Table 8).

Adherence to statin treatment was taken into account in twelve of the 18 studies. Non-adherence was caused by adverse events leading to discontinuation of statin therapy or other non-specified reasons. The effectiveness of statins was assumed to be reduced in patients without full adherence.

Nine of the 18 studies took into account adverse events of using statins. Table 11 provides an overview of adverse events of statin treatment and CVD events that were included in the economic evaluations. Myopathy and rhabdomyolysis were the most often included adverse events. Myopathy is a disease of the muscle in which the muscle fibres do not function properly, which results in muscular weakness. Rhabdomyolysis is a condition in which damaged skeletal muscle breaks down rapidly, resulting in muscle pain, weakness, vomiting, and confusion. Some studies only included the impact of adverse events on the effect side by applying utility decrements and not on the cost side of the economic evaluation.[48 49]

The CVD events that were taken into account are provided in Table 11. All studies included the impact of statins on the occurrence of myocardial infarction and almost every study included the occurrence of ischemic strokes. In addition, the occurrences of unstable angina and coronary revascularisations were often included.

The risk of CVD events was calculated by importing the patient characteristics into the underlying risk scoring systems or based on observed event rates in trials or observational cohort studies. In half of the economic evaluations there was variation in the cardiovascular risk scoring system that was used to divide patients into different risk categories (Table 8). Only one study used the scoring system recommended by the European Society of Cardiology (ESC): Systematic Coronary Risk Evaluation (SCORE).

In the existing models patients were assigned in a risk group at baseline and only in half of the studies (n=9) the CVD events risk was updated during the time horizon of the model based on age.[41 44-46 48 50-53] The other parameters in the risk equations were assumed to be constant. In some studies, this can be explained by the fact that the time horizon was equal to the cardiovascular risk period provided by the risk scoring systems (i.e. 10-year CVD risk and 10 year model time horizon). In some studies with longer time horizons, CVD risk was updated every year to account for increasing age.[41 46 48 50-52] However, only in the study of Pandya et al. the updated cardiovascular risk was dependent on other parameters included in the risk equations besides age.[53]

Background mortality (i.e. non-CVD related causes of death) was included in the majority of studies. Six of these studies adjusted the general population mortality for deaths due to CVD. In the other studies, double counting of deaths related to CVD may have occurred.

Input parameters – utilities

The utilities without CVD events were dependent on age in seven studies (i.e. utility decreases as age increases). All studies applied disutilities for CVD events, except for Stomberg et al.[47] Stomberg et al. used a mean change in QALYs due to statin use versus no statin use or low-dose versus high-dose statin use

derived from a previous cost-effectiveness studies.[54] Most studies applied constant disutilities for CVD events, but in some studies the disutilities were reduced after the first post-event year. In six studies, adverse events were associated with disutilities. Finally, five studies applied a small disutility for taking a pill every day.

Study outcomes

The main cost-effectiveness findings of the identified studies are summarised in Table 9. Except for Onishi et al.[52], all studies concluded that statin use for primary prevention of CVD was cost-effective in some CVD risk groups. However, the cost-effectiveness results were difficult to compare between studies because they all used different risk scoring systems and/or patient populations. In general, statin treatment for primary prevention of CVD was more cost-effective among higher CVD risk groups. In addition, ICERs were lower in older age groups and in men compared to women.

All of the five studies that examined the cost-effectiveness of statin use for primary prevention of CVD in patients with normal LDL-C levels but elevated hs-CRP levels concluded that rosuvastatin was cost-effective compared to no statin treatment.[41 44-46 55] They also agreed that rosuvastatin was even more cost-effective in patients with a 10-year cardiovascular risk score (Framingham risk score) of more than 10%.

The three studies focusing on the use of statins for primary prevention of CVD in diabetes type 2-patients agreed that statins were cost-effective compared to no treatment in this patient population.[40 43 51] However, de Vries et al. noted that with real-world adherence rates, prescribing statins to diabetes type 2-patients younger than 45 years would not be cost-effective.[51]

Multiple studies concluded that treatment adherence had a major impact on cost-effectiveness results of statin use in primary prevention.[42 43 48 50 51] When real-world adherence was taken into account, the ICERs were higher than in full adherence scenarios. In addition, the costs of statins and disutility of taking a pill every day influenced the cost-effectiveness results.

Finally, the chosen time horizon of the economic evaluation had a large influence on the results. Statins were more likely to be cost-effective when longer (especially lifetime) time horizons were applied. Only two of the included studies performed a budget impact analysis. In their study, Conly et al. predicted statin expenditures in Canada for low risk patients using various definitions of low risk, these included: a) patients aged 40+ years without heart disease, diabetes or stroke who are not currently on a statin, b) men aged 50+ years and women aged 60+ years without heart disease, diabetes or stroke who are not currently on a statin, and c) men aged 50+ years and women aged 60+ years without heart disease, diabetes or stroke and either hypertensive or smoker who are not currently on a statin.[42] Additional scenarios were included considering treatment regardless of LDL-C levels, only if LDL-C > 2.5 mmol/L, and only if LDL-C > 4.5 mmol/L. Conly et al. conclude that in their most unlikely scenario (all patients aged 40+ years without heart disease, diabetes or stroke who are not currently on a statin) the eligible population would increase by 11.6

million people which results in an increased expenditure of statins of $9.17 billion annually. However, the budget impact analysis did not take into account potential savings from averted cardiovascular events, or additional costs related to life years gained due to statin use.[42]

Stomberg et al. estimated the budget impact of over-the-counter (OTC) statins under the 2013 American College of Cardiology/ American Heart Association Guidelines.[47] The analysis by Stomberg et al. includes three groups of OTC statin eligible people: a) previously untreated patients who meet statin guidelines, b) previously untreated patients who do not meet statin guidelines, and c) previous prescription statin users who take up OTC statin treatment. They estimate an increase in total costs to the health system by approximately $12.6 billion. This budget impact analysis did not account for differences in compliance rates between OTC and prescription settings.

Preliminary quality appraisal

Table 12 shows the preliminary quality appraisal of the included studies using the CHEC checklist. The studies scored well on the items regarding the study design. Although a lifetime horizon is generally preferred due to the (potentially) lifetime effect of statins on CVD morbidity and mortality, some studies applied a shorter time horizon as the CVD risk was determined for 10 years. Therefore, only studies with a time horizon shorter than 10 years were penalised on this item.

The studies were not scored for the questions with regards to included costs and outcomes (question 7-12), because this requires an in-depth analysis to determine which costs should be included and what the optimal measurement and valuation methods are. Instead we provided an overview of included costs and outcomes in Table 10 and Table 11.

The included studies also performed well regarding reporting and interpreting the results; all studies performed incremental analyses and their conclusions followed from the reported data. Further, almost all studies discounted both costs and effects and most studies subjected all important uncertain variables to sensitivity analyses. However, almost half of the studies did not discuss generalisability of the results and only one study discussed ethical and distributional issues. Furthermore, in eight studies at least some of the authors were sponsored by pharmaceutical companies.

Table 8. Study characteristics

First author	Year	Study population	Cardiovascular risk scoring system used	Cardiovascular risk and risks groups*	Mean age or age groups (in years)	Proportion male/female (%)	Intervention	Comparator	Source effectiveness of statins
General population without cardiovascular disease									
Aarnio[50]	2015	Adults without CVD	FINRISK	≥5%, ≥10%, ≥15%, ≥20%	45, 50, 55, 60, 65	Subgroup analyses	Statin treatment (distribution of different statins among new Finnish statin users)	No statin treatment	Meta-analysis Taylor et al. 2013[2]
Conly[42]	2011	Adults with low CVD events risk (approximates risk among adults without CVD and diabetes)	Any cardiovascular risk scoring system specifying risk of cardiovascular-related death or nonfatal MI	≥10%, ≥20%	59	NR	Statin treatment with low-potency statins (fluvastatin, lovastatin, pravastatin and simvastatin) or high-potency statins (atorvastatin and rosuvastatin)	No statin treatment	Meta-analysis Tonelli et al. 2011[56]
Greving[48]	2011	Adults without CVD	Any cardiovascular risk scoring system specifying risk of vascular disease (MI or stroke)	≥1%, ≥2.5%, ≥5%, ≥7.5%, ≥10%, ≥15%, ≥20%, ≥25%, ≥30%	45, 55, 65, 75	Subgroup analyses	Low dose statin treatment (costs of 40 mg generic simvastatin)	No statin treatment	Meta-analysis Brugts et al. 2009[57]
Odden[49]	2015	Adults aged 75 years or older	2013 ACC/AHA pooled cohort equations	LDL-C≥4.91 mmol/L (190 mg/dL); LDL-C≥4.14 mmol/L (160 mg/dL); LDL-C≥3.36 mmol/L (130 mg/dL); pres-	75-94	Subgroup analyses	Statin treatment with moderate-dose statins (atorvastatin, simvastatin, pravastatin, lovastatin)	No statin treatment (only secondary prevention)	Cholesterol Treatment Trialists' meta-analysis / PROSPER[58]

				ence of diabetes; or 10-year CVD risk score ≥7.5%					
Pandya[53]	2015	Adults without CVD	2013 ACC/AHA pooled cohort equations	≥30%, ≥20%, ≥15%, ≥10%, ≥7.5%, ≥5%, ≥4%, ≥3%, ≥2%, ≥1%, in addition to treating all patients and no CVD risk–based treatment strategies.	40-75	NR	Statin treatment (simvastatin, atorvastatin, rosuvastatin)	No CVD threshold: eligible for statins through other criteria (history of CVD or diabetes or elevated LDL cholesterol)	Meta-analysis Baigent et al. 2005[59]
Romanens[39]	2017	Adults without CVD	SCORE	≥2.5%, ≥5%, ≥7.5%	40-65	Switzerland: 51/49 Germany: 66/34	Statin treatment	No statin treatment	The effect of statins is assumed to be 1 mmol/l LDL reduction. The impact of a 1 mmol/l LDL reduction was taken from Cholesterol Treatment Trialists' (CTT) Collaborators
Shiffman[60]	2016	Patients without CVD, diabetes or hypercholesterolaemia but at intermediate risk of CVD	Any cardiovascular risk scoring system specifying risk of cardiovascular disease	5%-7.5%	40-75	NR	Moderate-intensity statin treatment	No statin treatment	NR
Stomberg[47]	2016	Non-institutionalised (non-inpatient) adults (includes outpatients already using statins)	Framingham risk score	<10%, 10%-20%, >20%	>20	NR	Over the counter (OTC) statin treatment	Only prescription use statins	Meta-analysis Baigent et al. 2010[59]
General population without cardiovascular disease but elevated hs-CRP levels									

