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Health Technology Assessment (HTA)

Scoping Report

Title	The treatment of primary hypercholesterolaemia and mixed/combined hyperlipidaemia with ezetimibe-containing medicines
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Technology	Ezetimibe-containing medicines
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Executive Summary:

Dyslipidaemia is a key risk factor in the development of atherosclerosis and cardiovascular diseases (CVDs). Ezetimibe, a cholesterol absorption inhibitor, is currently used to treat dyslipidaemias and CVDs in Switzerland; however, there is ongoing debate regarding its effectiveness. In light of this, the Swiss Federal Office of Public Health is re-evaluating the indications for the reimbursement of ezetimibe. This report aims to determine the feasibility of conducting a health technology assessment (HTA) of ezetimibe based on the clinical, economic, legal, social, ethical and organisation data identified during the scoping phase.

The objective of the HTA is to evaluate the safety, efficacy, effectiveness, cost-effectiveness and budgetary impact of ezetimibe (by itself or in combination with statins or fenofibrate) compared to placebo, statins or fenofibrate monotherapies in patients who have (i) primary hypercholesterolaemia (familial and non-familial) with or without pre-existing atherosclerotic cardiovascular disease (ASCVD) or (ii) mixed/combined hyperlipidaemia with or without pre-existing ASCVD. A systematic literature search was conducted in eight biomedical, ethical and legal and economic databases, in addition to clinical trial registries and specialty websites. From the 14,003 search results, 76 randomised controlled trials were suitable for inclusion. Twelve existing economic evaluations broadly matching the PICO criteria were identified; however, their applicability to the Swiss context was limited. Six social-, one ethical- and one organisational-related studies were identified from the systematic search. No legal studies were identified.

There is sufficient evidence to undertake a full HTA on the efficacy, safety and the economic impact of ezetimibe. However, there is insufficient evidence from pragmatic randomised controlled trials (RCTs) to evaluate effectiveness; the HTA will need to include non-randomised study designs for the evaluation of effectiveness. For the economic evaluation, the construction of a de novo economic model is likely to be the most appropriate approach. Projected budgetary impacts will be additionally considered. Limited evidence was identified for legal, social, ethical and organisational issues. An

additional non-systematic search will be conducted at the HTA phase to ensure all appropriate literature has been identified.

Zusammenfassung:

Die Dyslipidämie ist ein Hauptrisikofaktor bei der Entstehung von Atherosklerose und Herz-Kreislauf-Erkrankungen (cardiovascular diseases, CVD). Ezetimib, ein Cholesterol-Absorptionshemmer, wird in der Schweiz gegenwärtig angewendet, um Dyslipidämien und CVD zu behandeln. Dessen Wirksamkeit wird allerdings diskutiert. Vor diesem Hintergrund bewertet das Bundesamt für Gesundheit die Indikationen im Hinblick auf die Rückerstattung für Ezetimib neu. Mit diesem Bericht soll die Machbarkeit eines Health Technology Assessments (HTA) für Ezetimib auf der Grundlage von während der Scoping-Phase gesammelten klinischen, wirtschaftlichen, rechtlichen, sozialen, ethischen und organisatorischen Daten bestimmt werden.

Das Ziel des HTAs ist die Prüfung der Sicherheit, der Wirksamkeit unter idealen Bedingungen (efficacy) und unter Alltagsbedingungen (effectiveness), der Wirtschaftlichkeit und der Budgetauswirkungen von Ezetimib (als Monotherapie oder als Kombinationstherapie mit Statinen oder Fenofibrat) im Vergleich zu Placebo oder Monotherapien mit Statinen oder Fenofibrat bei Patienten (i) mit primärer (familiärer oder nicht-familiärer) Hypercholesterinämie mit oder ohne vorbestehender atherosklerotischer Herz-Kreislauf-Erkrankung (ASCVD) oder (ii) mit gemischter/kombinierter Hyperlipidämie mit oder ohne vorbestehender ASCVD. Es wurde eine systematische Literaturrecherche in acht biomedizinischen, ethischen, rechtlichen und wirtschaftlichen Datenbanken sowie in Registern klinischer Versuche und auf spezialisierten Plattformen durchgeführt. Aus den 14’003 Suchergebnissen erfüllten 76 randomisierte kontrollierte Studien (RCT) die Einschlusskriterien. Es wurden zwölf bestehende wirtschaftliche Evaluationen identifiziert, welche die PICO-Kriterien weitgehend erfüllen; allerdings lassen sie sich nur begrenzt auf den Schweizer Kontext übertragen. Die systematische Suche ergab sechs Studien zu sozialen und je eine zu ethischen bzw. organisatorischen Aspekten. Es wurde keine rechtliche Studie identifiziert.

Die gesammelten Daten reichten aus, um ein vollständiges HTA zur Wirksamkeit unter idealen Bedingungen, Sicherheit und Wirtschaftlichkeit von Ezetimib vorzunehmen. Es liegen jedoch nicht genügend Daten aus pragmatischen RCTs vor, um die Wirksamkeit unter Alltagsbedingungen zu bewerten. Für die Bewertung der Wirksamkeit unter Alltagsbedingungen im Rahmen des HTAs werden deshalb nicht-randomisierte Studien eingeschlossen werden müssen. Zur ökonomischen Evaluation ist die Entwicklung eines wirtschaftlichen *de novo* Modells wahrscheinlich der am besten

geeignete Ansatz. Projizierte Budgetauswirkungen werden zusätzlich berücksichtigt.
Für die rechtlichen, sozialen, ethischen und organisatorischen Aspekte konnten nur begrenzt Daten zusammengetragen werden. Im Rahmen der HTA-Phase wird eine zusätzliche nicht-systematische Suche durchgeführt werden, um sicherzustellen, dass alle relevanten Literaturbeiträge gefunden wurden.

Synthèse :

La dyslipidémie est un facteur de risque clé dans le développement de l'athérosclérose et de maladies cardio-vasculaires (CVD). L'ézétimibe, un inhibiteur de l'absorption du cholestérol, est actuellement utilisé en Suisse pour traiter les dyslipidémies et les CVD; cependant, son efficacité fait l'objet d'un débat permanent. Dans cette optique, l'Office fédéral de la santé publique réévalue les indications pour le remboursement de l'ézétimibe en Suisse. Le présent rapport vise à déterminer la faisabilité d'une évaluation des technologies de la santé (ETS) de l'ézétimibe qui se base sur des données cliniques, économiques, légales, sociales, éthiques et organisationnelles identifiées durant la phase de scoping.

L'objectif de cette ETS consiste à évaluer la sécurité, l'efficacité en conditions idéales et réelles, le rapport coût-efficacité et l'impact budgétaire de l'ézétimibe (seul ou combiné à des statines ou du fénofibrate) comparé aux traitements placebo ou à la monothérapie avec des statines ou du fénofibrate chez les patients qui ont (i) une hypercholestérolémie primaire (familiale et non-familiale) avec ou sans maladie cardiovasculaire athérosclérotique pré-existante (ASCVD) ou (ii) hyperlipidémie mixte/combinée avec ou sans ASCVD pré-existante. On a procédé à une étude systématique de la littérature dans huit bases de données biomédicales, éthiques, juridiques et économiques, en plus des registres d'essais cliniques et des sites internet spécialisés. Sur les 14 003 résultats de recherche, 76 essais randomisés contrôlés ont pu être inclus. Douze évaluations économiques existantes correspondant largement aux critères PICO ont été mises en évidence; toutefois, leur applicabilité au contexte suisse était limitée. Six études portant sur le social, une étude portant sur l'éthique et une portant sur l'organisationnel ont pu être dégagées par la recherche systématique. Aucune étude juridique n'a été identifiée.

Il existe suffisamment de preuves pour procéder à une ETS complète de l'efficacité en conditions idéales, de la sécurité et de l'impact économique de l'ézétimibe. Cependant, les preuves tirées des essais randomisés contrôlés (ERC) pragmatiques sont insuffisantes pour évaluer l'efficacité en conditions réelles; l'ETS devra inclure des modèles d'études non randomisés pour y parvenir. Pour l'évaluation économique, la construction d'un modèle économique *de novo* est probablement

l’approche la plus appropriée. Les impacts budgétaires estimés seront également pris en compte. Peu de données ont pu être prises en compte pour les questions juridiques, sociales, éthiques et organisationnelles. Une recherche supplémentaire non systématique sera effectuée lors de la phase d’ETS afin de s’assurer que toute la littérature appropriée a été identifiée.

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Abbreviations and acronyms

ACS	Acute coronary syndrome
AGLA	Arbeitsgruppe Lipide und Atherosklerose
APOB	Gene coding for the apolipoprotein B protein
Apo-B	Apolipoprotein B
ASCVD	Atherosclerotic cardiovascular disease
cIMT	Carotid intima-media thickness
CEA	Cost-effectiveness analysis
CHD	Coronary heart disease
CUA	Cost-utility analysis
CVD	Cardiovascular disease
EAS	European Atherosclerosis Society
EMA	European Medicines Agency
ESC	European Society of Cardiology
FOPH	Federal Office of Public Health
HDL	High density lipoprotein
HMG-CoA	3-Hydroxy 3-methylglutaryl-coenzyme A
HTA	Health technology assessment
IVUS	Intravascular ultrasound
LDL-c	Low density lipoprotein-cholesterol
LDLR	Gene coding for low-density lipoprotein receptors
NA	Not applicable
NR	Not reported
PCSK9	Proprotein convertase subtilisin/kexin type 9 protein
PICO (EO)	Population, intervention, comparator, outcome, (economic outcomes)
PPAR	Peroxisome proliferator-activated receptors

Figures

Tables

Objective of the HTA scoping report

The objective of the scoping report is to conduct a systematic literature search and provide an overview of the available evidence base addressing the main health technology assessment (HTA) domains, i.e. clinical effectiveness/safety, costs/budget impact/cost-effectiveness, legal/social/ethical and organisational issues. In the report the analytical methods that are to be used when an HTA is pursued are described. Based on quantity and quality of the extracted evidence the feasibility of pursuing an HTA is judged. Analysis of the individual study outcomes is not the objective of the scoping report.

1 Policy question and context

Lipid-lowering therapies with ezetimibe, ezetimibe in fixed combination with simvastatin, and ezetimibe in free combination with any statin licensed in Switzerland are covered by the mandatory health insurance without any limitation for the treatment of patients with primary hypercholesterolaemia and mixed/combined hyperlipidaemia.

Different HTA reports, systematic reviews and several recent clinical studies found no evidence for the clinical effectiveness of the different ezetimibe therapies in regard to vascular and all-cause mortality in the above-mentioned dyslipidaemia diseases. Therefore, the applicant (santésuisse) suggests limiting the use of the ezetimibe mono- and combination therapies to patients who i) under statin monotherapies do not reach proposed LDL targets ii) cannot tolerate high statin monotherapy doses and iii) patients that were hospitalised due to acute coronary syndrome (ACS).

The HTA will aim to address the policy question by first considering the overall clinical and economic impact of ezetimibe. Subsequent analyses will determine whether limiting the indication for reimbursement to the proposed groups is appropriate in Switzerland.

2 Research questions

The planned HTA aims to address the following research questions:

1. What is the safety, efficacy, effectiveness, cost-effectiveness and budgetary impact of ezetimibe (by itself or in combination with statins or fenofibrate) compared to placebo, statins or fenofibrate monotherapy in patients who have (i) primary hypercholesterolaemia with or without pre-existing ASCVD or (ii) mixed/combined hyperlipidaemia with or without pre-existing ASCVD?
2. Are there any legal, social, ethical and organisational issues associated with ezetimibe, ezetimibe-statin and ezetimibe-fenofibrate therapy?

3 Medical background

3.1 Medical context, disease description and natural course

Cardiovascular disease is a broad term encompassing a range of diseases that affect the heart and blood vessels, including coronary heart disease, cerebrovascular disease and peripheral artery disease.[1] These diseases can lead to acute events such as myocardial infarction or stroke, which result in significant morbidity or mortality.[1] A major risk factor for CVD is atherosclerosis, the accumulation of plaque (a build-up of substances including lipids, calcium, and connective tissue) in blood vessels.[2] Overtime, the build-up of plaque causes vessels to narrow and harden, increasing the risk of thrombo-embolic events such as stroke, transient ischaemic attack, pulmonary embolism and ischaemic heart disease.[2 3] The exact cause of atherosclerosis and plaque build-up is currently unknown. However, there are several modifiable life risk factors associated with its progression, including smoking, hypertension, diabetes, and dyslipidaemia.[2] Of relevance to this scoping report is dyslipidaemia. **Dyslipidaemia**, also known as **hyperlipidaemia**, is a broad class of diseases characterised by abnormal lipoprotein, lipid, cholesterol or triglycerides levels in the blood.[4 5] Specific dyslipidaemias include:

Hypercholesterolaemia, a sub-type of dyslipidaemia, is characterised by higher-than-normal circulating low-density lipoprotein cholesterol (LDL-c) levels.[5] Defined thresholds for abnormal levels are complex, and take into account age, sex, ethnicity and patient history.[6] The origin of this disorder in patients can be familial (genetic) and/or non-familial. Non-familial causes of hypercholesterolaemia include lifestyle factors such as a high saturated-fat diet, smoking and a lack of physical activity, along with pre-existing conditions (e.g. diabetes) and certain medications (e.g. diuretics).[5 7] Familial hypercholesterolaemia is a group of inherited disorders resulting from defects in genes associated with the synthesis, metabolism or transport of lipoproteins or cholesterol (for example, *LDLR, APOB, PCSK9*).[8] The genetic defect leads to an abnormally low uptake of LDL-c by the liver, resulting in the accumulation of cholesterol in the circulatory system, and increased LDL-c particles found in plasma.[9] Irrespective of the underlying cause of hypercholesterolaemia, the resulting high cholesterol concentration is thought to cause the accumulation of plaque in blood vessels.[6]

Mixed/combined hyperlipidaemia is characterised by increased LDL-c coupled with increased triglycerides and/or decreased high density lipoproteins (HDL). Like hypercholesterolaemia it commonly has a familial origin. Mixed/combined hyperlipidaemia can be acquired through lifestyle factors and is associated with concomitant diseases such as metabolic syndrome or non-alcoholic fatty liver disease.[10 11]

Individuals with hypercholesterolaemia or mixed/combined hyperlipidaemia are at an increased risk of CVD, including ACS, angina and myocardial infarction, and death.[6] For these individuals, medications that aim to lower blood concentration of LDL-c, a lipoprotein involved in the transport of cholesterol, are often prescribed.[12] LDL-c particles also contain high levels of Apolipoprotein B (Apo-B), a lipoprotein pivotally involved in the initiation and progression of lipid deposition and the accumulation of plaque in arteries.[6] Interventions aimed at lowering LDL-c are thought to reduce the lipid deposition and plaque accumulation, thereby reducing overall cardiovascular risk (i.e. primary prevention).[6] In individuals who have experienced an adverse cardiac event (e.g. myocardial infarction or stroke), LDL-c lowering medications are intended to lower the risk of further adverse events (i.e. secondary prevention).[13]

In summary, individuals with hypercholesterolaemia or mixed/combined hyperlipidaemia utilising lipid-lowering interventions who are yet to experience an adverse cardiac event are denoted as the primary prevention population. By contrast, individual's utilising lipid-lowering therapies and have experienced an adverse cardiac event are denoted as the secondary prevention population.