Choudhry[41]	2011	Adults with elevated levels of hs-CRP and normal levels of LDL-C without CVD	Framingham risk score	≤10%, >10%	men >50; women >60	NR	Rosuvastatin (20 mg)	Placebo	JUPITER trial[61]
Ohsfeldt[44]	2010	Adults with elevated levels of hs-CRP and normal levels of LDL-C without CVD	Framingham risk score	≥10%	67	61/39	Rosuvastatin (20 mg)	Placebo	JUPITER trial[61]
Ohsfeldt[45]	2012	Adults with elevated levels of hs-CRP and normal levels of LDL-C without CVD	Framingham risk score	≥20%	66	60/40	Rosuvastatin (20 mg)	Placebo	JUPITER trial[61]
MacDonald[55]	2010	Adults with elevated levels of hs-CRP and normal levels of LDL-C without CVD	Framingham risk score	≤10%, >10%	66	NR	Rosuvastatin (20 mg)	Placebo	JUPITER trial[61]
Slejko[46]	2010	Adults with elevated levels of hs-CRP and normal levels of LDL-C without CVD	NA	hs-CRP levels <2.0 mg/L, ≥2.0 mg/L	57	NR	Simvastatin (80 mg, equipotent to rosuvastatin 20 mg)	Placebo	JUPITER trial[61]
General population without cardiovascular disease with hypercholesterolaemia									
Onishi[52]	2013	Adults with hyperlipidaemia without CVD	JALS-ECC (5-year AMI risk)	Predicted incidence of AMI for four age groups divided by sex and other cardiac risk factors	45, 55, 65, 75	Subgroup analyses	Pravastatin (10 mg)	No statin treatment	Meta-analysis Brugts et al. 2009[57]

McConnachie[38]	2014	Men with hypercholesterolaemia without a history of myocardial infarction	ASSIGN risk score	10.3%, 17.1%, 28.0%	45–54	100/0	Pravastatin (40 mg)	Placebo	WOSCOPS trial[54]
Diabetes type 2 patients									
Annemans[40]	2010	Type 2 diabetes patients without CVD	NA	NA	40-75	68/32	Atorvastatin (10 mg)	No statin treatment	CARDS trial[62]
de Vries[51]	2013	Type 2 diabetes patients without CVD	UKPDS risk engine	Risks groups varied by age group	<45; 45-55, 55-65	49/51	Statin treatment (costs of simvastatin 40 mg)	No lipid-regulating treatment (i.e. no statins or any other lipid-lowering treatment)	Meta-analysis de Vries et al. 2012[63]
Khoury[43]	2009	Type 2 diabetes patients without CVD	NA	NA	61	52/48	Atorvastatin (10 mg)	Placebo	CARDS trial[62]

*10-year CVD risk, unless stated otherwise. Abbreviations: CVD = Cardiovascular disease; LDL-C = low-density lipoprotein cholesterol; hs-CRP = high-sensitivity C-reactive protein

Table 9. Model characteristics and main cost-effectiveness findings

First author	Year	Type of model	Perspective, Country	Time horizon, in years (first is base case)	Discount rates (costs/effects)	Main cost-effectiveness findings	Budget impact analysis performed
General population without cardiovascular disease							
Aarnio[50]	2015	Markov model	Societal, Finland	10; 15	3%/3%	- Statin treatment is more cost-effective among the older patient groups; - Within age groups statin treatment was more cost-effective in higher risk groups; - Statins were less cost-effective in real world adherence scenarios compared to full adherence scenarios; - Statins were cost-effective at lower CVD risk thresholds in men compared to women; - Treatment adherence has a major impact on	No

						cost-effectiveness results of statins; - Statin treatment is more cost-effective when using a longer time horizon; - Statin treatment did not seem to be cost-effective for patients with a 10-year CVD risk of <10% even with the full adherence scenario; - Apart from treatment adherence, cost-effectiveness results were sensitive to monitoring costs in primary prevention, selected time horizon, and the cost of statins.	
Conly[42]	2011	Markov model	Healthcare payer, Canada	Lifetime	5%/5%	- High-potency statins in patients at low CVD risk seem to be cost-effective; - High-potency statins seem to be more cost-effective than low-potency statins.	Yes
Greving[48]	2011	Markov model	Healthcare payer, the Netherlands	10; 20; lifetime	4%/1,5%	- Even at current low costs for generic statin pills, statin treatment seemed not to be cost-effective for low risk primary prevention populations (10-year vascular disease risk <5%) in the Netherlands, when non-adherence was considered; - Statin treatment is more cost-effective among the older patient groups; - Within age groups statin treatment was more cost-effective in higher risk groups; - Statins were cost-effective at lower CVD risk thresholds in men compared to women; - Statin treatment is more cost-effective when using a longer time horizon; - The cost-effectiveness results were sensitive to the costs of statin treatment, statin effectiveness, non-adherence, disutility of taking medication daily, and the time horizon of the model.	No
Odden[49]	2015	Markov model	Healthcare payer, USA	10	3%/3%	- Statins are projected to be cost-effective in a population of adults aged 75 to 94 years (all 10-year CVD risk ≥7.5%); - However, even a small increased risk for functional limitation or cognitive impairment due to ageing could offset the cardiovascular benefit; - Statins were more cost-effective in patients with higher LDL-C levels; - Statins were more cost-effective in younger age	No

						groups; - Statins were more cost-effective in men than in women.	
Pandya[53]	2015	Microsimulation model	Healthcare payer, USA	Lifetime	3%/3%	- The use of statins in patients with a 10-year CVD risk threshold of ≥7.5% used in the ACC-AHA guidelines is cost-effective. - Statin treatment was more cost-effective in higher risk groups; - The cost-effectiveness was sensitive to patient preferences for taking a pill daily, changes to statin price, and the risk of statin-induced diabetes.	No
Romanens[39]	2017	Simple calculation model	Healthcare payer, Germany/Switzerland	10; 5	Not substantiated	- The SMB recommendation to use statins only above the 7.5% SCORE risk threshold cannot be derived from the Swiss Medical Board (SMB) model; - Cost-effectiveness of statins is acceptable at a SCORE risk below 5% for statin eligibility; - Statin treatment is more cost-effective when using a longer time horizon.	No
Shiffman[60]	2016	Markov model	Healthcare payer, USA	5	3%/3%	- High-potency statins was the most cost-effective strategy for patients at intermediate CVD risk compared to moderate-potency statins or do-not-treat strategy; - Moderate-potency statins for those in the top decile of LDL-P levels was cost-effective compared to do-not-treat strategy.	No
Stomberg[47]	2016	Markov model	Healthcare payer, USA	10	1%/0%	- OTC statins will be used by patients who meet statin guidelines and are not taking prescription statins, patients who do not meet statin guidelines and are not taking prescription statins, and patients who are using prescription statins and will switch to OTC statins. - With proper labelling and consumer education, it is very likely that OTC statins would be cost-effective.	Yes
General population without cardiovascular disease but elevated hs-CRP levels							
Choudhry[41]	2011	Markov model	Societal, USA	Lifetime	3%/3%	- Hs-CRP testing and rosuvastatin treatment in patients with hs-CRP≥2.0 mg/l was cost-effective'	No

						- Hs-CRP testing and rosuvastatin treatment in patients with hs-CRP≥2.0 mg/l was even more cost-effective in intermediate-risk patients (i.e. FRS≥10%); - If the price of rosuvastatin were reduced to $0.86, treatment of intermediate-risk patients with elevated hs-CRP levels may not only be cost-effective, but also cost-saving.	
Ohsfeldt[44]	2010	Microsimulation model	Healthcare payer, USA	Lifetime; 20; 10	3%/3%	- Rosuvastatin was cost-effective compared to no treatment in patients with elevated hs-CRP and FRS of ≥10%; - The cost-effectiveness improved with increasing baseline risk of the population; - The cost-effectiveness improved when using a longer time horizon.	No
Ohsfeldt[45]	2012	Microsimulation model	Healthcare payer, Sweden	Lifetime; 20; 10	3%/3%	- Rosuvastatin was cost-effective compared to no treatment in patients with elevated hs-CRP and FRS of ≥20%; - Rosuvastatin remained cost-effective in all patients with elevated hs-CRP regardless of CVD risk; - The cost-effectiveness improved (lower) when using a longer time horizon.	No
MacDonald[55]	2010	Markov model	Healthcare payer, USA	10	3%/3%	- Rosuvastatin was cost-effective compared to no treatment in patients with elevated hs-CRP and FRS of >10%; - In patients with elevated hs-CRP and FRS ≤10%, the cost-effectiveness of rosuvastatin is considered favourable only when this drug's price is less than $2.35 per tablet.	No
Slejko[46]	2010	Markov model	Societal, USA	Lifetime	3%/3%	- Rosuvastatin was cost-effective compared to no treatment in patients with elevated hs-CRP; - Cost-effectiveness varied depending on assumptions of statin cost and age but remained cost-effective.	No
General population without cardiovascular disease with hypercholesterolaemia							
Onishi[52]	2013	Markov model	Healthcare payer, Japan	Lifetime	3%/3%	- Pravastatin was not cost-effective compared with no-drug therapy. - In all subgroups, the QALY gain was lower in	No

						women and resulted in higher ICERs compared with men.	
McConnachie[38]	2014	Not Applicable (trial-based economic evaluation)	Healthcare payer, Scotland	Follow-up period: 15 years	3.5%/3.5%	- Five years' primary prevention treatment of middle-aged men with a statin significantly reduces healthcare resource utilisation, is cost saving, and increases QALYs. - Treatment of even younger, lower risk individuals than included in this study is likely to be cost-effective.	No
Diabetes type 2 patients							
Annemans[40]	2010	Markov model	Healthcare payer, Belgium	5; lifetime	3%/1.5%	- Use of atorvastatin in patients with diabetes type 2 improves CVD outcomes and is cost saving over a lifetime horizon.	No
de Vries[51]	2013	Markov model	Healthcare payer, the Netherlands	10; 5	4%/1,5%	- 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.	No
Khoury[43]	2009	Markov model	Healthcare payer, Canada	5; 10; 25	5%/ 5%	- Atorvastatin in patients with diabetes type 2 is a cost-effective strategy for the primary prevention of CVD	No

Abbreviations: CHD = Coronary heart disease; CVD = Cardiovascular disease; hs-CRP = high-sensitivity C-reactive protein; LDL-C = Low-density lipoprotein cholesterol; LDL-P = Low-density lipoprotein particle number; OTC = over the counter; FRS = Framingham risk score; QALY= quality-adjusted life year; ICER = Incremental cost-effectiveness ratio