3.2 Symptoms and diagnostic pathway

Most patients with dyslipidaemias present with elevated blood lipid levels (for example, LDL-c > 100mg/dL and triglyceride > 177mg/dL) noting specific values are dependent on age and other risk factors.[14] Further, patients often do not exhibit clinical symptoms indicative of CVD. However, in severe cases, dyslipidaemias can cause skin or tendon lesions (xanthomas) and cholesterol deposits in the eye (arcus cornea).[15]

To ascertain whether the dyslipidaemia is familial or non-familial, age, genetic testing, family history and blood lipid levels are considered.[9] [16] Patients that have first-degree relatives with a history of elevated LDL-c levels, tendon xanthomas or arcus cornealis, premature CVD or have died from a cardiovascular event are candidates for genetic testing.[14] Genetic testing generally screens for mutations in *LDLR, APOB* and *PCSK9* genes; however, approximately 10 – 40 per cent of patients with phenotypical characteristics of familial hypercholesterolaemia do not exhibit genetic defects in these genes and the inheritance of hyperlipidaemias are often polygeneic.[14] Lastly, LDL-c measures are generally higher in familial than non-familial hypercholesterolaemia.

Similarly, to differentiate between the type of dyslipidaemia (hypercholesterolaemia and mixed/combined hyperlipidaemia), blood lipid levels and genetic testing are used.[14] [17] Individuals with hypercholesterolaemia typically present with elevated LDL-c levels. By contrast, individuals with mixed/combined hyperlipidaemia present with elevated LDL-c and/or triglyceride levels with or without reduced HDL levels. [14] [17] Further, investigations to rule out secondary causes of dyslipidaemia such as

hypothyroidism, nephrotic syndrome and some medications (cyclosporin and anti-retroviral drugs) are additionally performed.[14]

Once diagnosed, the individual's cardiovascular risk score is calculated. The cardiovascular risk score determines the absolute risk of a fatal coronary event or non-fatal myocardial infarction within 10 years.[17] This in turn determines the appropriate treatment strategy and goals. A summary of the risk categories and their corresponding criteria is shown in ***Table 1***, noting however, this table represents a simplified risk score, as additional considerations such as age, blood pressure, sex, smoking habits and diabetes influence the individuals overall risk categorisation.[17]

Table 1 Summary of risk categories as reported by the Arbeitsgruppe Lipide und Atherosklerose (AGLA)[17]

Cardiovascular risk categories	Criteria	Target LDL-c	Target non-HDL-c	Target HDL-c	Target total cholesterol	Target Triglyceride
Very high risk	Known cardiovascular diseases or atherosclerosis [a] ; type 2 diabetes mellitus; type 1 diabetes mellitus with end organ damage like microalbuminuria; chronic renal failure with eGFR <30 ml/min / 1.73 m^2	<70mg/dL (1.8mmol/L)	<100mg/dL (2.6mmol/L)	No treatment target, but remains highly recommended for risk assessment. Low HDL is associated with increased cardiovascular risk. When viewing HDL-c as an isolated measure, < 39mg/dL (1mmol/L) is the recommended level. Correct lifestyle factors and evaluate other risk factors to address HDL concerns.	No treatment target, but highly recommended for risk assessment. Use LDL-c values to determine appropriate levels.	**Moderate hypertriglyceridemia** **TG, 177 – 886mg/dL (2 – 10mmol/L)** Primary goal is to lower LDL-c and non-HDL-c to target levels. Secondary goal is to treat underlying diseases if applicable. **Severe hypertriglyceridemia** **TG >886mg/dL (>10mmol/L)** Primary goal is to prevent acute pancreatitis, lower triglycerides, eliminate chylomicronemia. Secondary goal is to treat underlying disease and reduce LDL-c and non-HDL-c to target levels. **Mixed hyperlipidaemia** **TC >233mg/dl (6mmol/L), TG >177mg/dL (2mmol/L)** Primary goal is to lower LDL-c and non-HDL-c to target levels. Secondary goal is to treat underlying disease.
High risk	10-year risk > 20% [b] Individual risk factors: LDL-C >4.9 mmol/L; Blood pressure >180/110 mmHg; chronic renal failure with eGFR 30-59 ml/min / 1.73 m^2	<100mg/dL (2.6mmol/L)	<131mg/dL (3.4mmol/L)			
Moderate risk	10-year risk 10-20% [b] Risk influenced by others risk factors	<116mg/dL (3.0mmol/L)	<147mg/dL (3.8mmol/L)			
Low risk	10-year risk <10% [b]	No target value: optimise lifestyle interventions	No target value			
General therapy recommendations: before starting pharmacological interventions, the lifestyle of the patient (activity, diet and body weight) should be accounted for and optimised. Exception: in secondary prevention; both pharmacological and lifestyle interventions should start at the same time.						

Abbreviations

eGFR = estimated glomerular filtration rate, **HDL** = high density lipoprotein, **LDL-c** = low density lipoprotein-cholesterol, **mg/dL** = milligram per decilitre, **ml/min** = millilitre per minute, **mmol/L** = millimole per litre, **TC** = total cholesterol, **TG** = total triglycerides.

Notes

a = Previous myocardial infarction, ACS, coronary revascularization and other arterial revascularization procedures, stroke/transient ischemic attack, aortic aneurysm, peripheral arterial occlusive disease.
b = Absolute risk in%, a fatal coronary event or a non-fatal event within 10 years to have myocardial infarction.
c = Total of atherogenic lipoproteins.

3.3 Prevalence and burden of disease

Cardiovascular disease

CVDs are the leading cause of mortality globally. In 2016, an estimated 17.9 million deaths were attributed to CVDs, of which 2.6 million deaths were attributable to raised cholesterol.[18] [19] Specifically, high cholesterol accounts for approximately one third of all ischaemic heart disease cases worldwide.[19] Raised cholesterol is a major cause of disease burden in developed and developing countries and its prevalence has remained fairly constant from 1980 – 2008.[19]

In 2016, CVDs were responsible for 31% of deaths in Switzerland, representing the major cause of death in both males and females over 85 years old and the second most common leading cause of death between the ages of 65 to 84 years.[20-22]

High cholesterol

Approximately 20 per cent of participants in the 2007 Swiss Health survey self-reported high cholesterol levels[23] with significant differences found between regions.[24] Ticino and the western part of Switzerland (Leman) reported the highest prevalence (22.9% and 21.9% of surveyed individuals, respectively) with the eastern part of Switzerland reporting the lowest rate (16.2%). Of the participants reporting high cholesterol 40 per cent reported they received appropriate treatment. Again, treatment rates where highest in Ticino and the western part of Switzerland (Leman) and lowest in the eastern part of Switzerland.[24]

In 2012, the prevalence of high cholesterol was similar – approximately 17 per cent of the sampled population. Notably, the prevalence was slightly higher among men than women (19% vs 16%) with the elderly (> 65 years) reporting the highest level of any age demographic.[25]

Dyslipidaemias

The Swiss Health survey provided information regarding the prevalence of high cholesterol. There is relatively little information, however, evaluating specific lipid disorders in Switzerland. No studies evaluating the prevalence of non-familial hypercholesterolaemia or mixed/combined hyperlipidaemia in Switzerland have been identified. The following summary aims to provide an estimate of the prevalence of dyslipidaemias and familial hypercholesterolaemia in Switzerland:

- An evaluation of a nationwide primary care database (FIRE) and hospital discharge statistics (MEDSTAT) estimated approximately 3.7 per cent of Swiss women and 6.3 to 6.7 per cent of Swiss men have dyslipidaemia.[26] The authors noted the prevalence of this condition changes depending on the sub-population studied (for example, age and gender) and other factors such as lifestyle and other pre-existing conditions (such as smoking and diabetes).[26] [27]

- An evaluation of Swiss patients hospitalised with ACS determined 1.6 and 17.8 per cent had probable/definite and possible familial hypercholesterolaemia, respectively.[28]
- A sample of the Swiss population determined 7 of the 2221 subjects had familial hypercholesterolaemia as inferred by mutations in the *LDLR*. This corresponded to a prevalence rate of 1/317 (0.3%).[29] The prevalence of familial hypercholesterolaemia due to all different genetic variants (*LDLR*, *PCSK9* and *APOB)* was 1/132 (0.7%).[29]
- The prevalence of *APOB* mutations in Switzerland was 1/209 (0.5%) across a combined cohort of healthy volunteers (n = 728) and families with primary hypercholesterolaemia (n = 520).[30]

More broadly, the prevalence of mixed/combined hyperlipidaemia, heterozygous and homozygous familial hypercholesterolaemia in Europe varies from 1:100, 1:200 to 1:500 and 1:500,000, respectively.[14]

3.4 Treatment pathway

3.4.1 Dyslipidaemia

The Swiss (Arbeitsgruppe Lipide und Atherosklerose [AGLA]) (***Figure 1***) and European (European Society of Cardiology and the European Atherosclerosis Society [ESC/EAS]) guidelines are fairly consistent with respect to the management of dyslipidaemias.[6 14] Both guidelines emphasise the role of risk calculators that utilise patient history and blood lipid levels to calculate an overall cardiovascular risk score. The corresponding risk level assists in determining the appropriate treatment approach (for further information on the risk calculator see AGLA 2019[31]). The European guidelines additionally emphasise the variability in the patient's response to lifestyle and pharmaceutical interventions and highlight that total risk reduction and treatment goals should be individualised in order to best achieve the desired outcomes.[6] The guidelines are broadly applicable to individuals with hypercholesterolaemia or mixed/combined hyperlipidaemia who have or have not experienced ASCVD (i.e. high and low risk groups, respectively), noting the cardiovascular risk and respective treatment goals differ reflecting their risk category. Similarly, treatment goals may vary between certain types of familial hypercholesterolaemia.[6 14] The guidelines are not applicable for adolescents and children which require separate treatment management strategies - a discussion of which is beyond the scope of this report. The following recommendations represent the Swiss guideline (***Figure 1***) with additional information supplemented from the European guidelines.

Lifestyle interventions are the first-line treatment for the management of dyslipidaemias (including both familial and non-familial hypercholesterolemia) irrespective of risk level.[6 14] These consist of lipid lowering diets, increased physical activity, and the cessation of smoking. If patients do not achieve their

respective goals or are classified as very high, high or moderate-risk, statins are recommended.[14] The response to statin treatment is often variable. Therefore, statin dosage is often titrated to the maximum tolerated dose before further treatments (such as fenofibrate) or higher potency statins are considered.[6] The statin initially selected should largely reflect the patient's overall cardiovascular risk and their respective treatment goals.[6] For patients with familial hypercholesterolaemia, LDL apheresis may additionally be considered at this stage. [6 14]

If patients do not reach their treatment goals, or are intolerant to statins, ezetimibe or ezetimibe-statin combination therapy is recommended.[6 14] ESC further suggests a bile acid sequestrant may be considered if patients do not reach their treatment goal, noting that the level of evidence and the class of recommendation is lower than for ezetimibe. Proprotein convertase subtilisin/kexin type 9 protein (PCSK9) inhibitors are recommended for patients with and without ASCVD, who are at very-high risk of not achieving their goals on a maximally tolerated dose of statin and ezetimibe.[14] In Switzerland, PCSK9 inhibitors are restricted to adults with hypercholesterolaemia, and adults and adolescents with homozygous familial hypercholesterolaemia that have a high or very high cardiovascular risk despite the use of maximally tolerated lipid-lowering medication.[32] Additionally, individuals must be intolerant to statins or have used the maximally tolerated dose of lipid-lowering therapy for at least 3 months.

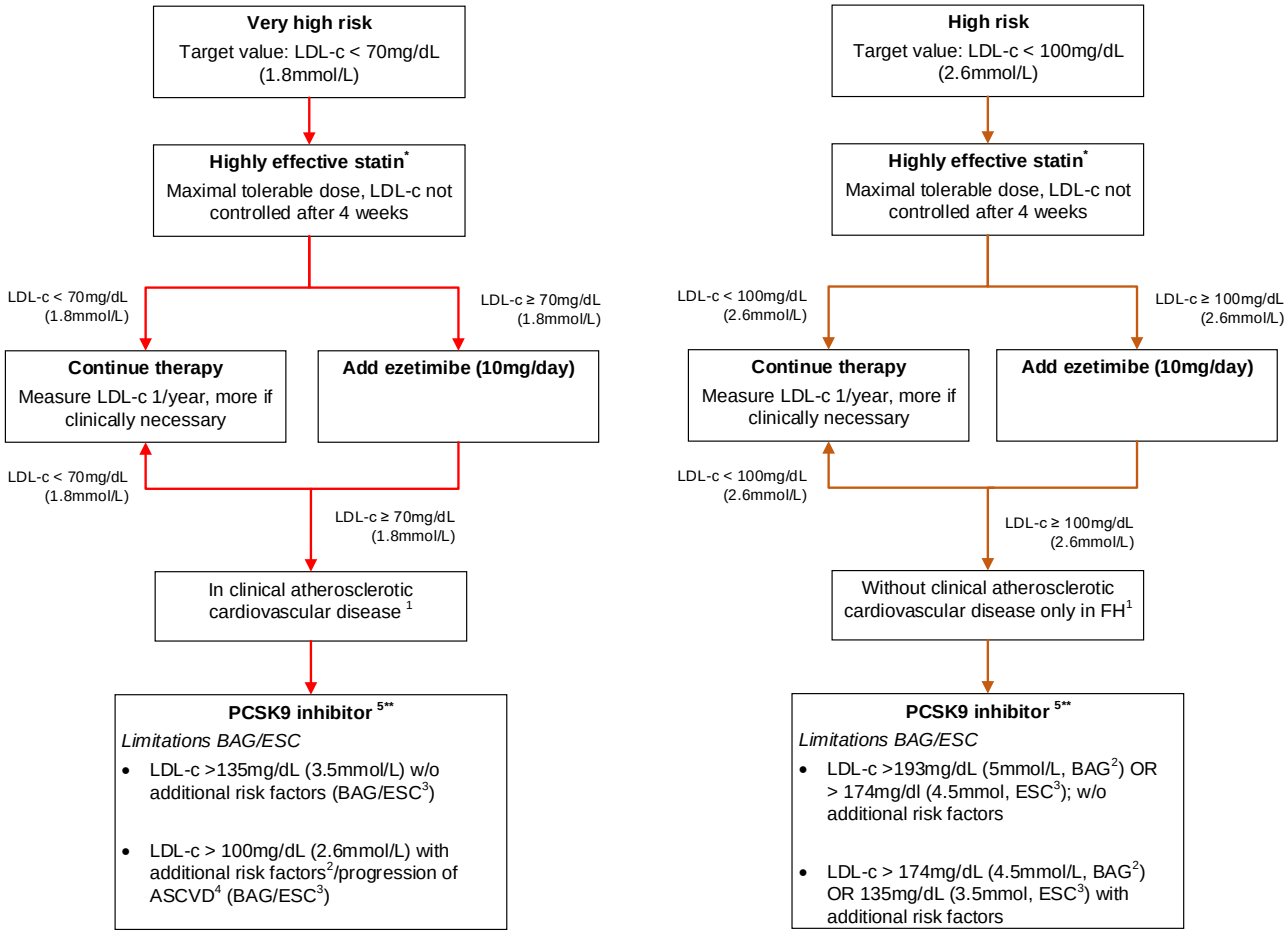

Figure 1 Clinical management pathway for dyslipidaemia (focus on hypercholesterolaemia) (AGLA)[17]

Abbreviations

ASCVD = atherosclerosis cardiovascular disease, **BAG** = Federal Office of Public Health, **ESC** = European Society for Cardiology, **LDL-c** = low density lipoprotein-cholesterol, **mg** = milligrams, **PCSK9** = proprotein convertase subtilisin/kexin type 9.