Table 10. Outcome measures - costs

COSTS	Aarnio 2015	Annemans 2010	Choudry 2011	Conly 2011	De Vries 2013	Greving 2011	Khoury 2009	MacDonald 2010	McConnachie 2014	Odden 2015	Ohsfeldt 2010	Ohsfeldt 2012	Onishi 2013	Pandya 2015	Romanens 2017	Shiffman 2016	Slejko 2010	Stomberg 2016
Prevention-related costs																		
Statin drug costs	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Monitoring and follow-up costs	✓		✓	✓	✓	✓		✓	✓	✓	✓	✓		✓	✓		✓	✓
Adverse event-related treatment costs			✓	✓	✓									✓		✓	✓	✓
CVD event-related costs																		
Non-fatal event costs	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Fatal event/death costs	✓				✓	✓		✓			✓	✓		✓		✓		
Long-term costs after CVD event	✓	✓	✓	✓	✓	✓	✓		✓		✓	✓	✓	✓	✓	✓		✓
Future unrelated healthcare costs																		
Future unrelated healthcare costs																		
Non-health care costs																		
Travel														✓				
Time														✓				✓
Informal care																		
Productivity	✓													✓				

Abbreviations: CVD = Cardiovascular disease

Table 11. Outcome measures - effectiveness and utilities

EFFECTIVENESS AND UTILITIES	Aarnio 2015	Annemans 2010	Choudry 2011	Conly 2011	De Vries 2013	Greving 2011	Khoury 2009	MacDonald 2010	McConnachie, 2010	Odden 2015	Ohsfeldt 2010	Ohsfeldt 2012	Onishi 2013	Pandya 2015	Romanens 2017	Shiffman 2016	Slejko 2010	Stomberg 2016
Adverse events																		
Myopathy			✓		✓	✓				✓				✓			✓	
Rhabdomyolysis			✓	✓	✓	✓								✓		✓	✓	✓
Diabetes			✓	✓										✓		✓		
Myalgia (muscle pain)														✓		✓		✓
Elevated liver enzymes/liver toxicity/failure			✓	✓													✓	
Renal disease			✓															
Haemorrhagic stroke										✓								
Cardiovascular events																		
Myocardial infarction	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Angina pectoris/unstable angina		✓	✓	✓			✓	✓		✓	✓	✓		✓			✓	
Coronary revascularisation		✓	✓	✓			✓	✓	✓		✓	✓		✓	✓	✓	✓	✓
Heart failure									✓									
Cardiac arrest (resuscitated)														✓				
Ischemic stroke		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓	✓	✓	✓	✓
Pulmonary embolism											✓	✓						

Venous thromboembolism			✓								✓	✓						
Background mortality																		
Non-CVD related deaths	✓*	✓*	✓*	✓	✓	✓	✓*	✓	✓*		✓*	✓	✓	✓			✓	
Utilities																		
Baseline utility age-dependent	✓		✓			✓			✓		✓	✓				✓	✓	
CVD events disutilities	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Long-term post-CVD events disutility	✓			✓							✓	✓						
Adverse events disutilities			✓	✓						✓						✓	✓	✓
Statin use disutility (‘taking a pill every day’)			✓		✓	✓								✓		✓		
Treatment adherence																		
Treatment adherence	✓	✓		✓	✓	✓	✓				✓	✓		✓		✓	✓	✓

*Background mortality adjusted for CVD-related deaths. Abbreviations: CVD = cardiovascular disease

Table 12. Preliminary critical appraisal using the CHEC checklist[31]

			Aarnio 2015	Annemans	Choudry	Conly 2011	DeVries	Greving	Khoury 2009	MacDonald	McConnachi	Odden 2015	Ohsfeldt	Ohsfeldt	Onishi 2013	Pandya 2015	Romanens 2017	Shiffman	Slejko 2010	Stomberg
Study design	**1**	Is the study population clearly described?	✓	✓	✓	✓	✓	✓	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
	2	Are competing alternatives clearly described?	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓	✓	✓
	3	Is a well-defined research question posed in answerable form?	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
	4	Is the economic study design appropriate to the stated objective?	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓	✓	
	5	Is the chosen time horizon appropriate in order to include relevant costs and consequences?	✓		✓	✓	✓	✓		✓	✓	✓	✓	✓	✓	✓	✓		✓	✓

	6	Is the actual perspective chosen appropriate?	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Costs	**7**	Are all important and relevant costs for each alternative identified?	More information in **Table 10**																	
	8	Are all costs measured appropriately in physical units?	-																	
	9	Are costs valued appropriately?	-																	
Outcomes	**10**	Are all important and relevant outcomes for each alternative identified?	More information in **Table 11**																	
	11	Are all outcomes measured appropriately?	-																	
	12	Are outcomes valued appropriately?	-																	
Interpretation and results	**13**	Is an incremental analysis of costs and outcomes of alternatives performed?	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
	14	Are all future costs and outcomes discounted appropriately?	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓	✓	
	15	Are all important variables, whose values are uncertain, appropriately subjected to sensitivity analysis?			✓	✓	✓	✓	✓	✓			✓	✓		✓		✓	✓	✓
	16	Do the conclusions follow from the data reported?	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
	17	Does the study discuss the generalisability of the results to other settings and patient/client groups?	✓	✓	✓		✓		✓		✓	✓		✓	✓			✓	✓	
	18	Does the article indicate that there is no potential conflict of interest of study researcher(s) and funder(s)?	✓			✓	✓	✓		✓	✓	✓			✓	✓	✓			
	19	Are ethical and distributional issues discussed appropriately?					✓													

1

6.3 Evidence base pertaining to legal, social, and ethical issues

Legal issues

The legal documents from the search in the Swiss legislation database did not include any information related to statin therapy. In the full HTA phase, this search may be re-conducted with other terms and in other databases after consultation with an expert knowledgeable in Swiss law from the FOPH.

Social issues

Two social issues were raised in several economic evaluations: adherence to statin therapy and disutility for the act of taking medication daily. Treatment adherence is especially relevant in primary prevention as 'healthy' people at low risk of cardiovascular events have a low perceived risk of disease and are therefore less likely to adhere to drug therapy.[64] A substantial proportion of patients who are prescribed statins do not adhere to treatment.[65] Patients with poor adherence may experience worse outcomes and higher health care costs than patients with good adherence.[66] Therefore, it is important to consider the impact of adherence to statin therapy when estimating the cost-effectiveness of statin therapy for primary prevention of CVD events.

Treatment adherence may be influenced by the reluctance of some patients to use medication every day. Several economic evaluations therefore included a disutility for the act of taking medication daily (see Table 11). Lisa Rosenbaum explored the reasons of nonadherence to taking heart disease medication.[67] She identified several reasons for nonadherence, including aversion of taking medication in general (e.g. because it is chemical and not natural), fear of side effects, patients do not want to feel sick, and lack of observable effects of the medication.

Ethical issues

De Vries et al. raised the ethical issue of the impact of immigration status and socioeconomic status on the risk for cardiovascular events and adherence.[50] They state that one could speculate that this might affect the estimated risks of cardiovascular events and the adherence rates in opposite directions.

Several studies showed the impact of adherence on cost-effectiveness results.[40 42-48 50 51 53 60] As a consequence of poor adherence, statin therapy might be considered not cost-effective in certain subgroups of patients. This raises the ethical question whether patients with good adherence to statin therapy in these subgroups should be denied reimbursement from statin therapy because a proportion of patients is not adherent to statin therapy.

6.4 Evidence base pertaining to organisational issues

There are 332 publications listed under the MESH subheadings of "Hydroxymethylglutaryl-CoA Reductase Inhibitors/organisation and administration" or "Hydroxymethylglutaryl-CoA Reductase Inhibitors/supply and distribution" in PubMed (MEDLINE) published since 2009. The titles and abstract of the search results were scanned and several potentially relevant topics were identified: prescribing behaviour by clinicians (e.g. a risk of physicians assigning patients to higher risk classifications to maintain/still

achieve reimbursement for statin therapy), treatment adherence by patients, patent expiration and introduction of generics, co-payments, socioeconomic inequalities in statin use and adherence, population-based CVD risk screening, etc. In the full HTA phase, the search will be updated and title/abstracts and full texts of these studies will be fully screened.

7. Adaptations of PICO for the HTA

The following adaptions of the PICO described in section 4.6 are suggested for the full HTA:

- **Patient population**: as different risk scores can lead to very different treatment decisions in the same patient[68 69], one risk scoring system for the classification of patients in low, moderate, and (very) high risk groups should be chosen in the full HTA.
- **Intervention**: no changes required.
- **Comparator**: no changes required.
- **Outcomes:**

  Clinical: predefined outcome change in blood cholesterol concentration (i.e. total blood cholesterol and LDL-C blood cholesterol) is out of scope and does not need to be considered in the full HTA.

  Economic: restrict to ICERs, incremental and total costs, QALYs and life years within a specific time period, as well as budget impact.

8. HTA key questions

8.1 Key questions - efficacy, effectiveness, and safety

For the evaluation of the technology the following key questions covering the efficacy, effectiveness, and safety will be addressed (definitions provided by the FOPH):

1. What is the efficacy* of statin therapy for prevention of cardiovascular events and mortality in adults without established CVD and with low, medium, and (very) high cardiovascular risks compared to placebo, or no treatment, and/or adaption of lifestyle?
   * What is the effectiveness* of statin therapy for prevention of cardiovascular events and mortality in adults without established CVD and with low, medium, and (very) high cardiovascular risks compared to placebo, or no treatment, and/or adaption of lifestyle?

2. What is the safety of statin therapy for prevention of cardiovascular events and mortality in adults without established CVD and with low, medium, and (very) high cardiovascular risks compared to placebo, or no treatment, and/or adaption of lifestyle?

8.2 Key questions - costs, budget impact, and cost-effectiveness

For the evaluation of the technology the following key questions covering the cost-effectiveness will be addressed:

1. What types and amounts of resources are used by patients with and without statin therapy (resource-use identification)?
2. What are the Swiss unit costs of the resources identified in question 1?
3. What are the utilities associated with statin therapy (including disutility of taking a pill every day), adverse events, and CVD events?
4. What are the estimated differences in costs and outcomes of the statin therapy for primary prevention of CVD compared to no statin therapy in adults without established CVD and with low, medium, and (very) high cardiovascular risk?
5. What is the likely budget impact of restricted use compared to unrestricted use of statin therapy for primary prevention of CVD in adults without established CVD and with low, medium, and (very) high cardiovascular risk?
6. What are the uncertainties surrounding the costs and outcomes of the statin therapy for primary prevention of CVD compared to no statin therapy in adults without established CVD and with low, medium, and (very) high cardiovascular risk?

8.3 Key questions - legal, social, and ethical issues

For the evaluation of the technology the following key questions covering the legal, social and ethical issues will be addressed:

1. Are there specific legal issues associated with a potential change in reimbursement of the statin therapy?
2. What are the morally relevant consequences of a potential change in reimbursement of statin therapy?

8.4 Key questions - organisational issues

For the evaluation of the technology the following key question covering the organisational question will be addressed:

1. What organisational issues are attached to statin therapy?

9. Feasibility HTA

The aim of this scoping report is to determine the feasibility of conducting a HTA evaluation comparing the efficacy, effectiveness, safety, and cost-effectiveness of statin therapy with no statin therapy in adults without established CVD and with low, medium, and (very) high cardiovascular risks. This Chapter summarises the outcomes of the scoping phase.

The evidence base for the efficacy, effectiveness, and safety systematic literature search showed that the outcomes of interest with regard to statin therapy for primary prevention of CVD are sufficiently covered in the selected high quality SRs of Yebyo et al. (2019)[23] and Taylor et al. (2013).[2] With our update search for RCTs based on the search strategies of these two SRs, no additional RCTs meeting our predefined PICO and inclusion criteria were included. Furthermore, two included non-randomised studies[36 37] provide additional data on the effectiveness and safety outcomes.

The evidence base for the cost-effectiveness systematic literature search included eighteen economic evaluations of statin therapy for primary prevention of CVD. The identified studies do not provide sufficient evidence on the cost-effectiveness of statin therapy versus no statin therapy for primary prevention of CVD in various risk groups in the Swiss context.

The only economic evaluation performed in Switzerland was a model-based study with many assumptions that were not substantiated.[22 39] For example, , it was assumed that all CVD events occurred uniformly after 50% of the total observation time. In addition, the study did not consider adverse events of statin therapy, disutility of taking a pill every day, or treatment adherence. A more sophisticated model is necessary to reliably estimate the cost-effectiveness of statin therapy in adults without established CVD with various cardiovascular risks in the Swiss context.

Although, there were several more comprehensive and well-performed economic evaluations among the included studies, none of them used the preferred risk scoring system in Switzerland (i.e. the PROCAM/AGLA tool or SCORE). As different risk scores can lead to different treatment decisions in the same patient, it is important to base a potential disinvestment decision on a model using the one of the preferred risk scoring systems in Switzerland.[68 69] In addition, the CVD risk should be updated during the model time horizon based on changes in the patient characteristics that are used in the chosen risk scoring system. None of the identified studies included these changes in patient characteristics over time.

Considering the lack of high-quality studies in the Swiss context, lack of studies using one of the preferred risk scoring systems in Switzerland, and recent changes in prices of statins due to the introduction of generics, a de-novo model that incorporates the most recent and (where possible) Switzerland-specific effectiveness, costs, and utility evidence seems to be necessary.

Based on the findings in this scoping report, conducting a full HTA for the situation in Switzerland is feasible. The next chapter provides a detailed description of the proposed full HTA.

10. Outlook

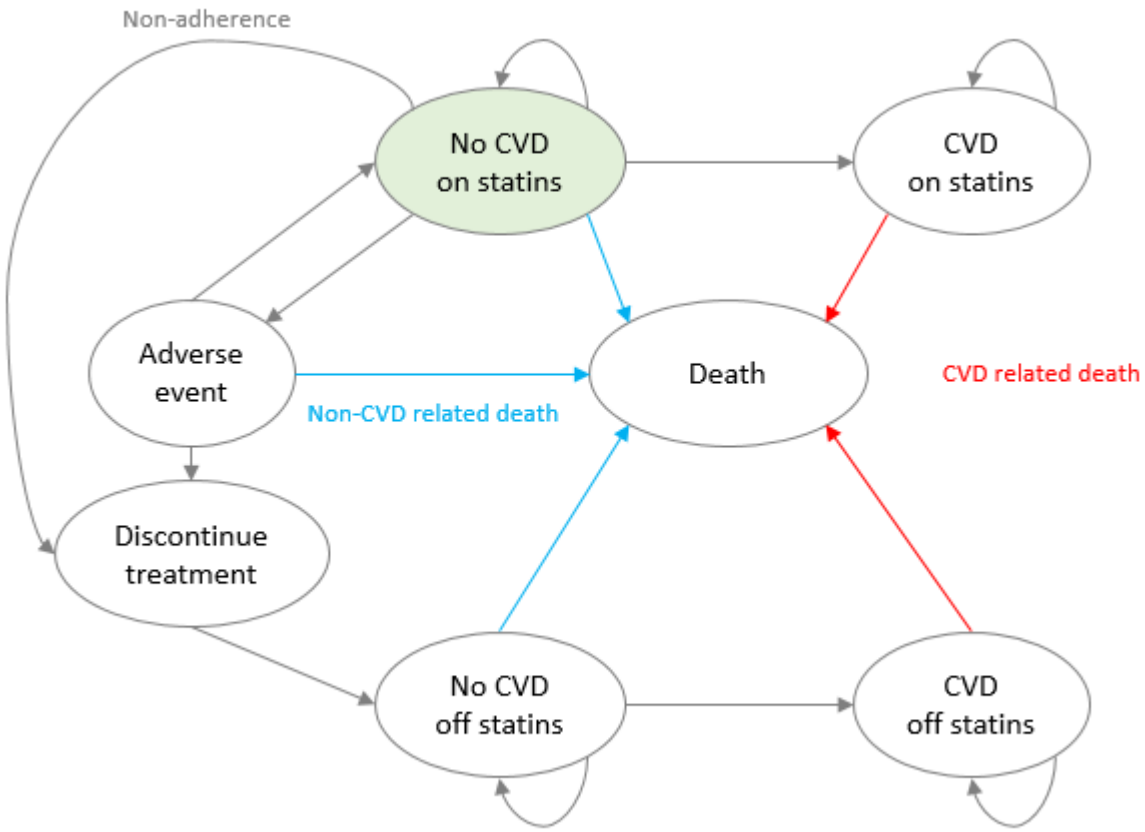
In the previous chapter, it was suggested that a full HTA specific for the Swiss context is necessary to answer the HTA key questions of the FOPH. In this chapter, the methodological steps to be taken for the full HTA will be shortly described.

For the efficacy, effectiveness, and safety review, a rigorous SR methodology, adhering to international methodological standards such as Cochrane and PRISMA, will be applied to further critically appraise, analyse, and summarise the relevant evidence on the outcomes of interest. This SR methodology will build on the methodology as applied during this scoping phase and will be outlined in a separate HTA protocol. A large amount of studies is published on statin therapy for the prevention of CVD events and mortality in adults without established CVD and good quality meta-analyses are conducted. In the HTA, a full data extraction will be done building on and synthesising the work of the two included SRs of Yebyo (2019)[23] and Taylor (2013)[2], which both cover all predefined outcomes of interest. If the data allows to, stratifications will be made for age groups as well as for risk groups and incorporated in the analyses. In addition, the prevalence of CVD cases will be updated based on the most recent data available.

For the cost-effectiveness, a de-novo economic model will be built to determine the cost-effectiveness of statin therapy with no statin therapy in adults without established CVD and with low, medium, and (very) high cardiovascular risks in Switzerland from a healthcare payer perspective. This includes the following steps: 1) developing a conceptual model; 2) collecting data for the input parameters of the model; 3) programming the economic model; and 4) analysing the results of the model.

Although the published studies do not provide sufficient information to draw firm conclusions about the cost-effectiveness of statin therapy for primary prevention of CVD in Switzerland, the model structures and findings of the published studies can be used as a starting point for the development of the conceptual model for the full HTA. For this scoping report, we developed a conceptual model that could be used as the basis for the full HTA (Figure 6). Note, however, that this is a preliminary conceptual model which may be adapted during the full HTA phase in which we plan to review clinical guidelines and consult a clinical expert to gain further understanding of the clinical pathway of primary prevention of CVD events with statins.

Figure 6. Preliminary conceptual model for the full HTA



Similar to the published models, our conceptual model will start with patients without CVD who start statin therapy and are at risk of CVD events (green box in Figure 6). The published models included in our review had different levels of granularity with regards to the types of CVD events and adverse events of statin therapy that are included. The final choice for inclusion of CVD and adverse events will depend on the results of the full systematic literature search of clinical outcomes (i.e. based on the incidence and severity of events) that will be performed in the full HTA phase and this choice will be discussed with the FOPH. The model will include all healthcare costs and disutilities associated with CVD and adverse events. The background mortality for non-CVD related deaths will be based on Swiss lifetables. To prevent double counting of deaths related to CVD, we aim to adjust the mortality risk of patients in no CVD health states for CVD related mortality by adjusting Swiss life tables for CVD related deaths. A theoretical disutility of taking a pill every day will be included either in the base case or scenario analysis.

As the main focus of this health economic analysis is the cost-effectiveness of primary prevention, we suggest applying a simplified approach and not incorporate the details of a patient's course after the first non-fatal CVD event. Instead, patients who experienced a CVD event move to one of two post-CVD event 'absorbing health states' (i.e. the states labelled as 'CVD on statins' and 'CVD off statins' in Figure 6), which will be associated with the average mortality risk, costs, and disutility seen amongst CVD patients. This approach was also used in several published studies.[42 44-46 48 50 51]

This approach prevents the model from becoming too complex (i.e. large amount of health states) and avoids additional data requirements that are beyond the scope of the clinical systematic literature search proposed in this scoping report.

Since the systematic literature search showed that treatment adherence had a major impact on the cost-effectiveness results of statin use in primary prevention, discontinuation of statin therapy due to non-adherence will be considered in the model. In addition to non-adherence, patients may also discontinue statin therapy due to adverse events. If feasible, the impact of adherence to statin therapy will be further explored in scenario analyses (i.e. full adherence scenario vs. real world adherence scenario).

The cost-effectiveness of statin therapy will be determined for several subgroups with varying CVD risk (e.g. low/intermediate/high), age, and gender. CVD risk will preferably be based the AGLA or SCORE risk scoring system reported in the newest guidelines.[70] A full data extraction of clinical outcomes will be done in the full HTA. We will describe the scoring systems which are reported in the included evidence and discuss the differences between the reported scoring systems. If the data allows to, stratifications will be made for risk groups and incorporated in the cost-effectiveness analyses. Based on predefined risk thresholds (e.g. based on the AGLA or SCORE risk scoring system presented in Table 13), patients are then categorised into low, intermediate, high, or very high CVD risk subgroups. The effect of statin therapy will be modelled by lowering the risk of CVD events in the intervention arm based on results from the efficacy, effectiveness, and safety review (e.g. using relative risks). Unless relevant data is found in the efficacy, effectiveness, and safety review, we will assume that the effectiveness of statins is equal across risk groups.