Notes

Moderate and low risk are not presented in the diagram however, they are summarised below.
Moderate risk: target value 116mg/dL (3mmol/L) LDL-c; treatments include lifestyle modification and statins.
Low risk: target values, none; treatments include lifestyle modification.
* = Atorvastatin or Rosuvastatin.
** = Evolocumab or Alirocumab.
1 = Clinical atherosclerotic cardiovascular diseases (ASCVD): coronary heart disease (CHD), symptomatic peripheral atherosclerosis or ischemic stroke.
2 = Risk factors according to BAG: diabetes mellitus; Lipoprotein a >50 mg/dl; pronounced arterial hypertension; premature (men <55 years, women <60 years) clinically manifested familial atherosclerotic cardiovascular disease (ASCVD).
3 = Additional risk indicators according to the ESC: diabetes mellitus with end organ damage or another serious risk factor (e.g. increased blood pressure ≥160 / 100 mmHg); lipoprotein a>50 mg/dl; serious risk factors: smoking, pronounced hypertension; age> 40 years without therapy; early ASCVD (men <55 years; women <60 years) with first-degree relatives; imaging indicators (high-risk markers in coronary CT) for severe/extensive atherosclerosis; rapid progression of the ASCVD.
4 = Progression according to the BAG limitation: progressive clinical atherosclerotic cardiovascular disease (repeated acute coronary syndrome, myocardial infarction, stroke, or unplanned repeated coronary revascularization within 5 years of the first cardiovascular event).
5 = See FOPH limitation for the use of PCSK9 inhibitors on p. 33/34.

3.4.2 Statin intolerance

Statins are the principle treatment for the management of dyslipidaemia. However, approximately one to five per cent of patients are intolerant to statins at any dose, leading to discontinuation of the drug.[33] Statin non-adherence, poor compliance due to patient- physician- and medication-related factors, increases the risk of adverse cardiovascular events, specifically myocardial infarction or coronary heart disease (CHD) as their baseline cardiovascular risk remains untreated.[34-36] While there is no consensus regarding the definition of statin intolerance[36], AGLA defines it as the inability to take statins due to the statin-associated myopathy, liver damage or other adverse events.[14] The diagnosis of statin intolerance typically relies on the presentation of myopathy and/or an increase in creatinine kinase (CK) (a marker of muscle injury). Symptoms generally begin within the first four weeks of treatment (occurs rarely after >12 weeks) and resolve after stopping the statin. Resuming the statin results in the reoccurrence of symptoms within four weeks.[14]

If there are no underlying causes contributing to statin intolerance, AGLA recommends starting another statin on the lowest recommended dosage and titrating up to the maximum tolerated dose. If the patient remains intolerant, non-statin treatments are recommended including fenofibrate, ezetimibe or PCSK9 inhibitors.[14] For further information regarding clinical management of statin-intolerance refer to ***Figure 2***.

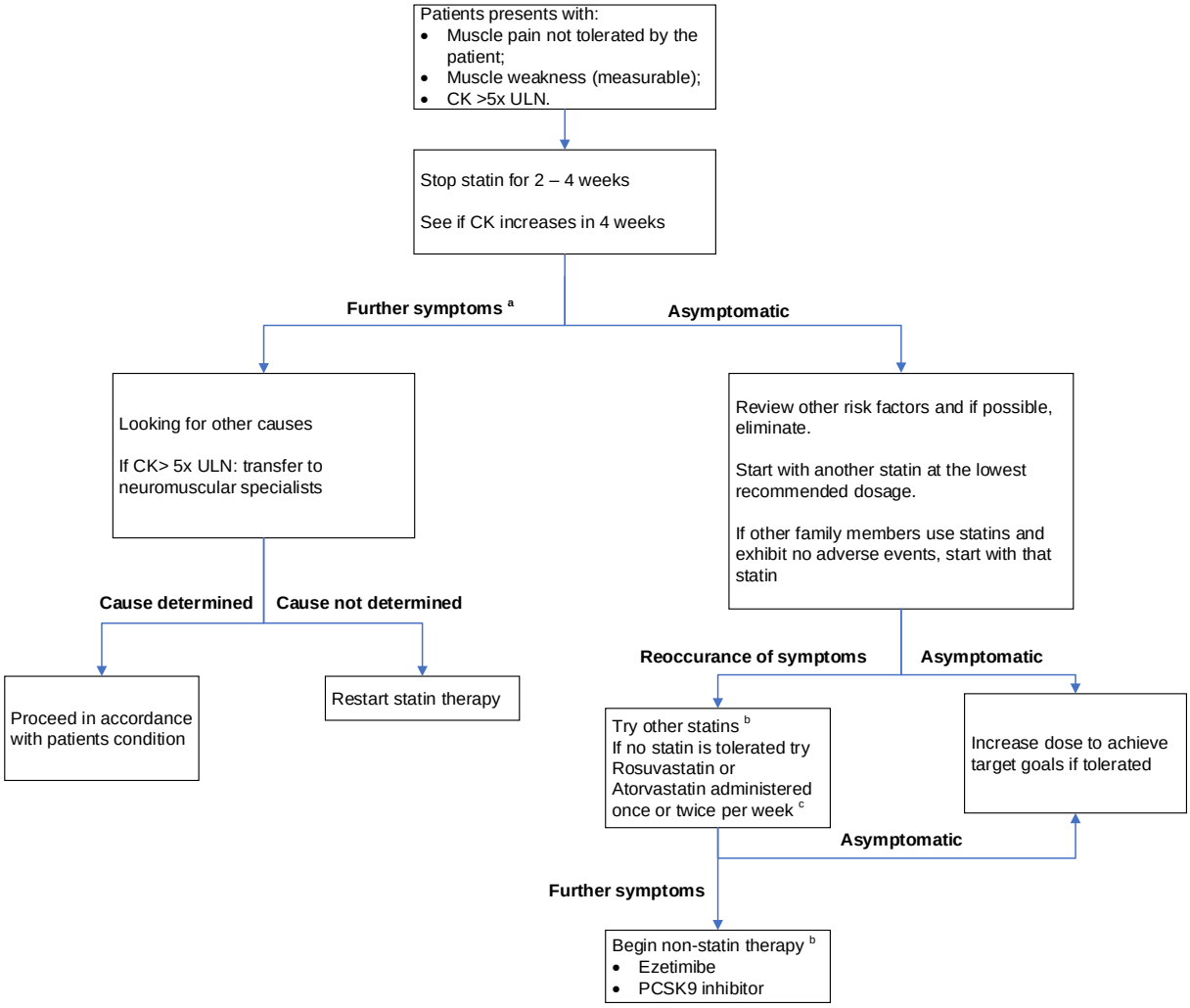

Figure 2 Clinical management pathway for statin intolerance (AGLA)[14]

Abbreviations

CK = creatinine kinase, **5x ULN** = 5 times the upper limit of normal, **PCSK9** = proprotein convertase subtilisin/kexin type 9.

Notes

a = Symptoms: clinical and / or CK increase.

b = After discontinuation of statin therapy due to intolerance: washout phase for 2-4 weeks before starting the alternative statin or non-statin therapy. The choice of alternative therapy depends on baseline LDL-c and target goal.

c = Statins are generally taken daily. If symptoms reoccur, the frequency of administration is reduced to once or twice per week.

4 Technology

4.1 Technology description

4.1.1 Medication description and availability in Switzerland

Ezetimibe is a cholesterol absorption inhibitor. Specifically, ezetimibe acts on the brush boarder cells of the intestine selectively inhibiting the cholesterol transport protein Nieman Pick C1 (NPC1L1).[37] Inhibition of NPC1L1 prevents the uptake of cholesterol-containing intestinal luminal micelles into enterocytes. This action reduces the amount of cholesterol delivered to the liver and effectively increases removal of LDL-c from the blood.[37]

In Switzerland, ezetimibe exists as an individual medicine[38] [39] or in fixed combination with statins including: simvastatin,[40] atorvastatin,[41] and rosuvastatin.[42] Ezetimibe is additionally licensed for free combinations with fenofibrate or other licensed statins (each drug is administered as a separate pill).[38] [39] Generic ezetimibe medications are also available (see ***Table 2*** for further information).

Ezetimibe-containing medicines are indicated for primary hetero-and homozygous familial and primary non-familial hypercholesterolaemia, mixed/combined hyperlipidaemia, and homozygous sitosterolemia (phytosterolemia).[35] AGLA guidelines further suggest ezetimibe should be used as a second-line treatment in patients who have not reached their goal despite using the maximum tolerated dose of statins or in statin intolerant patients.[14] For an overview of ezetimibe containing medications available in Switzerland, refer to ***Table 2***. Non-ezetimibe components of combination therapies (i.e. statins, fibrates) are described further in ***Section 4***.

Table 2 Key formulations of ezetimibe available in Switzerland

Name (manufacturer)	Active ingredient (dose) Administration	Indications	Contraindications	Limitations for reimbursement
Ezetimibe				
Ezetrol®, Ezetimibe MSD® (Merck Sharp & Dohme) Ezetimib Zentiva® (Helvepharm AG) Ezetimib Spirig HC® (Spirig HealthCare AG)	Ezetimibe (10mg) Available as a tablet taken once daily at any time regardless of food intake. The patient should follow a lipid-lowering diet while taking the medication. Can be taken with a statin or fenofibrate	Primary hetero- and homozygous familial and primary non-familial hypercholesterolaemia Mixed/combined hyperlipidaemia Homozygous sitosterolemia (phytosterolemia) [a]	Contraindicated in patients with hypersensitivity to ezetimibe or active liver disease. Not recommended in children under 10 years.	No limitations

Name (manufacturer)	Active ingredient (dose) Administration	Indications	Contraindications	Limitations for reimbursement
Ezetimib Sandoz® (Sandoz Pharmaceuticals AG) Ezetimib-Mepha Teva (Mepha Pharma AG) Ezetimib Axapharm (Axapharm AG)	however, a combination with both statin and fenofibrate is not permitted.			
Ezetimibe + simvastatin				
Inegy® (MSD Merck Sharp & Dohme) Ezetimib Simvastatin Zentiva® (Helvepharm AG) Ezetimib Simvastatin Sandoz® (Sandoz Pharmaceuticals AG) Ezetimib-Simvastatin-Mepha (Mepha Pharma AG) Ezetimib Simvastatin Axapharm (Axapharm AG) Ezetimib Simva Spirig HC® (Spirig HealthCare AG)	Ezetimibe (10mg) + simvastatin (10, 20, 40 or 80mg) Available as a tablet taken once daily in the evening regardless of food intake. The patient should follow a lipid-lowering diet while taking the medication. The dosage is based on the individuals baseline LDL-c levels, treatment goals and response to therapy.	Primary hetero- and homozygous familial Primary non-familial hypercholesterolaemia Mixed/combined hyperlipidaemia	Contraindicated in patients with hypersensitivity to ezetimibe or simvastatin; active liver disease (moderate to severe); are pregnant, breast feeding; or are using CYP3A4 inhibitors and gemfibrozil, cyclosporine or danazol. Not recommended for children or adolescent under 18 years. Should be used with caution in elderly patients (>65 years).	No limitations
Ezetimibe + atorvastatin				
Atozet® (MSD Merck Sharp & Dohme)	Ezetimibe (10mg) + atorvastatin (10, 20, 40 or 80mg) Available as a tablet taken once daily regardless of the time of day and food intake. The patient should follow a lipid-lowering	Primary hetero- and homozygous familial Primary non-familial hypercholesterolaemia Mixed/combined hyperlipidaemia	Contraindicated in patients with; hypersensitivity to ezetimibe or atorvastatin, active liver disease (moderate to severe); or are pregnant or breast feeding. Not recommended for children or	To reduce cardiovascular risk in the presence of a very high resp. high risk category (according to the AGLA risk category), if the corresponding LDL-c target values (70mg/dL [1.8 mmol/l] at very high risk or 97mg/dL [2.5

Name (manufacturer)	Active ingredient (dose) Administration	Indications	Contraindications	Limitations for reimbursement
	diet while taking the medication. The dosage is based on the individual's baseline LDL-c levels, treatment goals and response to therapy.		adolescent under 18 years. Should be used with caution in elderly patients (>65 years).	mmol/l] at high risk) were not reached under maximum tolerated statin therapy.
Ezetimibe + rosuvastatin				
Ezetimib-Rosuvastatin Mepha (Mepha Pharma AG)	Ezetimibe (10mg) + rosuvastatin (10 or 20mg) Available as a tablet taken once daily at the same time of day regardless of food intake. The patient should follow a lipid-lowering diet while taking the medication. The dosage is based on the individuals baseline LDL-c levels, treatment goals and response to therapy.	Indicated as a replacement therapy in adults receiving ezetimibe and rosuvastatin as separate tablets.	Contraindicated in patients with hypersensitivity to ezetimibe or rosuvastatin; are taking cyclosporin; have myopathy, active liver disease, renal impairment; or are pregnant or breast feeding. Not recommended for children or adolescent under 18 years. In the elderly (>65 years), fixed dose combination is not suitable as initial therapy.	Ezetimibe-rosuvastatin-Mepha is indicated as a replacement therapy in adult patients already receiving ezetimibe and rosuvastatin as separate tablets at the same dose level.

Abbreviations

LDL-c = low density lipoprotein-cholesterol, **mg** = milligram.

Notes

a = Ezetimibe is indicated for the treatment of non-familial and heterozygous familial hypercholesterolaemia (as monotherapy or in combination with a statin), and for homozygous familial hypercholesterolaemia in combination with a statin. It is also indicated for the treatment of mixed/combined hyperlipidaemia in combination with the fibrate fenofibrate and as mono-therapy for the treatment of homozygous sitosterolaemia.

4.1.2 Route of administration, dosage and treatment duration

Ezetimibe is prescribed by General Practitioners and Cardiologists and is administered as a fixed dose (10mg) irrespective of whether it is in a combination or by itself.[38 40-42] For combination treatments the dose of the statin varies from 10 to 80mg for simvastatin and atorvastatin[40 41] and 10 to 20mg for rosuvastatin.[42] Ezetimibe tablets are taken once daily regardless of the time of day or food intake. It may be taken at the same time as fenofibrate or statins, however, a break of two to four hours is required before taking bile acid sequestrants.[43]

Once consumed, ezetimibe is rapidly absorbed and metabolised to its active form ezetimibe-glucuronide, which has a half-life of approximately 22 hours.[37 44] There are no significant effects of sex or race on the pharmacokinetics of ezetimibe;[44] however, ezetimibe-statin combinations are not recommended in children, and caution should be taken when administering to older individuals (>65 years) owing to increased risk of myopathy.[40 42] Further, no dose adjustments are required for ezetimibe or ezetimibe in combination with simvastatin or atorvastatin in patients with mild hepatic impairment or moderate renal insufficiency.[41 42]

It is unclear how long-term ezetimibe can or should be used for because contemporary guidelines do not mention prescription limitations, and there are few studies evaluating long-term risks associated with ezetimibe.[45]

4.1.3 Adverse effects and contraindications

Adverse effects associated with ezetimibe are generally mild and self-limiting and include: abdominal pain, diarrhea, flatulence, headache and myalgia.[38] Uncommon adverse effects include but are not limited to: dyspepsia, cough, body aches, back pain, chest pain, joint pain, fatigue and weakness.[38 40] Early reports observed an increased incidence of cancer associated with ezetimibe use[46]; however, pooled data from three clinical trials noted the incidence of cancer was similar between ezetimibe and placebo.[47]

There are two contraindications for ezetimibe: patients should not take the drug if they are hypersensitive to ezetimibe or have active liver disease.[38] Ezetimibe-statin combinations are associated with greater contraindications, for example, patients should not take these combinations if they are: taking gemfibrozil, cyclosporine or danazol or CYP3A4 inhibitors, have active liver disease or renal insufficiency, and are pregnant or breast feeding. Combination treatments are not recommended in children; however, it is unclear whether this is a contraindication.[40-42]

4.2 Alternative technologies

4.2.1 Lifestyle interventions

Patients with dyslipidaemia are advised to undertake lifestyle changes which include lipid-lowering diets, smoking reduction or cessation, and increased physical activity with the aim to reduce cardiovascular risk factors and prevent CVD.[48 49] Lifestyle interventions are considered a first-line treatment. If patients do not achieve their respective goals or are classified as very high, high or moderate-risk they are recommended for pharmacotherapy. Other possible treatments for these disorders are dietary supplements with fish oil, omega-3 fatty acids, and plant sterol-containing products. Fish oil supplementation has been shown to reduce triglycerides in adults;[50 51] however, there is limited evidence supporting the remaining supplements.[6 52]

4.2.2 Statins

In addition to lifestyle changes, statins are often considered first-line treatment for primary dyslipidaemia and secondary prevention.[6 14] Statins inhibit the 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, an enzyme involved in the synthesis of cholesterol. Inhibiting HMG-CoA reductase, and cholesterol biosynthesis, increases LDL receptor expression which promotes the uptake of cholesterol, thereby reducing circulating LDL-c.[6 53] By lowering LDL-c concentrations, the rate of plaque formation is reduced, and the overall CVD risk is decreased. Despite being the most commonly prescribed treatment for dyslipidaemia, patients can present with statin intolerance and resistance. Statin medications can sometimes contain statin combined with another active ingredient such as ezetimibe (***Table 2***) or fibrates. Six statins are currently covered by Swiss mandatory health insurance of which three are additionally found in fixed combination with ezetimibe (atorvastatin, simvastatin and rosuvastatin). For the purposes of this evaluation, all statins licensed and reimbursed in Switzerland are of interest (see ***Table 3*** for further information).