Table 13. CVD risk group classification according to AGLA and SCORE

Risk group	**Low**	**Intermediate**	**High**	**Very High**
AGLA[71]				
10-year risk of fatal CVD event or non-fatal MI	<10%	10-20%	>20%	>20%
LDL-C			>4.9 mmol/l	>4.9 mmol/l
Blood pressure			>180 mmHg	>180 mmHg
Other				- Known CAD/ Atherosclerosis - Type 2 diabetes mellitus; Type 1 diabetes mellitus with organ damage - GFR <30 ml/ min/ 1.73 m^2
SCORE[70]				
10-year risk of fatal CVD event	<1%	1-5%	≥5%	

Total cholesterol			>8.0 mmol/l	
Blood pressure			≥180 mmHg	

Abbreviations: CVD = cardiovascular disease, AGLA = Swiss Atherosclerosis Association, SCORE = Systematic COronary Risk Evaluation, MI = myocardial infarction.

The cycle length will be one year. The time horizon of the model will be at least 10 years. If possible, the time horizon will be lifetime. However, since most risk scoring systems provide 10-year CVD risks, a time horizon beyond 10 years requires updating of the CVD risk. Updating the risk scores requires data or assumptions about the development of CVD risk over time. This aspect will be further investigated in the full HTA phase.

It is expected that the efficacy, effectiveness, and safety review and a full GRADE assessment[25] of the outcomes, together with other targeted searches and clinical expert inputs, will provide sufficient evidence to populate the clinical input parameters of the de-novo economic model. For the full HTA, safety, efficacy, and effectiveness outcomes will be reported based on statins as a class.

The cost input parameters may be based on the source used in the identified Swiss study of Romanens et al.[39], in which the costs of inpatient care were estimated on data of all inpatient hospital stays in a Swiss hospital in 2008.[72] In the HTA phase we may perform an additional search for costing studies in combination with key words regarding Switzerland to find studies that provide more recent relevant costing data for Switzerland. In addition, searches on medical databases and the Swiss medical databases (e.g. Swiss DRG or Tariff Pool) may be performed in collaboration with the FOPH to determine medication use, healthcare resource use and unit costs.

The conceptual model and collected input parameters will then be translated into an economic model that can estimate the cost-effectiveness of statin therapy in adults without established CVD at various cardiovascular risks levels in Switzerland. The results of the full HTA can be used to inform the decision on reimbursement of statins in various CVD risk groups.

In addition to the cost-effectiveness model, the full HTA phase will also include the development of a budget impact model (BI model) to calculate the projected population-level five-year overall costs of statin therapy for the primary prevention of CVD events. The BI will be estimated for different reimbursement strategies (i.e. varying from reimbursing statin therapy for all risk groups to only reimbursing statin therapy for high risk groups). The BI model will be built as an extension to the cost-effectiveness model, described above. Hence, the core model characteristics for the BI model will be largely the same as those used for the cost-effectiveness model. The time horizon of the BI model will be restricted to 5 years. For the BI model, data is required about the distribution of people over the CVD risk subgroups in Switzerland. If this data is not available, assumptions will be made based on data from other comparable countries and/or expert opinion.

The two important social issues that were identified, treatment adherence and disutility of taking a statin pill every day, will be included in the de-novo economic model. The information retrieval attempts for legal, organisational, and other ethical issues did not yield sufficient evidence for the time being. In the

full HTA phase, the legal search may be re-conducted with other terms and in other databases, a systematic literature search may be performed in PubMed (MEDLINE) and Embase.com for social and ethical issues, and the systematic literature search for organisational issues performed in the scoping report will be updated and title/abstracts and full-texts of these studies will be fully screened.

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Appendix 1. Search strategy efficacy, effectiveness, and safety

Table I: Search strategy PubMed (MEDLINE) efficacy, effectiveness, and safety

	I. SRs/meta-analyses	II. RCTs	III. Non-randomised studies
CVD	("cardiovascular diseases"[Mesh] OR cardiovascular disease*[tiab] OR cardio-vascular disease*[tiab] OR CVD[tiab] OR CVDs[tiab])	("cardiovascular diseases"[Mesh] OR CVD[tiab] OR CVDs[tiab] OR stroke*[tiab] OR coronary*[tiab] OR heart*[tiab] OR cardio*[tiab] OR cardia*[tiab] OR myocardia*[tiab] OR angina*[tiab] OR hypertensi*[tiab] OR "hyperlipidemias"[Mesh] OR hyperlip*[tiab] OR triglycerid*[tiab] OR hypertriglycerid*[tiab] OR hyperlipoprotein*[tiab] OR "cholesterol"[Mesh] OR hypercholesterol*[tiab] OR cholesterol*[tiab] OR HDL[tiab] OR LDL[tiab])	
Statins	(statin[tiab] OR statins[tiab] OR "atorvastatin"[Mesh] OR atorvastatin[tiab] OR atorva[tiab] OR sortis[tiab] OR "fluvastatin"[Mesh] OR fluvastatin[tiab] OR lescol[tiab] OR "pitavastatin"[Supplementary Concept] OR pitavastatin[tiab] OR livazo[tiab] OR "pravastatin"[Mesh] OR pravastatin[tiab] OR selipran[tiab] OR mevalotin[tiab] OR "rosuvastatin calcium"[Mesh] OR rosuvastatin[tiab] OR crestor[tiab] OR "simvastatin"[Mesh] OR simvastatin[tiab] OR zocor[tiab])		
Primary prevention	("primary prevention"[Mesh] OR primary[tiab])	("primary prevention"[Mesh] OR primary prevent*[tiab] OR primordial prevent*[tiab] OR risk*[tiab])	
Study design	(((systematic*[tiab] OR comprehensive*[tiab]) AND (bibliographic*[tiab] OR literature[tiab] OR review*[tiab])) OR literature review*[tiab] OR meta-analysis[pt] OR meta-analys*[tiab] OR meta-analyz*[tiab] OR meta-analyt*[tiab] OR metaanalys*[tiab] OR metaanalyz*[tiab] OR metaanalyt*[tiab])	("randomized controlled trial"[pt] OR "controlled clinical trial"[pt] OR RCT[tiab] OR RCTs[tiab] OR random*[tiab] OR controlled[tiab] OR control-treated[tiab] OR placebo[tiab] OR cross-over studies[Mesh] OR "single-blind method"[Mesh] OR single-blind*[tiab] OR singleblind*[tiab] OR single-masked[tiab] OR double-blind method[Mesh] OR double-blind*[tiab] OR doubleblind*[tiab] OR double-masked[tiab] OR triple-blind*[tiab] OR tripleblind*[tiab] OR triple-masked[tiab])	(nonrandomized[tiab] OR non-randomized[tiab] OR nonrandomised[tiab] OR non-randomised[tiab] OR quasiexperimental[tiab] OR quasi-experimental[tiab] OR non-equivalent control*[tiab] OR non-equivalent control*[tiab] OR "cohort studies"[Mesh] OR prospective*[tiab] OR retrospective*[tiab] OR follow-up stud*[tiab] OR followup stud*[tiab] OR longitudinal stud*[tiab] OR cohort[tiab] OR "comparative effectiveness research"[Mesh] OR comparative effectiveness[tiab] OR real-world[tiab] OR real-life[tiab] OR “case-control studies”[Mesh] OR case-control[tiab] OR case-control[tiab] OR case-comparison[tiab] OR case-referent[tiab])
Limits	Publication period: 2013 - 22 May 2019	Publication period: 2012 - 9 July 2019	Publication period: 2013 - 9 July 2019
	Language: English	Language: English, French, German, Dutch	
		No animal studies: NOT (Animals[Mesh] NOT (Humans[Mesh] AND Animals[Mesh]))	
		No case reports and irrelevant publication types: NOT (case reports[pt] OR editorial[pt] OR letter[pt] OR news[pt] OR comment[pt])	
		No reviews and meta-analyses: NOT ("systematic review"[pt] OR review[ti] OR "meta-analysis"[pt] OR meta-analysis[ti])	

Table II: Search strategy Embase.com efficacy, effectiveness, and safety

	I. SRs/meta-analyses	II. RCTs	III. Non-randomised studies
CVD	('cardiovascular disease'/exp OR cardiovascular disease*:ti,ab OR cardio-vascular disease*:ti,ab OR CVD:ti,ab OR CVDs:ti,ab)	('cardiovascular disease'/exp OR CVD:ti,ab OR CVDs:ti,ab OR stroke*:ti,ab OR coronary*:ti,ab OR heart*:ti,ab OR cardio*:ti,ab OR cardia*:ti,ab OR myocardia*:ti,ab OR angina*:ti,ab OR hypertensi*:ti,ab OR 'hyperlipidemia'/exp OR hyperlip*:ti,ab OR triglycerid*:ti,ab OR hypertriglycerid*:ti,ab OR hyperlipoprotein*:ti,ab OR 'cholesterol'/exp OR hypercholesterol*:ti,ab OR cholesterol*:ti,ab OR HDL:ti,ab OR LDL:ti,ab)	
Statins	(statin:ti,ab OR statins:ti,ab OR 'atorvastatin'/exp OR atorvastatin:ti,ab OR atorva:ti,ab OR sortis:ti,ab OR 'fluindostatin'/exp OR fluvastatin:ti,ab OR lescol:ti,ab OR 'pitavastatin'/exp OR pitavastatin:ti,ab OR livazo:ti,ab OR 'pravastatin'/exp OR pravastatin:ti,ab OR selipran:ti,ab OR mevalotin:ti,ab OR 'rosuvastatin'/exp OR rosuvastatin:ti,ab OR crestor:ti,ab OR 'simvastatin'/exp OR simvastatin:ti,ab OR zocor:ti,ab)		
Primary prevention	('primary prevention'/exp OR primary:ti,ab)	('primary prevention'/exp OR "primary prevent*":ti,ab OR "primordial prevent*":ti,ab OR risk*:ti,ab)	
Study design	(((systematic*:ti,ab OR comprehensive*:ti,ab) AND (bibliographic*:ti,ab OR literature:ti,ab OR review*:ti,ab)) OR "literature review*":ti,ab OR 'meta analysis'/exp OR meta-analys*:ti,ab OR meta-analyz*:ti,ab OR meta-analyt*:ti,ab OR metaanalys*:ti,ab OR metaanalyz*:ti,ab OR metaanalyt*:ti,ab)	('randomized controlled trial'/exp OR 'controlled clinical trial'/exp OR RCT:ti,ab OR RCTs:ti,ab OR random*:ti,ab OR controlled:ti,ab OR control-treated:ti,ab OR placebo:ti,ab OR 'crossover procedure'/exp OR 'single blind procedure'/exp OR single-blind*:ti,ab OR singleblind*:ti,ab OR single-masked:ti,ab OR 'double blind procedure'/exp OR double-blind*:ti,ab OR double-blind*:ti,ab OR double-masked:ti,ab OR 'triple blind procedure'/exp OR triple-blind*:ti,ab OR tripleblind*:ti,ab OR triple-masked:ti,ab)	(nonrandomized:ti,ab OR non-randomized:ti,ab OR nonrandomised:ti,ab OR non-randomised:ti,ab OR quasiexperimental:ti,ab OR quasi-experimental:ti,ab OR "non-equivalent control*":ti,ab OR "non-equivalent control*":ti,ab OR 'cohort analysis'/exp OR prospective*:ti,ab OR retrospective*:ti,ab OR "follow-up stud*":ti,ab OR "followup stud*":ti,ab OR "longitudinal stud*":ti,ab OR cohort:ti,ab OR 'comparative effectiveness'/exp OR "comparative effectiveness":ti,ab OR real-world:ti,ab OR real-life:ti,ab OR 'case control study'/exp OR case-control:ti,ab OR casecontrol:ti,ab OR case-comparison:ti,ab OR case-referent:ti,ab)
Limits	Publication period: 2013 - 22 May 2019	Publication period: 2012 - 9 July 2019	Publication period: 2013 - 9 July 2019
	Language: English	Language: English, French, German, Dutch	
		No animal studies: NOT ([animal cell]/lim OR [animal experiment]/lim OR [animal model]/lim OR [animal tissue]/lim)	
		Relevant publication types: ([article]/lim OR [article in press]/lim OR [conference paper]/lim OR [data papers]/lim OR [erratum]/lim OR [note]/lim OR [short survey]/lim)	
		No reviews and meta-analyses: NOT ('systematic review'/exp OR review:ti OR 'meta analysis'/exp OR meta-analysis:ti)	

Appendix 2. Excluded SRs during full-text selection efficacy, effectiveness, and safety search

Table I: Excluded SRs

Reference	Reason for exclusion
Byrne P, Cullinan J, Smith A, Smith SM. Statins for the primary prevention of cardiovascular disease: an overview of systematic reviews. BMJ open. 2019;9(4):e023085.	Review which was reported in the review protocol, but is excluded in this scoping report based on narrative data synthesis
Chou R, Dana T, Blazina I, Daeges M, Jeanne TL. Statins for Prevention of Cardiovascular Disease in Adults: Evidence Report and Systematic Review for the US Preventive Services Task Force. JAMA. 2016;316(19):2008-2024.	Review which was reported in the review protocol, but is excluded in this scoping report based on most RCTs were covered in the reviews of Yebyo, 2019/Taylor, 2013 (see Table II for study characteristics and Table III for a comparison of the review results)
De Vera MA, Bhole V, Burns LC, Lacaille D. Impact of statin adherence on cardiovascular disease and mortality outcomes: a systematic review. Br J Clin Pharmacol. 2014;78(4):684-98.	No data on objectives
Fulcher J, O'Connell R, Voysey M, Emberson J, Blackwell L, Mihaylova B, et al. Efficacy and safety of LDL-lowering therapy among men and women: meta-analysis of individual data from 174,000 participants in 27 randomised trials. Lancet (London, England). 2015;385(9976):1397-405.	Comparator not in line with PICO
He Y, Li X, Gasevic D, Brunt E, McLachlan F, Millenson M, et al. Statins and Multiple Noncardiovascular Outcomes: Umbrella Review of Meta-analyses of Observational Studies and Randomized Controlled Trials. Annals of internal medicine. 2018;169(8):543-53.	No data on objectives
Kristensen ML, Christensen PM, Hallas J. The effect of statins on average survival in randomised trials, an analysis of end point postponement. BMJ open. 2015;5(9):e007118.	Review which was reported in the review protocol, but is excluded in this scoping report based on no outcome of interest reported
Kunutsor SK, Seidu S, Khunti K. Statins and primary prevention of venous thromboembolism: a systematic review and meta-analysis. The Lancet Haematology. 2017;4(2):e83-e93.	Systematic review on one specific disease
Li M, Wang X, Li X, Chen H, Hu Y, Zhang X, et al. Statins for the Primary Prevention of Coronary Heart Disease. BioMed research international. 2019;2019.	Systematic review on one specific disease
Lowe RN, Vande Griend JP, Saseen JJ. Statins for the primary prevention of cardiovascular disease in the elderly. The Consultant pharmacist : the journal of the American Society of Consultant Pharmacists. 2015;30(1):20-30.	Lacking review methodology
Martin-Ruiz E, Olry-de-Labry-Lima A, Ocaña-Riola R, Epstein D. Systematic Review of the Effect of Adherence to Statin Treatment on Critical Cardiovascular Events and Mortality in Primary Prevention. Journal of cardiovascular pharmacology and therapeutics. 2018;23(3):200-15.	No data on objectives
Naci H, Brugts JJ, Fleurence R, Tsoi B, Toor H, Ades AE. Comparative benefits of statins in the primary and secondary prevention of major coronary events and all-cause mortality: a network meta-analysis of placebo-controlled and active-comparator trials. European journal of preventive cardiology.	Review which was reported in the review protocol, but is excluded in this scoping report based on same outcomes reported and less recent review compared to Yebyo,

2013;20(4):641-57.	2019/Taylor, 2013 (see Table II for study characteristics and Table III for a comparison of the review results)
Nunes JP. Statins in primary prevention: impact on mortality. A meta-analysis study. Minerva cardioangiologica. 2017;65(5):531-8.	Lacking review methodology
Ponce OJ, Larrea-Mantilla L, Hemmingsen B, Serrano V, Rodriguez-Gutierrez R, Spencer-Bonilla G, et al. Lipid-Lowering Agents in Older Individuals: A Systematic Review and Meta-Analysis of Randomized Clinical Trials. The Journal of clinical endocrinology and metabolism. 2019;104(5):1585-94.	Population of older persons only
Preiss D, Campbell RT, Murray HM, Ford I, Packard CJ, Sattar N, et al. The effect of statin therapy on heart failure events: a collaborative meta-analysis of unpublished data from major randomized trials. European heart journal. 2015;36(24):1536-46.	Meta-analysis includes primary and secondary prevention trials
Ridker PM, Lonn E, Paynter NP, Glynn R, Yusuf S. Primary Prevention With Statin Therapy in the Elderly: New Meta-Analyses From the Contemporary JUPITER and HOPE-3 Randomized Trials. Circulation. 2017;135(20):1979-81.	Non-pertinent publication type
Savarese G, Gotto AM, Jr., Paolillo S, D'Amore C, Losco T, Musella F, et al. Benefits of statins in elderly subjects without established cardiovascular disease: a meta-analysis. Journal of the American College of Cardiology. 2013;62(22):2090-9.	Population of older persons only
Swiss Medical Board. Statine zur Primärprävention kardiovaskulärer Erkrankungen. Zollikon, 2013.	Review which was reported in the review protocol, but is excluded in this scoping report based on narrative data synthesis
Teng M, Lin L, Zhao YJ, Khoo AL, Davis BR, Yong QW, et al. Statins for Primary Prevention of Cardiovascular Disease in Elderly Patients: Systematic Review and Meta-Analysis. Drugs & aging. 2015;32(8):649-61.	Population of older persons only
Wang W, Zhang B. Statins for the prevention of stroke: a meta-analysis of randomized controlled trials. PloS one. 2014;9(3):e92388.	Meta-analysis includes primary and secondary prevention trials
Waters DD. Meta-analyses of statin trials: clear benefit for primary prevention in the elderly. Journal of the American College of Cardiology. 2013;62(22):2100-1.	Non-pertinent publication type

Table II. Study characteristics of two excluded SRs (Chou 2016 and Naci, 2013) on primary prevention in CVD

Reference	SR objective	Data sources, search period, language, data synthesis	Exclusion criteria	Study population	Intervention	Comparator	Included studies on primary prevention
Chou, 2016	To systematically review benefits and harms of statins for prevention of CVD to inform the US Preventive Services Task Force	- Cochrane Central Register of Controlled Trials (from 1991) - Cochrane Database of Systematic Reviews (from 2005) - Ovid MEDLINE the Cochrane Central Register of Controlled Trials (from 1991) - Cochrane Database of Systematic Reviews (from 2005) - Ovid MEDLINE (from 1946) to June 2016 English Meta-analysis	- Populations in age group <40 years or with a prior CVD-related event - Not original study - Outcomes not all-cause mortality, coronary heart disease, stroke-related morbidity or mortality, or harms of treatment (including muscle injury, cognitive loss, incident diabetes, and hepatic injury) - No RCT, except large cohort and case-control studies of statin use vs. nonuse for diabetes incidence - Wrong study design for key question - Studies not on statin treatment adjusted to achieve target LDL-C levels vs. fixed-dose or other treatment strategies - Studies that not evaluated effects of statin therapy intensity on benefits and harm - Comparison is not placebo or no statin (except type of studies mentioned above)	Adults 40 years and older without prior CVD events *Age* (*range of mean age)*: 51-66 y *Sex:* NR *Ethnicity*: NR *Risk group* - Presence of dyslipidemia: n=6 - Early cerebrovascular disease: n=3 - Diabetes: n=4 - Hypertension: n=2 - Mild to moderate aortic stenosis: n=1 - Microalbuminuria: n=1 - Elevated CRP level (≥20 mg/L): n=1 - At least 1 of a number of risk factors (elevated waist-to-hip ratio, dyslipidemia, dysglycemia, and mild renal dysfunction): n=1	Statins (lovastatin; atorvastatin; rosuvastatin; cerivastatin, switch to simvastatin; pravastatin; simvastatin; fluvastatin)	- Placebo - Standard lipid control with diet only	- n=19 RCTs - n=71,344 participants - Duration of follow-up ranged from 6 mo-6 y Included studies dated from 1994 to 2016 6 RCTs were of good quality, 11 of fair quality and 1 of poor quality (n=1 NR)

			- Intervention not statin therapy (except type of studies mentioned above) - Abstract only				
Naci, 2013	To evaluate the effect of statins on major coronary events and all-cause mortality across all populations, in addition to secondary and primary prevention of CVD separately. To compare the effectiveness of different statins head-to-head in these patient populations taking into account dose differences across the included set of trials	- MEDLINE - EMBASE - Cochrane Database of Systematic Reviews - Cochrane Central Register of Controlled Trials (studies published between 1 January 1985 and 1 January 2011) All languages Network meta-analysis	- No open-label and double-blind RCT - ≤50 participants per trial arm - Lasted ≤4 weeks - Did not report major coronary events or all-cause mortality - Trials conducted in patients with renal insufficiency - Combination therapy - Not used in CVD	Adults without coronary heart disease at baseline Age (range of mean age): 55.1-67.1 y *Sex:* NR *Ethnicity*: NR *Risk group* NR	Statins (atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, simvastatin)	- Placebo - Usual care - Diet - Simvastatin - Pravastatin - Atorvastatin	- n=19 studies: n=12 double blinded, n=1 not blinded, n-4 open label, n=2 NR - n=67,927 participants Included studies dated from 1989 to 2008 Overall quality of included trials was rated as moderate