Table 3 Formulations of statins available in Switzerland

Name/ manufacturer(s)	Active ingredient/ dose/ administration	Indications/applications	Contraindications/ recommendations
Atorvastatin [54] Axapharm AG, Drossapharm AG, Helvepharm AG, Mepha Pharma AG, Pfizer PFE, Sandoz Pharmaceuticals AG, Sandoz Pharmaceuticals AG, Spirig HealthCare AG and Streuli Pharma AG	Atorvastatinum 10, 20, 40 or 80mg/day Oral	Individuals with dyslipidaemia or primary hypercholesterolaemia (familial and non-familial) who have failed dietary interventions. Patients with existing, or at high risk of cardiovascular risk.	Patients who are hypersensitive to the active ingredient or any of the excipients; have active liver disease or unexplained persistent elevations of serum transaminases; or are pregnant and lactating.

Name/ manufacturer(s)	Active ingredient/ dose/ administration	Indications/applications	Contraindications/ recommendations
Fluvastatin [55] Mepha Pharma AG and Novartis Pharma Schweiz AG, Sandoz Pharmaceuticals AG	Fluvastatinum 20, 40 or 80mg/day Oral	Adults with coronary heart disease, mixed dyslipidaemia or primary hypercholesterolaemia who have failed dietary interventions. Males (9 – 16 years), and post-menarche females (10 – 16 years) with familial hypercholesterolaemia.	Patients who are hypersensitive to the active ingredient or any of the excipients; have active liver disease or unexplained persistent elevations of serum transaminases; or are pregnant and lactating.
Pitavastatin [56] Recordati AG	Pitavastatinum 1, 2 or 4mg/day Oral	Adults with mixed dyslipidaemia and primary hypercholesterolaemia who have failed dietary and other non-pharmacological interventions.	Patients who are hypersensitive to the active ingredient or any of the excipients; have active liver disease or unexplained persistent elevations of serum transaminases, myopathy; using cyclosporine; or are pregnant and lactating. It is not recommended for individuals under 18 years.
Pravastatin [57] Bristol-Meyers Squibb SA, Axapharm AG, Daiichi Sankyo AG, Drossapharm AG, Helvepharm AG, Mepha Pharama AG, Sandoz Pharmaceuticals AG, Spirig HealthCare AG, Steuli Pharma AG	Pravastatinum natricum 10, 20 or 40mg/day Oral	Individuals with primary hypercholesterolaemia, combined hyperlipidaemia, coronary heart disease, angina pectoris or post-myocardial infarction.	Patients who are hypersensitive to the active ingredient or any of the excipients; have active liver disease or unexplained persistent elevations of serum transaminases; or are pregnant and lactating. It is not recommended in children under the age of 8
Rosuvastatin [58] AstraZeneca AG Axapharm AG, Drossapharm AG Helvepharm, Sandoz Pharmaceuticals AG, Spirig HealthCare AG, and Mepha Pharma AG	Rosuvastatinum 5, 10 or 20mg/day Oral	Adults with mixed dyslipidaemia, primary hypercholesterolaemia or who are at high cardiovascular risk	Patients who are of Asian descent or hypersensitive to the active ingredient or any of the excipients; have hereditary muscle diseases, muscular toxic complications from statins, active liver disease or unexplained persistent elevations of serum transaminases, moderate renal impairment, hypothyroidism, alcohol abuse, myopathy; using cyclosporine or fibrates; or are pregnant and lactating. It is not recommended in children under the age of 10.

Name/ manufacturer(s)	Active ingredient/ dose/ administration	Indications/applications	Contraindications/ recommendations
Simvastatin [59] Helvepharm AG, Mepha Pharma AG, MSD Merck Sharp & Dohme AG, Sandoz Pharmaceuticals AG and Spirig HealthCare AG	Simvastatinum 10, 20, 40 or 80mg/day Oral	Patients with dyslipidaemia and primary hypercholesterolaemia who have failed dietary interventions. Patients with existing, or at high risk of coronary heart disease.	Patients who are hypersensitive to the active ingredient or any of the excipients; have active liver disease or unexplained persistent elevations of serum transaminases; using CYP3A4 inhibitors, gemfibrozil, cyclosporine or danazol; or are pregnant and lactating.

Abbreviations
mg = milligrams.

4.2.3 Fibrates

Peroxisome proliferator-activated receptors (PPAR) are nuclear receptors that regulate the expression of specific genes by binding to response elements present within the promoter region of the target genes.[60 61] Fibrates are agonists of the PPAR-α and regulate steps involved with lipid and lipoprotein metabolism. Consequently, fibrates lower lipoprotein levels, triglycerides and triglyceride-rich lipoprotein remnant particles.[60 61]

Fibrates are generally well tolerated by most patients, with less than two and five per cent of users reporting skin rashes and gastrointestinal incidents[62]. However, fibrates are also associated with several serious adverse effects, the most common being myopathy, liver-enzyme elevations and cholelithiasis (gallstone formation).[62]

- Several fibrate medications are available in Switzerland. Of relevance to the scoping report is Lipanthyl® 200M/267M (Mylan Pharma GmbH), a fibrate medication containing fenofibratum. The typical starting dose for this medication is 200mg daily (one tablet). Lipanthyl® is contraindicated in cases of hepatic issues, pancreatitis, kidney failure and gallbladder issues.[63] It is currently reimbursed by the mandatory health insurance.

4.2.4 Other treatments

Non-statin therapies, apart from ezetimibe, include bile acid sequestrants, PCSK9 inhibitors, lomitapide, mipomersen, n-3 fatty acids, nicotinic acid and cholestoryl ester transfer protein inhibitors.[6 14] Bile acid sequestrants, mipomersen, nicotinic acid and cholestoryl ester transfer protein inhibitors, lomitapide and PCSK9 are either not widely used in Switzerland, have limited efficacy or are considered third-line treatments.[6 14 64] Consequently, these drugs will not be included as comparators and will not be discussed further in this report.

5 PICO

5.1 Population

The study populations of interest reflect the Swiss context in which ezetimibe is used. Specifically, trial populations from European countries (i.e. Western populations) evaluating ezetimibe for primary hypercholesterolaemia or mixed/combined hyperlipidaemia with or without ASCVD will be prioritised during study selection. Western populations from non-European countries will additionally be considered noting their applicability to the Swiss context may vary.

The population includes patients with primary (hetero- and homozygous familial and non-familial) hypercholesterolemia and mixed/combined hyperlipidaemia (ICD-10 codes E78.0, 78.4 and 78.5 for pure hypercholesterolaemia, other and unspecific hyperlipidaemia, respectively). Given ezetimibe is currently reimbursed without restriction in Switzerland, no limitations will be placed in terms of type, duration, severity of hypercholesterolaemia or hyperlipidaemia, or cardiovascular risk category.

In Switzerland, ezetimibe is not recommended for use in children under the age of 10.[35] However, the drug is considered safe to use in older children and adolescents, noting clinical experience is limited to homozygous familial hypercholesterolaemia. By contrast, combination regimes including ezetimibe plus atorvastatin, simvastatin or rosuvastatin are not recommended for individuals under the age of 10.[40-42] Further, the pharmacokinetics of these drugs differ in the elderly (> 65 years) compared to younger patients.[38] Given the uncertainty and potentially different response in these age groups, subgroup analysis evaluating the elderly, children and adolescents will be performed in the HTA phase if there are suitable number of studies.

Statin intolerance increases the risk of cardiovascular events such as myocardial infarction and CHD compared to individuals who are successfully treated with statins.[34 35] These two populations have different cardiovascular risk profiles and require different treatment management strategies and respond differently to lipid-lowering medication.[36] Therefore, these two populations will be investigated in subgroup analyses to determine whether their response to ezetimibe differs.

The AGLA guideline stratifies patients based on their overall cardiovascular risk as determined by age, blood pressure, smoking status, the presence of diabetes, ASCVD and familial cardiac events (for example, myocardial infarction) as well as LDL, HDL and triglyceride levels.[17] Patients stratified into very high, high, moderate and low risk categories have different cardiovascular risk and consequently, their treatment management strategies and goals also differ. Therefore, where applicable, very high, high, moderate and low risk populations will undergo subgroup analysis to determine whether their response to ezetimibe differs.

It is unlikely there will be specific studies stratifying patients based on risk scores (specifically AGLA). In the absence of specific cardiovascular risk scores, sub-group analysis will be conducted to investigate whether treatment outcomes differ between patients with and without pre-existing ASCVDs (secondary and primary prevention populations, respectively). Patients with pre-existing ASCVDs (i.e. secondary prevention population) represent a population with a high cardiovascular risk. These patients have already experienced an adverse cardiac event and therefore have a greater cardiovascular risk and require different treatment strategies/goals compared to patients who do not have ASCVDs (i.e. primary prevention population).[65 66] Patients without ASCVDs are likely to have a lower cardiovascular risk. While these two groups may not necessarily reflect AGLA-specific groups, they provide value information regarding high and low-risk patients, respectively. In Switzerland, the product information sheet for ezetimibe containing medicines do not specify whether they are indicated for secondary prevention.

5.2 Intervention

The technology under investigation is ezetimibe alone or in combination (fixed or free) with a statin or fenofibrate. In Switzerland, there are four ezetimibe containing medicines registered, these include: ezetimibe, ezetimibe with simvastatin, ezetimibe with atorvastatin and ezetimibe with rosuvastatin (***Table 2***). Ezetimibe is available in 10mg tablets taken once daily.[14 38] Statins are administered in fixed or free combination with 10mg of ezetimibe. The dose of concomitant statins varies and can be increased reflecting the individual's response. For example, when added to ezetimibe, simvastatin and atorvastatin have doses ranging from 10mg to 80mg. Rosuvastatin is dosed between 10mg to 20mg.[40-42] The differing doses reflect the different class and potency of the statins, with rosuvastatin exhibiting the greatest reduction in LDL-c compared to atorvastatin and simvastatin.[67] Consequently, subgroup analysis will be used to determine the relative effectiveness between classes of statins (as inferred by their metabolic pathways) used in conjunction with ezetimibe. In addition to these combinations, therapeutic regimes combining ezetimibe to fenofibrate will also be included.

5.3 Comparator

The EAS/ESC and AGLA guidelines recommend statins as the primary medication for patients with dyslipidaemias who have a moderate, high or very high cardiovascular risk.[6] Failure to achieve the desired LDL-c goal despite using the highest tolerated dose necessitates changing the type of statin or adding ezetimibe followed by a PCSK9 inhibitor.[6 14] PCSK9 inhibitors are the last-line treatment for primary and secondary prevention and strictly limited in reimbursement.[14 64] Consequently, they are excluded from the report. Fenofibrate is an additional comparator given it is prescribed in (free) combination with ezetimibe. Other medications such as niacin, bile acid sequestrants and n-3 fatty acids are not reported in the AGLA guidelines and are therefore excluded.

Placebo or active comparator trials provide the most informative evidence regarding the efficacy of ezetimibe. By contrast, trials conducted in a real-world setting will provide evidence regarding the effectiveness of ezetimibe.

5.4 Outcomes

5.4.1 Efficacy and effectiveness outcomes

5.4.1.1 Critical

Major adverse cardiovascular events (MACE) is a composite endpoint of clinical events reflecting both safety and effectiveness outcomes, and is recommended as the primary efficacy outcome by the European Medicines Agency (EMA) for trials investigating treatments of lipid disorders.[68] There is no standardised definition of MACE and different definitions can lead to different conclusions.[69] In this instance, the EMAs recommendation for MACE will be utilised which encompasses cardiovascular mortality, non-fatal stroke and non-fatal myocardial infarction.[68] The individual events forming MACE will be included and reported/analysed separately as well. Decreasing the risk and incidence of MACE would reflect improved survival and potentially quality of life. In addition to MACE, **non-cardiovascular mortality, hospitalisation for unstable angina** and **coronary revascularisation** will also be considered.

Health-related quality of life is a self-reported assessment of the individuals physical and mental health. The SF-12 or 36 and the EuroQoL-5D (EQ-5D) are commonly used measures evaluating quality of life. These tools require patients to self-asses their current status across multiple dimensions including mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Any health-related quality of life measure will be considered.[70-72]

5.4.1.2 Important

Total cholesterol, triglycerides, HDL and LDL-c are lipid or lipoproteins and are surrogate markers used to infer cardiovascular risk. Swiss[14], European[6] and American guidelines[73] utilise lipid and lipoprotein levels as treatment targets and goals and delineate risk categories for primary and secondary prevention. No minimally important clinical differences were identified for these markers.

LDL-c is a measure of blood cholesterol and Apo-B[6], a lipoprotein involved in lipid deposition and the progression of atherosclerotic plaques.[2] Multiple studies have demonstrated a relationship between changes in LDL-c and cardiovascular risk and mortality.[74 75] Consequently, most clinical guidelines used LDL-c levels as a measure to determine overall cardiovascular risk and set treatment goals.[6 31] For example, AGLA recommends target goals for very high, high and moderate risk groups are 70, 100 and 115mg/dL, respectively.[14 76] However, there is conjecture regarding the role of LDL-c in atherosclerosis

and recent publications highlight a lack of association between LDL-c and mortality in specific groups.[77-79] Consequently, the EMA recommends LDL-c as a suitable primary efficacy outcome for hypercholesterolaemia provided the medication's claims are limited to their lipid lowering effect.[68]

HDL is a measure of a variety of lipoproteins (most notable ApoA) and cholesterol.[6] HDL is involved in reverse cholesterol transport and is therefore thought to play an important role in prevention of atherosclerosis.[80] HDL is inversely associated with cardiovascular risk however, a causal relationship between HDL and atherosclerosis has not been established.[6] Contemporary guidelines, including AGLA, do not have treatment goals associated with HDL and the EMA suggests HDL should only be viewed in conjunction with other non-HDL cholesterol markers to determine the efficacy of lipid-lowering drugs.[68]

Triglycerides are a measure of circulating fat which are typically carried throughout the body in lipoproteins.[81] Triglycerides are associated with an increased risk of CVD and are routinely used in clinical risk calculators;[31] however, the association between triglycerides and CVD is minimal after adjusting for non-HDL-c (an estimate of all Apo-B-containing lipoproteins).[81-84] This reflects the hypothesis that the cholesterol component of triglyceride rich lipoproteins are responsible for atherosclerosis and CVD, rather than triglycerides themselves.[81] Like HDL, the EMA recommends triglycerides should be viewed in conjunction with other non-HDL cholesterol to determine the efficacy of lipid-lowering drugs.[68]

Total cholesterol is a composite measure of LDL-c, HDL and other lipid components. Total cholesterol levels are associated with the risk of developing CVD in adults and is therefore included in risk calculators.[31 85 86] However, guidelines recommend total cholesterol should only be viewed in the context of other lipoprotein markers or when those markers are unavailable.