Abbreviations: CVD = cardiovascular disease, LDL-C = low density lipoprotein cholesterol, mo = months; NR = not reported, RCT = randomised controlled trial US = United States, y = years

Table III. Comparison of the results and conclusions of two excluded SRs (Chou 2016 and Naci, 2013) with the two included SRs (Yebyo, 2019 and Taylor, 2013) to check if the review outcomes are in line

	Yebyo, 2019	**Taylor, 2013**	**Chou, 2016**	**Naci, 2013**
SR results	Statins as a class showed statistically significant risk reductions on (RR; 95% CI): - **Non-fatal MI** (0.62; 0.53-0.72) - **CVD mortality** (0.80; 0.71-	Reduced by statins (RR; 95% CI): - **All-cause mortality** (OR 0.86; 0.79-0.94) - **Combined fatal and non-fatal**	Statin therapy was associated with decreased risk of (RR; 95% CI): - **All-cause mortality** (0.86; 0.80-0.93]	In primary prevention, statins significantly reduced (OR; 95% CI): - **Deaths** (0.91; 0.83-0.99) - **Major coronary events** (0.69; 0.61-0.79)

	0.91) - **All-cause mortality** (0.89; 0.85-0.93) - **Non-fatal stroke** (0.83; 0.75-0.92) - **Unstable angina** (0.75; 0.63-0.91) - **Composite major cardiovascular events** (0.74; 0.67-0.81) Statins increased statistically significantly relative risks of (RR; 95% CI): - **Myopathy** (1.08; 1.01-1.15) - **Renal dysfunction** (1.12; 1.00-1.26) - **Hepatic dysfunction** (1.16; 1.02-1.31)	**CVD** (0.75; 0.70-0.81) - **Combined fatal and non-fatal CHD events** (0.73; 0.67-0.80) - **Combined fatal and non-fatal stroke** (0.78; 0.68-0.89) - **Revascularisation rates** (0.62; 0.54-0.72) - Total cholesterol and LDL cholesterol were reduced in all trials, but there was evidence of heterogeneity of effects - There was no evidence of any **serious harm** caused by statin prescription	- **Cardiovascular mortality** (0.69; 0.54-0.88) - **Stroke** (0.71; 0.62-0.82) - **Myocardial infarction** (0.64; 0.57-0.71) - **Composite cardiovascular outcomes** (0.70; 0.63-0.78) Statins were not associated with increased risk of (RR; 95% CI): - **Serious adverse events** (0.99; 0.94-1.04) - **Myalgias** (0.96; 0.79-1.16) - **Liver-related harms** (1.10; 0.90-1.35) - **Diabetes** (1.05; 0.91-1.20)	
SR conclusion	All statins showed statistically significant risk reduction of CVD and all-cause mortality in primary prevention populations while increasing the risk for some harm risks	Reductions in all-cause mortality, major vascular events and revascularisations were found with no excess of adverse events among people without evidence of CVD treated with statins	In adults at increased CVD risk but without prior CVD events, statin therapy was associated with reduced risk of all-cause and cardiovascular mortality and CVD events	Statins significantly reduce the incidence of all-cause mortality and major coronary events as compared to control

Table IV: Excluded RCTs

Reference	Reason for exclusion
Choi SH, Lim S, Hong ES, Seo JA, Park CY, Noh JH, et al. PROPIT: A PROspective comparative clinical study evaluating the efficacy and safety of PITavastatin in patients with metabolic syndrome. Clinical endocrinology. 2015;82(5):670-7.	Non-western country
Ford I, Murray H, McCowan C, Packard CJ. Long-Term Safety and Efficacy of Lowering Low-Density Lipoprotein Cholesterol With Statin Therapy: 20-Year Follow-Up of West of Scotland Coronary Prevention Study. Circulation. 2016;133(11):1073-80.	Article/outcomes already included in SR selected for scoping report
Gupta A, Thompson D, Whitehouse A, Collier T, Dahlof B, Poulter N, et al. Adverse events associated with unblinded, but not with blinded, statin therapy in the Anglo-Scandinavian Cardiac Outcomes Trial—Lipid-Lowering Arm (ASCOT-LLA): a randomised double-blind placebo-controlled trial and its non-randomised non-blind extension phase. The Lancet. 2017;389(10088):2473-81.	Article/outcomes already included in SR selected for scoping report
Han BH, Sutin D, Williamson JD, Davis BR, Piller LB, Pervin H, et al. Effect of Statin Treatment vs Usual Care on Primary Cardiovascular Prevention Among Older Adults: The ALLHAT-LLT Randomized Clinical Trial. JAMA internal medicine. 2017;177(7):955-65.	Article/outcomes already included in SR selected for scoping report
Huesch MD. Serious Adverse Events Among SPRINT Trial Participants Taking Statins at Baseline. Drugs in R&D. 2017;17(4):623-9.	No data on objectives
Lloyd SM, Stott DJ, de Craen AJ, Kearney PM, Sattar N, Perry I, et al. Long-term effects of statin treatment in elderly people: extended follow-up of the PROspective Study of Pravastatin in the Elderly at Risk (PROSPER). PloS one. 2013;8(9):e72642.	Study population not in line with PICO
Nishimura R, Sone H, Nakagami T, Tajima N. Importance of high-density lipoprotein cholesterol control during pravastatin treatment in hypercholesterolemic Japanese with type 2 diabetes mellitus: a post hoc analysis of MEGA study. Diabetes research and clinical practice. 2013;100(2):e31-3.	Post-hoc/subgroup analysis of RCT already included in SR selected for scoping report
Ridker PM, Mora S, Rose L. Percent reduction in LDL cholesterol following high-intensity statin therapy: potential implications for guidelines and for the prescription of emerging lipid-lowering agents. European heart journal. 2016;37(17):1373-9.	Post-hoc/subgroup analysis of RCT already included in SR selected for scoping report
Yusuf S, Bosch J, Dagenais G, Zhu J, Xavier D, Liu L, et al. Cholesterol Lowering in Intermediate-Risk Persons without Cardiovascular Disease. The New England journal of medicine. 2016;374(21):2021-31.	Article/outcomes already included in SR selected for scoping report

Table V: Excluded non-randomised studies

Reference	Reason for exclusion
Alperovitch A, Kurth T, Bertrand M, Ancelin ML, Helmer C, Debette S, et al. Primary prevention with lipid lowering drugs and long term risk of vascular events in older people: population based cohort study. BMJ (Clinical research ed). 2015;350:h2335.	Treatment duration/follow-up does not fulfill the inclusion criteria
Asberg S, Eriksson M. Statin therapy and the risk of intracerebral haemorrhage: a nationwide observational study. International journal of stroke : official journal of the International Stroke Society. 2015;10 Suppl A100:46-9.	Treatment duration/follow-up does not fulfill the inclusion criteria
Ashrani AA, Barsoum MK, Crusan DJ, Petterson TM, Bailey	Study comparison not in line with PICO

KR, Heit JA. Is lipid lowering therapy an independent risk factor for venous thromboembolism? A population-based case-control study. Thrombosis research. 2015;135(6):1110-6.	
Baptista LC, Verissimo MT, Martins RA. Statin combined with exercise training is more effective to improve functional status in dyslipidemic older adults. Scandinavian journal of medicine & science in sports. 2018;28(12):2659-67.	Study population not in line with PICO
Besseling J, Hovingh GK, Huijgen R, Kastelein JJP, Hutten BA. Statins in Familial Hypercholesterolemia: Consequences for Coronary Artery Disease and All-Cause Mortality. Journal of the American College of Cardiology. 2016;68(3):252-60.	Treatment duration/follow-up does not fulfill the inclusion criteria
Bezin J, Moore N, Mansiaux Y, Steg PG, Pariente A. Real-Life Benefits of Statins for Cardiovascular Prevention in Elderly Subjects: A Population-Based Cohort Study. The American journal of medicine. 2019;132(6):740-8.e7.	Treatment duration/follow-up does not fulfill the inclusion criteria
Ble A, Hughes PM, Delgado J, Masoli JA, Bowman K, Zirk-Sadowski J, et al. Safety and Effectiveness of Statins for Prevention of Recurrent Myocardial Infarction in 12 156 Typical Older Patients: A Quasi-Experimental Study. The journals of gerontology Series A, Biological sciences and medical sciences. 2017;72(2):243-50.	Study population not in line with PICO
Daida H, Teramoto T, Kitagawa Y, Matsushita Y, Sugihara M. The relationship between low-density lipoprotein cholesterol levels and the incidence of cardiovascular disease in high-risk patients treated with pravastatin: main results of the APPROACH-J study. International heart journal. 2014;55(1):39-47.	Study design does not fulfill the inclusion criteria
Garcia-Gil M, Comas-Cufi M, Blanch J, Marti R, Ponjoan A, Alves-Cabratosa L, et al. Effectiveness of Statins as Primary Prevention in People With Different Cardiovascular Risk: A Population-Based Cohort Study. Clinical pharmacology and therapeutics. 2018;104(4):719-32.	Treatment duration/follow-up does not fulfill the inclusion criteria
Hayashi T, Kubota K, Kawashima S, Sone H, Watanabe H, Ohrui T, et al. Efficacy of HMG-CoA reductase inhibitors in the prevention of cerebrovascular attack in 1016 patients older than 75 years among 4014 type 2 diabetic individuals. International journal of cardiology. 2014;177(3):860-6.	Description of methods and results not clear
Hung RK, Al-Mallah MH, Qadi MA, Shaya GE, Blumenthal RS, Nasir K, et al. Cardiorespiratory fitness attenuates risk for major adverse cardiac events in hyperlipidemic men and women independent of statin therapy: The Henry Ford ExercIse Testing Project. American heart journal. 2015;170(2):390-9.	No data on objectives
Jones M, Tett S, Peeters GMEE, Mishra GD, Dobson A. New-Onset Diabetes After Statin Exposure in Elderly Women: The Australian Longitudinal Study on Women's Health. Drugs and Aging. 2017;34(3):203-9.	Study population not in line with PICO
Kim K, Lee CJ, Shim CY, Kim JS, Kim BK, Park S, et al. Statin and clinical outcomes of primary prevention in individuals aged >75years: The SCOPE-75 study. Atherosclerosis. 2019;284:31-6.	Non-Western country
Kokkinos P, Faselis C, Myers J, Kokkinos JP, Doumas M, Pittaras A, et al. Statin therapy, fitness, and mortality risk in middle-aged hypertensive male veterans. American journal of hypertension. 2014;27(3):422-30.	Study population not in line with PICO
Kokkinos PF, Faselis C, Myers J, Panagiotakos D, Doumas M. Interactive effects of fitness and statin treatment on mortality risk in veterans with dyslipidaemia: a cohort study. Lancet (London, England). 2013;381(9864):394-9.	Study population not in line with PICO
Lassila R, Jula A, Pitkaniemi J, Haukka J. The association of statin use with reduced incidence of venous thromboembolism: a population-based cohort study. BMJ open.	Treatment duration/follow-up does not fulfill the inclusion criteria

2014;4(11):e005862.	
Mitchell JD, Fergestrom N, Gage BF, Paisley R, Moon P, Novak E, et al. Impact of Statins on Cardiovascular Outcomes Following Coronary Artery Calcium Scoring. Journal of the American College of Cardiology. 2018;72(25):3233-42.	Treatment duration/follow-up does not fulfill the inclusion criteria
Orkaby AR, Gaziano JM, Djousse L, Driver JA. Statins for Primary Prevention of Cardiovascular Events and Mortality in Older Men. Journal of the American Geriatrics Society. 2017;65(11):2362-8.	Study population not in line with PICO
Porath A, Arbelle JE, Fund N, Cohen A, Mosseri M. Statin Therapy: Diabetes Mellitus Risk and Cardiovascular Benefit in Primary Prevention. The Israel Medical Association journal : IMAJ. 2018;20(8):480-5.	Non-Western country
Ribe AR, Vestergaard CH, Vestergaard M, Fenger-Gron M, Pedersen HS, Lietzen LW, et al. Statins and Risk of Intracerebral Haemorrhage in a Stroke-Free Population: A Nationwide Danish Propensity Score Matched Cohort Study. EClinicalMedicine. 2019;8:78-84.	Study population not in line with PICO
Tagalakis V, Eberg M, Kahn S, Azoulay L. Use of statins and reduced risk of recurrence of VTE in an older population. A population-based cohort study. Thrombosis and haemostasis. 2016;115(6):1220-8.	Study population not in line with PICO
Veronese G, Montomoli J, Schmidt M, Horvath-Puho E, Sorensen HT. Statin Use and Risk of Atrial Fibrillation or Flutter: A Population-based Case-Control Study. American journal of therapeutics. 2015;22(3):186-94.	No data on objectives
Yokomichi H, Nagai A, Hirata M, Tamakoshi A, Kiyohara Y, Kamatani Y, et al. Statin use and all-cause and cancer mortality: BioBank Japan cohort. Journal of epidemiology. 2017;27(3):S84-S91.	Study population not in line with PICO

Appendix 3. Search strategy cost-effectiveness

Table I: Search strategy PubMed (MEDLINE) cost-effectiveness

PubMed	Economic evaluations
CVD	(''cardiovascular diseases''[Mesh] OR CVD[tiab] OR CVDs[tiab] OR stroke*[tiab] OR coronary*[tiab] OR heart*[tiab] OR cardio*[tiab] OR cardia*[tiab] OR myocardia*[tiab] OR angina*[tiab] OR hypertensi*[tiab] OR ''hyperlipidemias''[Mesh] OR hyperlip*[tiab] OR triglycerid*[tiab] OR hypertriglycerid*[tiab] OR hyperlipoprotein*[tiab] OR ''cholesterol''[Mesh] OR hypercholesterol*[tiab] OR cholesterol*[tiab] OR HDL[tiab] OR LDL[tiab])
Statins	(statin[tiab] OR statins[tiab] OR ''atorvastatin''[Mesh] OR atorvastatin[tiab] OR atorva[tiab] OR sortis[tiab] OR ''fluvastatin''[Mesh] OR fluvastatin[tiab] OR lescol[tiab] OR ''pitavastatin''[Supplementary Concept] OR pitavastatin[tiab] OR livazo[tiab] OR ''pravastatin''[Mesh] OR pravastatin[tiab] OR selipran[tiab] OR mevalotin[tiab] OR ''rosuvastatin calcium''[Mesh] OR rosuvastatin[tiab] OR crestor[tiab] OR ''simvastatin''[Mesh] OR simvastatin[tiab] OR zocor[tiab])
Cost-effectiveness	(“Technology Assessment, Biomedical”[Mesh] OR “Cost-Benefit Analysis”[Mesh] OR “Quality-Adjusted Life Years”[Mesh] OR “technology assessment” [tiab] OR “economic evaluation” [tiab] OR “economic value” [tiab] OR “cost-benefit” [tiab] OR “cost-effective” [tiab] OR “cost-effectiveness” [tiab] OR “cost-utility” [tiab] OR “cost-consequence” [tiab] OR “quality-adjusted life year” [tiab] OR “QALY” [tiab])

Table II: Search strategy Embase.com cost-effectiveness review

EMBASE	Economic evaluations
CVD	('cardiovascular disease'/exp OR CVD:ti,ab OR CVDs:ti,ab OR stroke*:ti,ab OR coronary*:ti,ab OR heart*:ti,ab OR cardio*:ti,ab OR cardia*:ti,ab OR myocardia*:ti,ab OR angina*:ti,ab OR hypertensi*:ti,ab OR 'hyperlipidemia'/exp OR hyperlip*:ti,ab OR triglycerid*:ti,ab OR hypertriglycerid*:ti,ab OR hyperlipoprotein*:ti,ab OR 'cholesterol'/exp OR hypercholesterol*:ti,ab OR cholesterol*:ti,ab OR HDL:ti,ab OR LDL:ti,ab)
Statins	(statin:ti,ab OR statins:ti,ab OR 'atorvastatin'/exp OR atorvastatin:ti,ab OR atorva:ti,ab OR sortis:ti,ab OR 'fluindostatin'/exp OR fluvastatin:ti,ab OR lescol:ti,ab OR 'pitavastatin'/exp OR pitavastatin:ti,ab OR livazo:ti,ab OR 'pravastatin'/exp OR pravastatin:ti,ab OR selipran:ti,ab OR mevalotin:ti,ab OR 'rosuvastatin'/exp OR rosuvastatin:ti,ab OR crestor:ti,ab OR 'simvastatin'/exp OR simvastatin:ti,ab OR zocor:ti,ab)
Cost-effectiveness	('biomedical technology assessment'/exp OR 'economic evaluation'/exp OR 'quality adjusted life year'/exp OR 'program cost effectiveness'/de OR ((technology NEAR/3 assessment*) OR (economic* NEAR/3 (evaluat* OR value)) OR ((cost OR costs) NEAR/3 (benefit* OR effectiv* OR efficien* OR efficac* OR minim* OR utilit* OR consequen*)) OR (qualit* NEAR/3 adjust* NEAR/3 (life-year* OR lifeyear*)) OR qaly*):ab,ti)

Table III: Search strategy NHS EED cost-effectiveness

NHS EED	Economic evaluations
CVD	cardiovascular
Statins	statin

Appendix 4. Excluded economic evaluations during full-text selection cost-effectiveness

Reference
Exclusion criteria: Population with previous CVE or other diseases
Erickson KF, Japa S, Owens DK, Chertow GM, Garber AM, Goldhaber-Fiebert JD. Cost-effectiveness of statins for primary cardiovascular prevention in chronic kidney disease. J Am Coll Cardiol. 2013 Mar-26;61(12):1250-8. PubMed PMID: 23500327. Heart Protection Study Collaborative Group. Statin cost-effectiveness in the United States for people at different vascular risk levels. Circ Cardiovasc Qual Outcomes. 2009 Mar;2(2):65-72. PubMed PMID: 20031817.
Exclusion criteria: Statin vs. statin or other cholesterol lowering drugs
Fragoulakis V, Kourlaba G, Maniadakis N. Economic evaluation of statins in high-risk patients treated for primary and secondary prevention of cardiovascular disease in Greece. Clinicoecon Outcomes Res. 2012 2012;4:135-43. PubMed PMID: 22719213. 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 Sep-19;136(12):1087-98. PubMed PMID: 28687710. Kok L, Engelfriet P, Jacobs-van der Bruggen MA, Hoogenveen RT, Boshuizen HC, Verschuren MW. The cost-effectiveness of implementing a new guideline for cardiovascular risk management in primary care in the Netherlands. Eur J Cardiovasc Prev Rehabil. 2009 Jun;16(3):371-6. PubMed PMID: 19305351. Lazar LD, Pletcher MJ, Coxson PG, Bibbins-Domingo K, Goldman L. Cost-effectiveness of statin therapy for primary prevention in a low-cost statin era. Circulation. 2012 Jul-12;124(2):146-53. PubMed PMID: 21709063. Marcus FI, Baumgarten AJ, Fritz WL, Nolan Jr PE. Alternate-day dosing with statins. American Journal of Medicine. 2013 2013;126(2):99-104. PubMed PMID: rayyan-3654912. Martikainen JA, Soini E, Paulsson T. Cost-effectiveness of single agent, uptitration and switching statin treatment strategies for lipid lowering in SwedenCost-effectiveness of statin treatment strategies. Current Medical Research and Opinion. 2010 2010;26(2):389-96. PubMed PMID: rayyan-3655301. Nakao S, Kawabe H, Takuma H, Shiragami M. Acceptable incremental cost effectiveness ratio for use of new drugs, cases in statin therapies. Yakugaku Zasshi. 2010 2010;130(10):1347-52. PubMed PMID: rayyan-3655230. Neyt M, De Laet C, Brab V, t 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 Cardiol. 2009 Feb;64(1):1-10. PubMed PMID: 19317290. Pletcher MJ, Lazar L, Bibbins-Domingo K, Moran A, Rodondi N, Coxson P, et al. Comparing impact and cost-effectiveness of primary prevention strategies for lipid-lowering. Ann Intern Med. 2009 Feb-17;150(4):243-54. PubMed PMID: 19221376. van Kempen BJ, Ferket BS, Hofman A, Spronk S, Steyerberg E, Hunink MG. Do different methods of modeling statin treatment effectiveness influence the optimal decision? Med Decis Making. 2012 May-Jun;32(3):507-16. PubMed PMID: 22472915. Wilson C, Huang CC, Shara N, Howard BV, Fleg JL, Henderson JA, et al. Cost-effectiveness of lower targets for blood pressure and low-density lipoprotein cholesterol in diabetes: The Stop Atherosclerosis in Native Diabetics Study (SANDS). Journal of Clinical Lipidology. 2010 2010;4(3):165-72. PubMed PMID: rayyan-3655282.

Exclusion criteria: no economic evaluation

Cochrane criticised for conclusions on statins. Australian Journal of Pharmacy. 2011 2011;92(1090):24. PubMed PMID: rayyan-3655170.

Abramson JD, Rosenberg HG, Jewell N, Wright JM. Should people at low risk of cardiovascular disease take a statin? BMJ (Online). 2013 2013;347(7930). PubMed PMID: rayyan-3654843.

Blaha MJ, Nasir K, Blumenthal RS. Statin therapy for healthy men identified as "increased risk". JAMA - Journal of the American Medical Association. 2012 2012;307(14):1489-90. PubMed PMID: rayyan-3655016.

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