Vascular damage, as inferred by narrowed blood vessels or increased atherosclerotic plaque size are markers of atherosclerosis progression. These pathological changes are typically measured using imagining techniques such as intravascular ultrasound (IVUS) and magnetic resonance imaging.[68] Importantly, vessel width (generally, intima media thickness measurement) and plaque volume as measured using these techniques correlate with end-point cardiovascular events such stroke, heart disease and death;[87] however, it is unclear whether imaging of vascular damage is limited to research settings or if it is utilised in clinical practice.

For efficacy- and effectiveness-related outcomes, RCTs, non-randomised controlled trial (non-RCTs), cohort studies, case series and pharmacovigilance/insurance databases are eligible for inclusion. RCTs will be prioritised over other levels of evidence. In the absence of, lower levels of evidence will be considered. The minimum length of follow-up is 12 months for efficacy and effectiveness-related studies.

5.4.2 Safety

5.4.2.1 Critical

Withdrawal or discontinuation due to adverse events or serious adverse events are the critical safety outcomes. These outcomes reflect the principle that patients should not be harmed in the process of treating their illness. In this context, a serious adverse event is characterised as an event that is life-threatening, requires hospitalisation, is disabling or permanently damaging, requiring intervention, causes death, or any other event deemed serious by the study investigators.[88] While the definition of serious may vary according to the study investigators, it is inappropriate to retrospectively apply the International Council for Harmonisation of Technical Requirements for Pharmaceutical for Human Use guidelines[89] to the studies given adverse events are often under-reported and lack detail. Therefore, any adverse events noted as serious by the study investigators will be included.

5.4.2.2 Important

Biochemical markers of liver or muscle injury and treatment compliance are important safety outcomes. Liver dysfunction and myalgia are relatively common adverse events experienced by patients taking statins, and often contribute to their discontinuation.[82] Consequently, routine monitoring of liver and muscle biomarkers is recommended. For liver dysfunction alanine aminotransferase (ALT) and aspartate aminotransferase (AST) are the most common measures. Creatine kinase (CK) is an indicator of muscle damage.

Treatment compliance, as assessed by pill counts, is the degree to which the patient adheres to the treatment regimen. Noncompliance is considered an important indicator of adverse events or negative attitude towards the therapy.[90]

For safety-related outcomes, RCTs, non-RCTs, cohort studies, case series and pharmacovigilance/insurance databases are eligible for inclusion. There is no minimum follow-up duration for safety-related studies.

5.5 PICO-Box

Table 4 Study selection criteria

P:	1. Patients who have primary (hetero- and homozygous familial and non-familial) hypercholesterolaemia with or without pre-existing ASCVD. 2. Patients who have mixed/combined hyperlipidaemia with or without pre-existing ASCVD. ***Sub-groups:*** *Children and adolescents, elderly (> 65 years), sex and individuals with diabetes, metabolic syndrome or statin-intolerance, AGLA risk categories, primary and secondary prevention populations.* ***Exclusion***: *Predominantly Asian, African and Latin-American populations.*
I & C:	1. Intervention: Ezetimibe monotherapy Comparator: Placebo, statin or fenofibrate 2. Intervention: Ezetimibe in combination with any statin licensed in Switzerland (fixed or free) Comparator: Statin, statin plus placebo 3. Intervention: Ezetimibe in combination with fenofibrate (fixed or free) Comparator: Fenofibrate, fenofibrate plus placebo ***Sub-groups for intervention:*** *ezetimibe in combination with atorvastatin, fluvastatin, pitavastatin, pravastatin, simvastatin or rosuvastatin.* ***Sub-groups for comparators:*** *atorvastatin, fluvastatin, pitavastatin, pravastatin, simvastatin or rosuvastatin*. ***Exclusion criteria:*** *niacin, n-3 fatty acids, bile sequestrants, cholesteryl ester transfer protein inhibitors, LDL apheresis, lomitapide and mipomersen, PCSK9 inhibitor.*

O:	**Efficacy/effectiveness[a]:**
	
	Critical outcomes
	• Major adverse cardiovascular events (defined as non-fatal stroke, non-fatal myocardial infarction and cardiovascular mortality)
	  ○ Non-fatal myocardial infarction[b]
	  ○ Non-fatal ischaemic stroke
	  ○ Cardiovascular mortality
	• Non-cardiovascular mortality
	• Coronary revascularisation
	• Hospitalisation for unstable angina
	• Health-related quality of life

Important outcomes

- Change in LDL-c concentration
- Change in HDL concentration
- Change in triglyceride concentration
- Change in total cholesterol concentration
- Vascular damage

Safety[c]:

Critical outcomes

- Severe treatment-related adverse events
- Withdrawal (i.e. treatment cessation) due to adverse events

Important outcomes

- Biochemical markers of liver or muscle injury
- Treatment compliance

Exclusion criteria: *Non-invasive imaging techniques detecting plaque burden, artery calcification or narrowing.*

E: **Economic outcomes**

- Costs
- Cost-effectiveness/utility
- Projected budgetary impact

Abbreviations

ACS = acute coronary syndrome, **ASCVD** = atherosclerotic cardiovascular disease, **HDL** = high density lipoprotein; **LDL-c** = low-density lipoprotein cholesterol, **PCSK9** = proprotein convertase subtilisin/kexin type 9, **RCTs** = randomised controlled trials.

Notes

a = Efficacy and effectiveness studies require a minimum follow-up period of at least 12-months.
b = MACE will be evaluated as a composite outcome. In addition, the individual outcomes will be analysed separately.
c = Safety outcomes have no minimum follow-up period.

6 HTA key questions

For the evaluation of the technology the following key questions covering the central HTA domains, as designated by the EUnetHTA Core Model (clinical effectiveness, safety, costs, cost-effectiveness, budget impact, legal, social, ethical and organisational aspects), are addressed:

1. Are ezetimibe monotherapy, ezetimibe-statin and ezetimibe-fenofibrate combination therapies effective/efficacious compared to placebo, fenofibrate or statin monotherapy?
2. Are ezetimibe monotherapy, ezetimibe-statin and ezetimibe-fenofibrate combination therapies safe compared to placebo, fenofibrate or statin monotherapy?
3. What are the costs associated with ezetimibe monotherapy, ezetimibe-statin and ezetimibe-fenofibrate combination therapies?
4. How cost-effective are ezetimibe monotherapy, ezetimibe-statin and ezetimibe-fenofibrate combination therapies compared to placebo, fenofibrate or statin monotherapy?
5. What is the budget impact of limiting the indication for reimbursement for ezetimibe monotherapy, ezetimibe-statin and ezetimibe-fenofibrate combination therapies?
6. Are there legal, social or ethical issues related to limiting the indication for reimbursement for ezetimibe monotherapy, ezetimibe-statin and ezetimibe-fenofibrate combination therapies?
7. Are there organisational issues related to limiting the indication for reimbursement for ezetimibe monotherapy, ezetimibe-statin and ezetimibe-fenofibrate combination therapies?

6.1 Additional question(s)

In addition to the key questions for the HTA report, the additional sub-questions from the EUnetHTA Core Model will be investigated:

1. *Safety*: Are the harms related to dosage or frequency of ezetimibe monotherapy, ezetimibe-statin and ezetimibe-fenofibrate combination therapies? (Element ID C0002)
2. *Effectiveness*: Will limiting the indication for reimbursement of ezetimibe monotherapy, ezetimibe-statin and ezetimibe-fenofibrate combination therapies modify the need for hospitalisation? (Element ID D0010)
3. *Resource utilisation*: How do ezetimibe monotherapy, ezetimibe-statin and ezetimibe-fenofibrate combination therapies modify the need for other technologies and use of resources? (Element ID D0023)
4. *Ethics*: What are the ethical consequences of the choice of endpoints, cut-off values and comparators/controls in the assessment? (F0017)

5. *Ethics*: Are there any ethical problems related to the data or the assumptions in the economic evaluation? (Element ID F0102)
6. *Organisational*: What kind of patient/participant flow is associated with limiting the indication for reimbursement for ezetimibe monotherapy, and ezetimibe-statin and ezetimibe-fenofibrate combination therapies to specific sub-groups? (Element ID G0100)

7 Methodology literature search

7.1 Databases and search strategy

A systematic literature search for the efficacy, effectiveness, safety, cost-effectiveness and budgetary impact of ezetimibe-containing medicines was conducted in eight biomedical databases (PubMed, Embase, Cochrane Library, CINAHL, York Centre for Reviews and Dissemination, EconLit, CEA Register and ETHMED (up to September – December 2019). In addition, the websites for HTA agencies were searched to identify relevant HTA reports that included cost-effectiveness analysis (CEA). Search terms consisted of a combination of key words and medical subject headings (MeSH) relating to ezetimibe. The full search strategy for each database is reported in ***Appendix A: Sources of Literature (databases)***. Search filters were applied to limit the results to humans and exclude conference abstracts. All languages were screened by title and abstract. However, the study selection was limited to English, French or German languages. Relevant studies in additional languages were identified to estimate the likelihood of language bias in the search results.

Study selection was conducted in duplicate by two authors. Both authors independently reviewed all records by title and abstracts, and then full text. Title and abstract selection were conducted using Rayyan software (QCRI, Hamad Bin Khalifa University). Differences in study selections were settled via consensus at each stage of the selection process. During the full-text screen, studies with a predominant Asian, African Central and South American trial population were excluded as they do not reflect the Swiss context and they have different cardiovascular risk profiles compared to Western populations.[91-93] Studies were considered eligible if they met the PICO criteria and were an RCT, non-RCTs, cohort study, case series or pharmacovigilance/insurance databases. Further, for efficacy and effectiveness studies, a minimum follow-up period of at least 12 months was required. There was no minimum follow-up period for safety outcomes. For economic studies, studies evaluating cost, cost-effectiveness/utility, or projected budgetary impact were considered eligible. Studies addressing any legal, social, ethical or organisational issue associated with ezetimibe were additionally included.

7.2 Other sources

Ongoing or unpublished clinical trials were searched in five clinical trial databases (ClinicalTrals.gov, Cochrane Central Register of Controlled Trials, EU Clinical Trials Registry, World Health Organization International Clinical Trials Registry Platform, Current Controlled Trials MetaRegister and Australian New Zealand Clinical Trials Registry). For the list of ongoing clinical trials refer to ***Appendix D: List of ongoing clinical trials***.

Targeted keyword searches for literature related to the social, legal, ethical and organisational domains were conducted in the grey literature, administrative and industry-specific websites outlined in ***Appendix A***.

8 Synthesis of evidence base

8.1 Overall search results

The results of the systematic literature searches are presented in ***Figure 3***. Databases searches and pearling of relevant studies identified 14,003 studies. After removal of duplicates, 9,824 studies were reviewed by title and abstract, of which 245 were reviewed by full-text. A total of 96 studies met the inclusion criteria for the report of which: 76 studies evaluated clinical outcomes; 12 studies evaluated economic outcomes; and 8 studies evaluated ethical, legal, organisational or social issues.

All the clinical studies were RCTs of which 70 were original studies and 6 were extensions trials. Ezetimibe was studied as an individual medicine or in fixed/free combination (with a statin or fenofibrate) in 16 and 73 studies, respectively (noting 13 studies assessed both forms).

Twelve studies performing economic analysis were considered relevant, with most studies performing Markov models and reporting cost per QALY gained. Eight studies evaluating the ethical, social or organisational issues were identified and considered relevant to the scoping report.

The included studies are as follows:

- **Efficacy**
    - 7 RCTs compared ezetimibe (in combination with a statin or fenofibrate) to statins or fenofibrate
- **Effectiveness**
    - 0 RCTs compared ezetimibe (in combination or by itself) to statins or fenofibrate
- **Safety**
    - 76 RCTs compared ezetimibe (in combination or by itself) to statins, fenofibrate, or placebo
- **Economic**
    - 12 Economic analysis studies
- **Ethical, legal and social**
    - 1 Ethical study (1 commentary)
    - 0 Legal
    - 6 Social studies (4 surveys and 2 analyses of registries)
- **Organisational**
    - 1 Organisational study (1 analysis of databases)

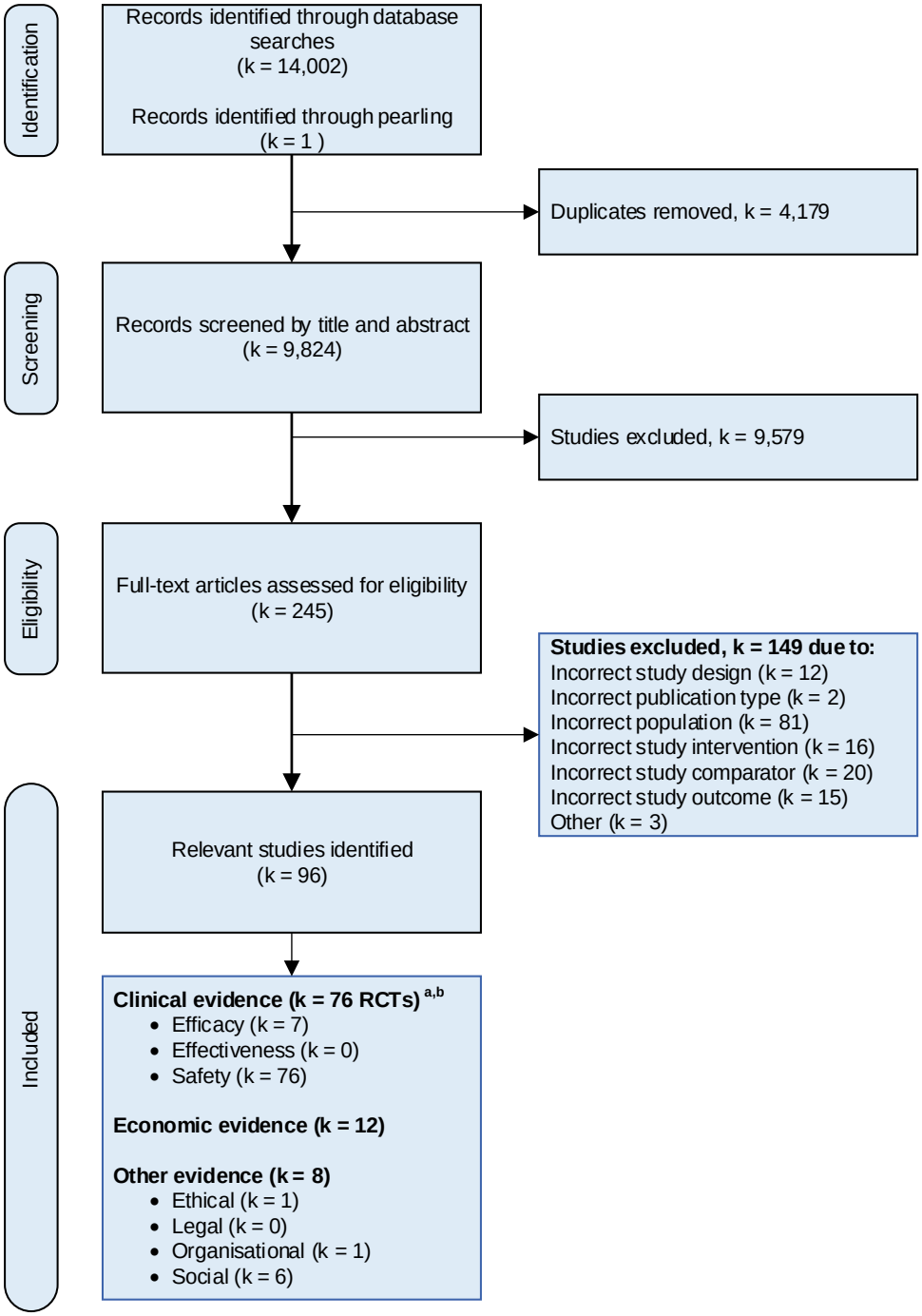

Figure 3 PRISMA flow chart for study inclusion

Abbreviations

RCT = randomised controlled trial.

Notes

a = For the scoping report only RCT data is presented, however, lower levels of evidence will not necessarily be excluded from the HTA phase.

b = A total of 76 clinical studies (RCTs) were included: 7 studies considered efficacy outcomes, 76 considered safety outcomes. Seven studies reported both safety and efficacy data.

8.2 Evidence base pertaining efficacy, effectiveness and safety

The evaluation of the overall effectiveness of the technology encompasses its efficacy, its effectiveness and its safety.

- Efficacy is the extent to which a specific health technology produces a beneficial, reproducible result under study conditions compared with alternative technologies (internal validity).
- 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 (external validity).
- 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 (serious adverse events) and those that occur repetitively and the most frequent (highest rate).

8.2.1 Search results

Overall, 76 RCTs were included, of which 70 were original studies and 6 were extensions trials. Given that the extension studies were conducted in the same location and contained all, or part, of the original trial's population, their characteristics (except for outcomes) will not be discussed below to prevent double-counting of the evidence base.

The included studies were predominately multicentre trials (k = 53) conducted in Europe (k = 39) or North America (k = 36). Several multicentre trials (predominately in Europe or North America) also included study locations in Africa, Asia, Australia or South America (k = 9). While the latter countries are unlikely to be representative of the Swiss population, they were part of larger international trials which pooled results across European and non-European countries. No study was fully conducted in Switzerland. Two international multicentre trial had centres in Switzerland, however, the exact location was not reported. There were 25 studies which were fully or partially conducted in central/western European countries including Austria, Belgium, Croatia, France, Germany, Poland and The Netherlands. It is likely the population in these studies are more generalizable to the Swiss context than trials outside this region.

8.2.2 Evidence table

A detailed extraction table reporting the characteristics of identified studies, including the extension trials are outlined in ***Appendix B: Characteristics of included trials***, ***Table 27*** and ***Table 28***.

8.2.3 Findings regarding efficacy, effectiveness and safety

Ezetimibe was studied primarily in the context of primary hypercholesterolaemia, undefined dyslipidaemia/hypercholesterolaemia and CHD (k = 17, 12 and 12, respectively). Patients with hypercholesterolaemia or dyslipidaemia typically required LDL-c levels between 130 – 200mg/dL and triglycerides below 400mg/dL in order to be eligible for the study. In contrast, the LDL-c requirement for patients with CHD was generally lower (100 – 160mg/dL) likely reflecting their increased risk or achievable treatment goals. Patient populations with elevated cholesterol, familial hypercholesterolaemia, mixed/combined hyperlipidaemia and dyslipidaemia were infrequently studied patient populations (k = 10). As were patients with CVD, ACS, myocardial infarction, recent vascular surgery, aortic stenosis and peripheral artery disease (k = 11). Three trials studied ezetimibe in specific patient populations - children[94], adolescents[95] and individuals aged greater than 65 years.[96] The median sample size of all trials was 366, ranging from 18 to 18,114.

Ezetimibe was administered in tablet form by itself, or in combination with a statin or fenofibrate. The dose of ezetimibe was fixed (10mg) across all studies; however, the dose of the combined statin varied from 10 to 80mg. Fenofibrate was dosed between 145 – 200mg. More studies evaluated ezetimibe in combination with statins (k = 61) than in combination with fenofibrate (k = 4) or ezetimibe alone (k = 19). Ezetimibe combined with simvastatin (k = 36) was the most frequently studied combination, noting the dose of simvastatin ranged from 10 to 80mg. Other ezetimibe-statin combinations including: rosuvastatin, fluvastatin and pravastatin were infrequently studied (k ranging from 1 to 4 studies). Five studies did not specify the type of statin in combination with ezetimibe.

The median follow-up time for safety and efficacy studies was 12 weeks ranging from 1 week to 7 years with most studies having follow-up times less than a year. Consequently, there are relatively few trials with sufficient follow-up duration assessing efficacy outcomes (k = 7) – noting the median sample size for efficacy studies are 262 patients.

The critical safety outcomes; adverse events, and withdrawals due to adverse events were the most frequently reported outcome (k = 74 and 72, respectively). Important safety outcomes; tolerability, and biochemical adverse events, were reported in 67 and 34 studies, respectively. The median length of follow up for safety studies was 12 weeks, ranging from 1 - 2 weeks to 7 years (depending on the outcome).

Total cholesterol, LDL-c and HDL levels (important outcomes) were the most frequently studied efficacy outcomes (k = 7 for each outcome). Four studies reported the critical efficacy outcome MACE and three studies evaluated the important outcome, vascular damage. No study reported health-related quality of life. The median length of follow up for efficacy outcomes is one year. However, the range differed

considerably: one to seven years. A summary of the number of studies reporting safety, efficacy and effectiveness outcomes per population is provided in ***Table 5***.

Table 5 Number of studies identified for the relevant outcomes

Outcome	**All populations** **Median (range)**
Efficacy	
MACE	k = 4 Follow-up = 1.5yrs (1 – 7yrs)
Cardiovascular mortality	k = 5 Follow-up = 1yr (1 – 7yrs)
Stroke	k = 3 Follow-up = 2yrs (1 – 7yrs)
Myocardial infarction	k = 3 Follow-up = 2yrs (1 – 7yrs)
Coronary revascularisation	k = 2 Follow-up = 4.5yrs (2 – 7yrs)
Hospitalisation for unstable angina	k = 2 Follow-up = 4yrs (1 – 7yrs)
Non-cardiovascular mortality	k = 5 Follow-up = 1yr (1 – 7yrs)
Health related quality of life	k = 0
HDL	k = 7 Follow-up = 1yr (1 – 7yrs)
LDL-c	k = 7 Follow-up = 1yr (1 – 7yrs)
Total cholesterol	k = 7 Follow-up = 1yr (1 – 7yrs)
Total triglycerides	k = 6 Follow-up = 1yr (1 – 7yrs)
Vascular damage	k = 3 Follow-up = 1yr (1 – 2yrs)
Safety	
Withdrawal due to adverse events	k = 72 Follow-up = 12wks (2wks – 7yrs)
Adverse events	k = 74 Follow-up = 12wks (1wks – 7yrs)
Biochemical marker of liver or muscle damage	k = 67 Follow-up = 12wks (2wks – 7yrs)
Treatment compliance	k = 34 Follow-up = 12wks (4wks – 2yrs)

Abbreviations
k = number of studies, **wks** = weeks, **yrs** = years.

8.2.4 Quality of evidence assessment

Most trials were double-blinded (k = 59), with few single-blind (k = 4) and open label (k = 9) studies. Four trials did not report blinding information. It is worth noting many studies utilized a 'wash-out' (a period where the subject tapers of existing medication and starts on the study-designated statin/fenofibrate) followed by a single-blind lead in period in which the participant started a specific diet, discontinued their existing medication and started on the placebo or a background drug. Following this period, the intervention and comparator medication were administered in a double-blind manner. Blinding is pertinent for subjective outcomes such adverse events to ensure that the effect estimates are unbiased. A full investigation of risk of bias will be conducted in the HTA report, using the Cochrane Risk of Bias tool for RCTs version 2.0.

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

8.3.1 Search results

A total of 26 studies identified in the systematic literature searches were reviewed by full-text for relevancy. The study selection focused on evaluations which were in line with the PICO, and priorities were given to studies which investigated populations from Europe or North America. Studies modelled in Asian, African and South American populations were treated with lower priorities due to the potential differences in how statin and ezetimibe are metabolised in those populations, cardiovascular disease risk, medical practice patterns, and pricing structures.[91-93] Also, studies including non-relevant drugs and regimens such as PCSK9 inhibitors were excluded. As the result of the full-text study selection, 12 studies were considered relevant and the remaining 14 studies were excluded.

8.3.2 Evidence table

A detailed extraction table reporting the characteristics of the included studies are outlined in ***Table 29*** (***Appendix C***).

8.3.3 Findings regarding costs, cost-effectiveness and budget impact

Statin regimen variations

Among the 12 relevant studies, 2 compared ezetimibe (as a monotherapy or combination therapy) to no treatment[106 107] and 10 compared ezetimibe (as a monotherapy or in combination with a statin) to a satin.[97-105 108] The statin regimens included atorvastatin, cerivastatin, fluvastatin, lovastatin, pravastatin,

rosuvastatin and simvastatin, in dosages variations ranging from 5mg up to 120mg. Two studies among this group did not specify statin regimens in detail.[100 107]

Table 6 provides an overview of the type and dose of the statins utilised across the included trials. Importantly, all trials compared statins to ezetimibe in fixed combination or by itself. The colour in each cell reflects the number of studies evaluating the specific statin regime; the darker the cell colour the more studies evaluating that particular dose and type of statin. The most common regimens include the atorvastatin in 20mg (9 studies) and 40mg (8 studies) and simvastatin in 20mg (6 studies) and 40mg (8 studies). The most commonly evaluated dosages for all statins were 10mg, 20mg and 40mg.

Table 6 Number of studies evaluating statins by type and dose

# of studies	5 mg	10 mg	20 mg	30 mg	40 mg	50 mg	60 mg	80 mg	120 mg
Atorvastatin		7	9	1	8	1	1	6	
Simvastatin		5	6	1	8	1	1	5	1
Rosuvastatin	2	4	5		3			1	
Pravastatin		3	3		3		1	1	
Lovastatin		1	2		2		1	1	1
Fluvastatin			2		2			1	
Cerivastatin*			1		1		1	1	

Notes
* = The regimen for cerivastatin was mg divided by 10.

Economic evaluation: Perspectives

The economic evaluations mostly took a healthcare payer's perspective. Four studies explicitly evaluated the health economic outcome of ezetimibe at the government and health system level.[98 100 104 107]

Economic evaluation: Populations in the studies

Regarding the modelled populations, most of the studies investigated patients at high-risk for cardiovascular conditions. The selection criteria were broadly in line with the population in the PICO. A history of CHD was used to select patients in seven studies,[98-101 104 105 107] with one study requiring patients to be hospitalised due to an ACS event.[104] Two studies investigated patients who were statin intolerant or contraindicated to statins as the eligibility to ezetimibe.[97 106] One study reported that patients would receive ezetimibe plus statin as a combination therapy if they could not achieve an LDL-c therapeutic goal pre-specified by a guideline program.[103] The remaining studies (k = 2) did not have specific eligibility requirements.[102 108] Therefore, four studies (1 for ACS hospitalisation requirement, 1 for statin failure and 2 for intolerance) performed an economic evaluation exclusively on the restricted population proposed in the policy question for this review.

Economic evaluation: Modelling techniques and uncertainty reduction

Most of the included studies were published in 2010 or earlier, with only two exceptions conducted in 2017[99] and in 2015.[101] As most of the studies were model-based economic evaluations (except one study using an unconventional "treat-to-target" method to accrue effects and costs)[103], long-term extrapolations were a shared feature where all extrapolations projected the disease process to a life-time. Five studies also did step evaluations where the cost-effectiveness at shorter time horizons were also produced, ranged from a short 2-year follow-up, up to 45-year extrapolations.[106 107 100 98 97]

Most of the included studies used similar modelling techniques. Cost and effectiveness in the long-term were accrued via Markov state transition models in all except two studies.[103 108] One study performed the economic evaluation using actuarial methodologies only targeting survived patients.[108] This could be considered as a dual state-transition model only with alive and dead states. The other did not use a modelled technique to evaluate the health economic outcome between statins and ezetimibe.[103] Annual costs were calculated based on a clinical endpoint and compared between statin regimens and the combination therapy of statin plus ezetimibe.

Among the studies that did use state-transition models for their economic evaluations, a common set of health states were shared across the included studies. It included myocardial infarction, angina, stroke, peripheral artery diseases, heart failures and transient ischaemic attacks. Some of the events can be fatal, hence the corresponding cause-specific death states were also introduced. The number of health states ranged from 4 to 28 depending on the modelling approach. Nevertheless, three health states mentioned above (myocardial infarction, angina and stroke) were the most commonly incorporated in their model structure. ***Table 7*** summarises the key health states used among the included studies.

Table 7 Summary of modelling information from the included studies

Model type	CUA and CEA
Modelling techniques	State transition Markov models
Common health state	Myocardial infarction, angina (stable or non-stable), stroke, peripheral arterial disease, heart failure and transient ischaemic attack Also including cause-specific and non-cause specific death
Quality of life measures	Commonly by EQ-5D, but some not specified
Primary outcomes	Incremental cost per quality of life gained for CUA Incremental cost per life year gained for CEA
Sensitivity analysis	Common targets including drug costs, comparative clinical effectiveness estimates (e.g. risk ratios for cardiovascular disease), utilities and discount. Probabilistic sensitivity analysis was used to elicit parameter uncertainties in some studies

Abbreviations
CUA = cost-utility analysis, **CEA** = cost-effectiveness analysis.

To explore the uncertainties of the modelling results, all the included studies performed sensitivity analysis using parameter variabilities (e.g. confidence intervals or standard deviations) or scenario

analyses. The common variables targeted by sensitivity analyses included drug costs (both statin and ezetimibe), baseline risk of CVD, relative reduction in CHD risk between statin and combination therapy (statin plus ezetimibe) and discount rates, which also varied at the base-case from 3% to 6%. Probabilistic sensitivity analyses and cost-effectiveness acceptability curves were also produced in three studies to facilitate understanding of the parameter uncertainties.[105-107]

Economic evaluation: Cost

Costs included in the economic evaluations can be categorised into three groups: i) medication costs, ii) costs of medical services related to the prescription of drugs and the management of relevant clinical events, and iii) costs involved in managing adverse effects due to the use of different drugs. Among the included studies, these costs were either identified from publicly available sources such as government information outlets (e.g. reimbursement pricing for drugs and services) or retrieved from private sources including pricing provided by pharmaceutical companies and the current market price.

Economic evaluation: Outcome

Incremental cost per quality of life gain was the primary outcome in nine studies,[97 99-102 104-107] of which EQ-5D was the quality of life measure in five.[97 99 105-107] The other four studies did not report the specific quality of life measure used in their model. Survival-specific outcomes, including cost per life year gained via the calculation of potential years of life lost, were also considered by six studies;[97 98 100 101 103 108] two of these examined the cost per life year gained as their exclusive economic outcomes without considering quality of life measures.[98 108] One study also investigated cost per percentage reduction of LDL-c as the economic outcome in addition to the evaluation of costs on survival benefits.[103]

Summary

Although many relevant studies were identified that compared the cost-effectiveness of ezetimibe and its comparator, the applicability of these studies to Swiss context is limited. None of the studies conducted the economic evaluations in the context of Swiss health system. Systemic differences in how drugs are priced as well as how services were accrued could be different compared to other health systems. Therefore, the outcome of the economic evaluations from the included studies are unlikely to be transferable. The populations modelled in the included studies were broadly in line with the PICO criteria proposed in this scoping report but lack the specific characteristics proposed in the policy question (see ***Section 1***). Finally, the studies were relatively old with most of them conducted more than 10 years ago. More up-to-date clinical and cost data are available that may alter the results of the existing models, especially given the publication of the largest RCT to date in 2015.[45]

8.4 Evidence base pertaining to ethical, legal and social issues

8.4.1 Evidence table

The systematic literature search identified limited evidence regarding ethical, legal and social issues associated with ezetimibe. Relevant studies are summarised in ***Table 8***.

Table 8 List of included studies evaluating ethical, legal and social issues

Author year Location	Study type	Outcomes
Patient and social issues		
Krempf 2015[109] 29 countries	Survey of physicians	Factors affecting physician's treatment recommendations for hypercholesterolaemia.
Kwok 2016[110] United Kingdom	Survey of physicians	Knowledge and adherence of guidelines and treatment recommendation for familial hypercholesterolaemia.
Setia 2015[111] Singapore	Survey of physicians	Knowledge and adherence of guidelines and treatment recommendation for atherosclerotic cardiovascular disease.
Tokgozoglu 2016[112] Turkey	Survey of patients	Identification of factors that influence adherence and discontinuation of lipid-lowering therapy.
Umeda 2019[113] Japan	Analysis of national pharmacy claims database	Identification of patient demographic factors that influence adherence and discontinuation of lipid-lowering therapy.
Wallach-Kildemoes 2015[114] Denmark	Analysis of national prescription registry	Identification of patient demographic factors that influence the utilisation of lipid-lowering therapies.
Ethical issues		
Greenland 2008[115]	Commentary	Highlights the influence on perceived conflict of interests on trial outcomes.

8.4.2 Findings regarding legal, social and ethical issues

Legal issues

No studies were identified addressing legal issues associated with ezetimibe.

Patient and social issues

Six studies evaluating patient or social perspectives were identified. The studies were from Denmark, Japan, Singapore, Turkey, the UK and the USA and consequently their applicability to Switzerland is uncertain. Three studies sought to determine the influence of patient and physician factors on clinical decision making for hypercholesterolaemia[109-111] and three studies aimed to identify sociodemographic factors influencing the initiation, adherence and discontinuation of ezetimibe. [112] [113] [114]

Ethical issues

One commentary was identified highlighting ethical issues associated with publication, media interpretation and perceived conflicts of interest associated with the ENHANCE trial.[115] While this is set in an American context, many of the issues discussed are likely relevant to a Swiss context.

8.5 Evidence base pertaining to organisational issues

8.5.1 Evidence table

The systematic literature search identified limited evidence regarding legal, social and ethical issues associated with ezetimibe. Relevant studies are summarised in ***Table 9***.

Table 9 List of included studies evaluating organisational issues

Author year Location	Study type	Outcomes
Alsabbagh 2013[116]	Analysis of provincial health administrative databases	Use and cost of ezetimibe as first and second-line treatments over time.

8.5.2 Findings regarding organisational issues

One study was identified evaluating the inappropriate utilization of ezetimibe in Saskatchewan, Canada.[116] The study examined the prevalence and cost of using ezetimibe as a first and second-line treatment (against current recommendations). This study may have implications for Switzerland if ezetimibe is not restricted to specific indications. No other organisational issues were identified.

9 Feasibility HTA

Overall evidence base

This scoping review has identified a large body of evidence evaluating the safety, and moderate body of evidence evaluating the efficacy of ezetimibe. There is sufficient evidence to conduct a meta-analysis comparing ezetimibe in combination with statins to statins for the critical and important safety and efficacy outcomes. Further, there is sufficient evidence to meta-analyse safety outcomes comparing ezetimibe to placebo. There is, however, insufficient evidence to meta-analyse non-statin medications (fenofibrate), or health-related quality of life. Where applicable, these results will be described narratively.

There is insufficient evidence from pragmatic RCTs to evaluate effectiveness; the HTA will need to include non-randomised study designs for the evaluation of effectiveness.

Economic evaluation

A moderate volume of existing economic evaluations of ezetimibe were identified. The generalisability of the existing economic studies is limited, but the existing models provide sufficient information and guidance on which structural elements should be considered for a new economic model. Further, sufficient clinical data have also been identified to support the construction of an independent health economic evaluation. Therefore, it is likely to be feasible to construct a Swiss-specific health economic model to update the cost-effectiveness of ezetimibe fitting the current PICO. Budget impact analysis will investigate the impact of restricting the reimbursement indications for ezetimibe on the Spezialitätenliste.

Social, legal, ethical and organisational evaluation

Limited evidence was identified for organisational, legal, social and ethical issues. An additional non-systematic search will be conducted at the HTA phase to ensue all appropriate literature has been identified.

Additional considerations

There are two ongoing clinical trials which may change the evidence base in the near future:

- NCT03044665, is comparing rosuvastatin to rosuvastatin with ezetimibe for patients with CVD. The trial is actively recruiting an anticipated 3,780 participants. The primary efficacy outcome is MACE at 3 years. The estimated completion date is February 2023.
- 2014-001069-28, is comparing omega-3 supplements compared to statin (with or without ezetimibe). The trial aims to recruit 13,000 patients with hypertriglyceridemia (a form of dyslipidaemia). The primary efficacy outcome is MACE at 5 years. The estimated completion

date is August 2020. It is important to note, it is unclear whether the study will stratify patients by ezetimibe use, thereby providing additional relevant information.

For further information pertaining to clinical trials refer to ***Table 30***.

Conclusion

There is sufficient evidence to undertake a full HTA on the efficacy, safety and economic and budgetary impact of ezetimibe.

10 Outlook

Clinical Evaluation

Where there is sufficient data, the clinical evaluation will include a meta-analysis of published RCTs comparing ezetimibe (in combination or alone) to statins, placebo, or fenofibrate. Where sufficient data is available, subgroup analysis will include:

- statin intolerant vs statin naïve patients
- sex (male vs female)
- at risk patients (children, adolescent and elderly, individuals with diabetes or metabolic syndrome)
- risk categories as specified by AGLA
- risk of bias parameters
- primary and secondary prevention

Where there is insufficient data to perform at meta-analysis, a narrative description of the studies will be performed. If gaps in the evidence base are identified, specifically regarding long-term safety and effectiveness data, lower levels of evidence will be considered (i.e. non-RCTs, cohort and case-control studies).

The populations proposed by the applicant – i.e. i) patients taking statin monotherapies that do not reach proposed LDL targets ii) cannot tolerate high statin monotherapy doses and iii) patients that were hospitalised due to acute coronary syndrome (ACS) – will be addressed through sub-group analysis, where data is available. In the absence of direct evidence, the generalisability/applicability of the broader evidence based to the specific populations will be narratively described to infer the effectiveness and safety of ezetimibe.

Economic Evaluation

If an economic evaluation were to proceed, a de novo evaluation would be required because of the limitations in the existing economic evaluations identified in ***Section 8.2***. Abundant literature and established models are available to inform the general modelling approach. A previous post-market review on ezetimibe conducted by the Pharmaceutical Benefits Scheme in Australia in 2017 also provided important assessment on the performance of various economic models, as well as eluded the key driver of the cost-effectiveness outcome.[117] While the Australian study had investigated some key areas of uncertainties from their included models the safety and effectiveness evidence base will be re-assessed to potentially increase certainty around model assumptions in the context of Swiss health

system. A classification matrix covering outcomes of clinical safety and effectiveness will be used to determine the type of economic evaluation to be conducted (***Table 10***).

Table 10 Classification of economic evaluation types

		Comparative effectiveness			
		Inferior	**Uncertain[a]**	**Non-inferior[b]**	**Superior**
Comparative safety	**Inferior**	Health forgone: need other supportive factors	Health forgone possible: need other supportive factors	Health forgone: need other supportive factors	? Likely CUA
	Uncertain[a]	Health forgone possible: need other supportive factors	?	?	? Likely CEA/CUA
	Non-inferior[b]	Health forgone: need other supportive factors	?	CMA	CEA/CUA
	Superior	? Likely CUA	? Likely CEA/CUA	CEA/CUA	CEA/CUA

Abbreviations
CEA = cost-effectiveness analysis, **CMA** = cost-minimisation analysis, **CUA** = cost-utility analysis.
Notes
? = reflects uncertainties and any identified health trade-offs in the economic evaluation, as a minimum in a cost-consequences analysis;
a = Uncertainty covers concepts such as inadequate minimisation of important sources of bias, lack of statistical significance in an underpowered trial, detecting clinically unimportant therapeutic differences, inconsistent results across trials, and trade-offs within the comparative effectiveness and/or the comparative safety considerations;
b = An adequate assessment of 'non-inferiority' is the preferred basis for demonstrating equivalence

Inputs for the potential economic evaluation will be obtained through a range of sources. The most up-to-date clinical data produced from the systematic review would be ideal to populate the de novo model. Relevant costs will be sourced from the Swiss Tarif System TARMED for outpatient care, diagnosis-related groups (DRGs) for inpatient care, and the Speciality List (Spezialitätenliste) for pharmaceutical interventions. Clinical expert advice will be sought if information cannot be identified through published sources. Key assumptions, particularly those sought from clinical advice, would be investigated via sensitivity analysis. It is likely that this model is to be conducted in TreeAge. To suit the Swiss context, EQ-5D is likely to be used to quantify HRQoL (if CUA is warranted) where Swiss mapping would be sought with priority.

Social, Legal, Ethical, Organisational Issues

Key social, legal, ethical and organisational issues will be summarised narratively based on published literature only. Where appropriate information cannot be identified through systematic searches of the literature, the evaluation will highlight key uncertainties around these domains.

11 References

1. World Health Organisation. Cardiovascular Diseases (CVDs) Fact sheet Geneva: World Health Organisation; 2019 [12 November 2019.

2. Libby P, Buring JE, Badimon L, et al. Atherosclerosis. *Nat Rev Dis Primers* 2019;5(1):56. doi: 10.1038/s41572-019-0106-z.

3. National Heart Lung and Blood Institute. Atherosclerosis ND; Available from: https://www.nhlbi.nih.gov/health-topics/atherosclerosis 10 November 2019.

4. Durrington P. Dyslipidaemia. *Lancet* 2003;362(9385):717-31. doi: 10.1016/S0140-6736(03)14234-1.

5. Karr S. Epidemiology and Management of Hyperlipidemia. *American Journal of Managed Care* 2017;23(9):S139-S48.

6. Mach F, Baigent C, Catapano AL, et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. *Eur Heart J* 2019;31(5556353)

7. Stone NJ, Robinson JG, Lichtenstein AH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Journal of the American College of Cardiology* 2014;63(25 Pt B):2889-934. doi: 10.1016/j.jacc.2013.11.002 [published Online First: 2013/11/19]

8. Berberich AJ, Hegele RA. The role of genetic testing in dyslipidaemia. *Pathology* 2019;51(2):184-92. doi: 10.1016/j.pathol.2018.10.014. Epub 18 Dec 14.

9. Mytilinaiou M, Kyrou I, Khan M, et al. Familial Hypercholesterolemia: New Horizons for Diagnosis and Effective Management. *Front Pharmacol* 2018;9:707.(doi):10.3389/fphar.2018.00707. eCollection 2018.

10. Gaddi A, Cicero AF, Odoo FO, et al. Practical guidelines for familial combined hyperlipidemia diagnosis: an up-date. *Vasc Health Risk Manag* 2007;3(6):877-86.

11. Viljoen A, Wierzbicki AS. Investigating mixed hyperlipidaemia. *BMJ* 2011;343:d5146.(doi):10.1136/bmj.d5146.

12. Catapano AL, Graham I, De Backer G, et al. 2016 ESC/EAS Guidelines for the Management of Dyslipidaemias. *Rev Esp Cardiol (Engl Ed)* 2017;70(2):115. doi: 10.1016/j.rec.2017.01.002.

13. Vrecer M, Turk S, Drinovec J, et al. Use of statins in primary and secondary prevention of coronary heart disease and ischemic stroke. Meta-analysis of randomized trials. *Int J Clin Pharmacol Ther* 2003;41(12):567-77. doi: 10.5414/cpp41567.

14. Arbeitsgruppe Lipide und Atherosklerose. Statin-Intoleranz Familiäre Hyperlipidämien Pocketbook: Arbeitsgruppe Lipide und Atherosklerose, 2019:29.

15. Bhatnagar D, Soran H, Durrington PN. Hypercholesterolaemia and its management. *BMJ* 2008;337:a993.(doi):10.1136/bmj.a993.

16. World Health Organization. Familial Hypercholesterolaemia (FH): Report of a second WHO consultation. Geneva: World Health Organization, 1999.

17. Arbeitsgruppe Lipide und Atherosklerose. Prävention der Atherosklerose Arbeitsgruppe Lipide und Atherosklerose, 2018:37.

18. World Health Organisation. Cardiovascular Diseases Geneva: World Health Organisation, 2019 Available from: https://www.who.int/health-topics/cardiovascular-diseases/ 12 November 2019.

19. World Health Organisation. Raised Cholesterol Geneva: World Health Organisation, ND; 12 November 2019.

20. IHME. HealthData Country Profiles Switzerland: IHME; 2017; Available from: http://www.healthdata.org/switzerland 10 November 2019.

21. World Health Organisation. Noncommunicable Diseases (NCD) Country Profiles Switzerland Geneva: World Health Organisation,; 2018; 12 November 2019.

22. Federal Statistical Office. Death and its main causes in Switzerland, 2016: Federal Statistical Office, 2019.

23. Federal Statistical Office. Swiss Health Survey 2007: Federal Statistical Office, 2008.

24. Marques-Vidal P, Paccaud F. Regional differences in self-reported screening, prevalence and management of cardiovascular risk factors in Switzerland. *BMC Public Health* 2012;12:246.(doi):10.1186/471-2458-12-246.

25. Federal Statistical Office. Swiss Health Survey 2012: Federal Statistical Office, 2013.

26. Zellweger U, Bopp M, Holzer BM, et al. Prevalence of chronic medical conditions in Switzerland: exploring estimates validity by comparing complementary data sources. *BMC public health* 2014;14:1157. doi: 10.1186/1471-2458-14-1157 [published Online First: 2014/11/08]

27. Firmann M, Marques-Vidal P, Paccaud F, et al. Prevalence, treatment and control of dyslipidaemia in Switzerland: still a long way to go. *European Journal of Cardiovascular Prevention & Rehabilitation* 2010;17(6):682-87. doi: 10.1097/HJR.0b013e32833a09ab

28. Nanchen D, Gencer B, Auer R, et al. Prevalence and management of familial hypercholesterolaemia in patients with acute coronary syndromes. *Eur Heart J* 2015;36(36):2438-45. doi: 10.1093/eurheartj/ehv289. Epub 2015 Jul 4.

29. Miserez AR, Martin FJ, Spirk D. DIAgnosis and Management Of familial hypercholesterolemia in a Nationwide Design (DIAMOND-FH): Prevalence in Switzerland, clinical characteristics and the diagnostic value of clinical scores. *Atherosclerosis* 2018;277:282-288.(doi):10.1016/j.atherosclerosis.2018.08.009.

30. Miserez AR, Laager R, Chiodetti N, et al. High prevalence of familial defective apolipoprotein B-100 in Switzerland. *J Lipid Res* 1994;35(4):574-83.

31. Arbeitsgruppe Lipide und Atherosklerose. AGLA Risk Calculator: Arbeitsgruppe Lipide und Atherosklerose, 2019; Available from: https://www.agla.ch/risikoberechnung/agla-risikorechner 10 November 2019.

32. Schweizerisches Heilmittelinstitut (Swissmedic). Product Information Repatha (65622): Schweizerisches Heilmittelinstitut, 2018.

33. Colantonio LD, Kent ST, Huang L, et al. Algorithms to Identify Statin Intolerance in Medicare Administrative Claim Data. *Cardiovascular drugs and therapy* 2016;30(5):525-33. doi: 10.1007/s10557-016-6680-3 [published Online First: 2016/07/09]

34. Banach M, Stulc T, Dent R, et al. Statin non-adherence and residual cardiovascular risk: There is need for substantial improvement. *Int J Cardiol* 2016;225:184-196.(doi):10.1016/j.ijcard.2016.09.075. Epub 16 Sep 26.

35. Serban MC, Colantonio LD, Manthripragada AD, et al. Statin Intolerance and Risk of Coronary Heart Events and All-Cause Mortality Following Myocardial Infarction. *J Am Coll Cardiol* 2017;69(11):1386-95. doi: 10.016/j.jacc.2016.12.036.

36. Toth PP, Patti AM, Giglio RV, et al. Management of Statin Intolerance in 2018: Still More Questions Than Answers. *Am J Cardiovasc Drugs* 2018;18(3):157-73. doi: 10.1007/s40256-017-0259-7.

37. Phan BA, Dayspring TD, Toth PP. Ezetimibe therapy: mechanism of action and clinical update. *Vasc Health Risk Manag* 2012;8:415-27. doi: 10.2147/vhrm.S33664 [published Online First: 2012/08/23]

38. Schweizerisches Heilmittelinstitut (Swissmedic). Product Information Ezetrol® (56195): Schweizerisches Heilmittelinstitut, 2018.

39. Schweizerisches Heilmittelinstitut (Swissmedic). Product Information Ezetimibe MSD®(66551): Schweizerisches Heilmittelinstitut, 2018.

40. Schweizerisches Heilmittelinstitut (Swissmedic). Product Information Inegy® (56953): Schweizerisches Heilmittelinstitut, 2018.

41. Schweizerisches Heilmittelinstitut (Swissmedic). Product Information Atozet® (65223): Schweizerisches Heilmittelinstitut, 2018.

42. Schweizerisches Heilmittelinstitut (Swissmedic). Product Information Ezetimib-Rosuvastatin-Mepha Kapseln (66835): Schweizerisches Heilmittelinstitut, 2018.

43. Brar KS. Ezetimibe (Zetia). *Medical journal, Armed Forces India* 2004;60(4):388-9. doi: 10.1016/s0377-1237(04)80019-4 [published Online First: 2004/10/01]

44. Kosoglou T, Statkevich P, Johnson-Levonas AO, et al. Ezetimibe: a review of its metabolism, pharmacokinetics and drug interactions. *Clin Pharmacokinet* 2005;44(5):467-94. doi: 10.2165/00003088-200544050-00002.

45. Cannon CP, Blazing MA, Giugliano RP, et al. Ezetimibe added to statin therapy after acute coronary syndromes. *New England Journal of Medicine* 2015;372(25):2387-97.

46. Rossebo AB, Pedersen TR, Boman K, et al. Intensive lipid lowering with simvastatin and ezetimibe in aortic stenosis. *BMJ* 2008;337:a1493.(doi):10.1136/bmj.a493.

47. Peto R, Emberson J, Landray M, et al. Analyses of cancer data from three ezetimibe trials. *N Engl J Med* 2008;359(13):1357-66. doi: 10.056/NEJMsa0806603. Epub 2008 Sep 2.

48. Catapano AL, Graham I, De Backer G, et al. 2016 ESC/EAS Guidelines for the Management of Dyslipidaemias. *European Heart Journal* 2016;37(39):2999-3058. doi: 10.1093/eurheartj/ehw272

49. Diabetes U, HEART U, Primary CCS, et al. JBS 2: Joint British Societies' guidelines on prevention of cardiovascular disease in clinical practice. *Heart (British Cardiac Society)* 2005;91:v1.

50. Mattar M, Obeid OJN, health. Fish oil and the management of hypertriglyceridemia. 2009;20(1):41-49.

51. Mattar M, Obeid O. Fish oil and the management of hypertriglyceridemia. *Nutrition and health* 2009;20(1):41-9. doi: 10.1177/026010600902000105 [published Online First: 2009/03/31]

52. Graham IM, Catapano AL, Wong ND. Current guidelines on prevention with a focus on dyslipidemias. *Cardiovascular diagnosis and therapy* 2017;7(Suppl 1):S4-s10. doi: 10.21037/cdt.2017.04.04 [published Online First: 2017/05/23]

53. Stancu C, Sima A. Statins: mechanism of action and effects. *J Cell Mol Med* 2001;5(4):378-87. doi: 10.1111/j.582-4934.2001.tb00172.x.

54. Schweizerisches Heilmittelinstitut (Swissmedic). Product Information Atovastatin-Axapharm (62044): Schweizerisches Heilmittelinstitut, 2018.

55. Schweizerisches Heilmittelinstitut (Swissmedic). Product Information Fluvastatin Mepha 80 retard Depotabs ® (58763): Schweizerisches Heilmittelinstitut, 2018.

56. Schweizerisches Heilmittelinstitut (Swissmedic). Product Information Livazo® (62329): Schweizerisches Heilmittelinstitut, 2018.

57. Schweizerisches Heilmittelinstitut (Swissmedic). Product Information Pravastatin Axapharm (65237): Schweizerisches Heilmittelinstitut, 2018.

58. Schweizerisches Heilmittelinstitut (Swissmedic). Product Information Rosuvastatin Axapharm (66415): Schweizerisches Heilmittelinstitut, 2018.

59. Schweizerisches Heilmittelinstitut (Swissmedic). Product Information Simvastatin Helvepharm (56527): Schweizerisches Heilmittelinstitut, 2018.

60. Fruchart JC, Duriez P. Mode of action of fibrates in the regulation of triglyceride and HDL-cholesterol metabolism. *Drugs Today (Barc)* 2006;42(1):39-64. doi: 10.1358/dot.2006.42.1.963528.

61. Staels B, Dallongeville J, Auwerx J, et al. Mechanism of action of fibrates on lipid and lipoprotein metabolism. *Circulation* 1998;98(19):2088-93. doi: 10.1161/01.cir.98.19.2088.

62. Davidson MH, Armani A, McKenney JM, et al. Safety considerations with fibrate therapy. *The American journal of cardiology* 2007;99(6a):3c-18c. doi: 10.1016/j.amjcard.2006.11.016 [published Online First: 2007/03/21

63. Schweizerisches Heilmittelinstitut (Swissmedic). Product Information Lipanthyl® (52620): Schweizerisches Heilmittelinstitut, 2018.

64. Federal Office of Public Health. Spezialitätenliste (SL): Federal Office of Public Health; 2019; Available from: http://www.xn--spezialittenliste-yqb.ch/Default.aspx 26 November 2019.

65. Hobbs FD. Cardiovascular disease: different strategies for primary and secondary prevention? *Heart* 2004;90(10):1217-23. doi: 10.136/hrt.2003.027680.

66. Qureshi AI, Suri MF, Kirmani JF, et al. The relative impact of inadequate primary and secondary prevention on cardiovascular mortality in the United States. *Stroke* 2004;35(10):2346-50. doi: 10.1161/01.STR.0000141417.66620.09. Epub 2004 Sep 2.

67. Chou R, Dana T, Blazina I, et al. Statins for Prevention of Cardiovascular Disease in Adults: Evidence Report and Systematic Review for the US Preventive Services Task Force. *JAMA* 2016;316(19):2008-24. doi: 10.1001/jama.2015.15629.

68. European Medicines Agency. Guideline on clinical investigation of medicinal products in the treatment of lipid disorders London, United Kingdom: European Medicines Agency,, 2013.

69. Kip KE, Hollabaugh K, Marroquin OC, et al. The problem with composite end points in cardiovascular studies: the story of major adverse cardiac events and percutaneous coronary intervention. *J Am Coll Cardiol* 2008;51(7):701-7. doi: 10.1016/j.jacc.2007.10.034.

70. Rabin R, de Charro F. EQ-5D: a measure of health status from the EuroQol Group. *Ann Med* 2001;33(5):337-43. doi: 10.3109/07853890109002087.

71. Ware J, Jr., Kosinski M, Keller SD. A 12-Item Short-Form Health Survey: construction of scales and preliminary tests of reliability and validity. *Med Care* 1996;34(3):220-33. doi: 10.1097/00005650-199603000-00003.

72. Ware JE, Jr. SF-36 health survey update. *Spine (Phila Pa* 2000;25(24):3130-9. doi: 10.1097/00007632-200012150-00008.

73. Grundy SM, Stone NJ. 2018 American Heart Association/American College of Cardiology Multisociety Guideline on the Management of Blood Cholesterol: Primary Prevention. *JAMA Cardiol* 2019;4(5):488-89. doi: 10.1001/jamacardio.2019.0777.

74. Baigent C, Blackwell L, Emberson J, et al. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. *Lancet* 2010;376(9753):1670-81. doi: 10.016/S0140-6736(10)61350-5. Epub 2010 Nov 8.

75. Di Angelantonio E, Gao P, Pennells L, et al. Lipid-related markers and cardiovascular disease prediction. *JAMA* 2012;307(23):2499-506. doi: 10.1001/jama.2012.6571.

76. Arbeitsgruppe Lipide und Atherosklerose. Diagnosis and target values for dyslipidemias Arbeitsgruppe Lipide und Atherosklerose, 2019; Available from: https://www.agla.ch/atherosklerose/praevention-der-atherosklerose/diagnostik-und-zielwerte-bei-dyslipiamien 10 November 2019.

77. Ravnskov U, de Lorgeril M, Diamond DM, et al. LDL-C does not cause cardiovascular disease: a comprehensive review of the current literature. *Expert Rev Clin Pharmacol* 2018;11(10):959-70. doi: 10.1080/17512433.2018.1519391. Epub 2018 Oct 11.

78. Ravnskov U, Diamond DM, Hama R, et al. Lack of an association or an inverse association between low-density-lipoprotein cholesterol and mortality in the elderly: a systematic review. *BMJ Open* 2016;6(6):e010401. doi: 10.1136/bmjopen-2015-01.

79. Sniderman AD, Williams K, Contois JH, et al. A meta-analysis of low-density lipoprotein cholesterol, non-high-density lipoprotein cholesterol, and apolipoprotein B as markers of cardiovascular risk. *Circ Cardiovasc Qual Outcomes* 2011;4(3):337-45. doi: 10.1161/CIRCOUTCOMES.110.959247. Epub 2011 Apr 12.

80. Nicholls SJ, Nelson AJ. HDL and cardiovascular disease. *Pathology* 2019;51(2):142-47. doi: 10.1016/j.pathol.2018.10.017. Epub 19 Jan 3.

81. Nordestgaard BG, Varbo A. Triglycerides and cardiovascular disease. *Lancet* 2014;384(9943):626-35. doi: 10.1016/S0140-6736(14)61177-6.

82. Wiklund O, Pirazzi C, Romeo S. Monitoring of lipids, enzymes, and creatine kinase in patients on lipid-lowering drug therapy. *Curr Cardiol Rep* 2013;15(9):397. doi: 10.1007/s11886-013-0397-8.

83. Roumeliotis A, Roumeliotis S, Panagoutsos S, et al. Carotid intima-media thickness is an independent predictor of all-cause mortality and cardiovascular morbidity in patients with diabetes mellitus type 2 and chronic kidney disease. *Ren Fail* 2019;41(1):131-38. doi: 10.1080/0886022X.2019.1585372.

84. Simon A, Chironi G, Levenson J. Comparative performance of subclinical atherosclerosis tests in predicting coronary heart disease in asymptomatic individuals. *Eur Heart J* 2007;28(24):2967-71. doi: 10.1093/eurheartj/ehm487. Epub 2007 Oct 29.

85. Jeong SM, Choi S, Kim K, et al. Effect of Change in Total Cholesterol Levels on Cardiovascular Disease Among Young Adults. *J Am Heart Assoc* 2018;7(12).(pii):JAHA.118.008819. doi: 10.1161/JAHA.118.19.

86. Peters SA, Singhateh Y, Mackay D, et al. Total cholesterol as a risk factor for coronary heart disease and stroke in women compared with men: A systematic review and meta-analysis. *Atherosclerosis* 2016;248:123-31.(doi):10.1016/j.atherosclerosis.2016.03.016. Epub 16 Mar 15.

87. Bots ML, Hoes AW, Hofman A, et al. Cross-sectionally assessed carotid intima-media thickness relates to long-term risk of stroke, coronary heart disease and death as estimated by available risk functions. *J Intern Med* 1999;245(3):269-76. doi: 10.1046/j.365-2796.1999.0442f.x.

88. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. Clinical Safety Data Management: Definitions and Standards for Expediated Reporting E2A. In: ICH, ed., 1994:12.

89. ICH. Safety Guidelines ND; Available from: https://www.ich.org/page/safety-guidelines 29 November 2020.

90. Jin J, Sklar GE, Min Sen Oh V, et al. Factors affecting therapeutic compliance: A review from the patient's perspective. *Ther Clin Risk Manag* 2008;4(1):269-86. doi: 10.2147/tcrm.s1458.

91. Chaturvedi N. Ethnic differences in cardiovascular disease. *Heart* 2003;89(6):681-6. doi: 10.1136/heart.89.6.681.

92. Kuller LH. Ethnic differences in atherosclerosis, cardiovascular disease and lipid metabolism. *Curr Opin Lipidol* 2004;15(2):109-13. doi: 10.1097/00041433-200404000-00003.

93. Leigh JA, Alvarez M, Rodriguez CJ. Ethnic Minorities and Coronary Heart Disease: an Update and Future Directions. *Curr Atheroscler Rep* 2016;18(2):9. doi: 10.1007/s11883-016-0559-4.

94. Kusters DM, Caceres M, Coll M, et al. Efficacy and safety of ezetimibe monotherapy in children with heterozygous familial or nonfamilial hypercholesterolemia. *Journal of Pediatrics* 2015;166(6):1377-84.e3.

95. van der Graaf A, Cuffie-Jackson C, Vissers MN, et al. Efficacy and Safety of Coadministration of Ezetimibe and Simvastatin in Adolescents With Heterozygous Familial Hypercholesterolemia. *Journal of the American College of Cardiology* 2008;52(17):1421-29.

96. Zieve F, Wenger NK, Ben-Yehuda O, et al. Safety and Efficacy of Ezetimibe Added to Atorvastatin Versus Up Titration of Atorvastatin to 40 mg in Patients >=65 Years of Age (from the ZETia in the ELDerly [ZETELD] Study). *American Journal of Cardiology* 2010;105(5):656-63.

97. Ara R, Tumur I, or A, et al. Ezetimibe for the treatment of hypercholesterolaemia: a systematic review and economic evaluation. *Health technology assessment (Winchester, England)* 2008b;12(21):iii, xi-xiii, 1-212.

98. Cook JR, Yin D, Alemao E, et al. Cost-effectiveness of ezetimibe coadministration in statin-treated patients not at cholesterol goal: Application to Germany, Spain and Norway. *PharmacoEconomics* 2004;22:49-61.

99. Davies GM, Vyas A, Baxter CA. Economic evaluation of ezetimibe treatment in combination with statin therapy in the United States. *Journal of Medical Economics* 2017;20(7):723-31.

100. Kohli M, Attard C, Lam A, et al. Cost effectiveness of adding ezetimibe to atorvastatin therapy in patients not at cholesterol treatment goal in Canada. *PharmacoEconomics* 2006;24(8):815-30.

101. Laires PA, Ejzykowicz F, Hsu TY, et al. Cost-effectiveness of adding ezetimibe to atorvastatin vs switching to rosuvastatin therapy in Portugal. *Journal of Medical Economics* 2015;18(8):565-72.

102. Nherera L, Calvert NW, Demott K, et al. Cost-effectiveness analysis of the use of a high-intensity statin compared to a low-intensity statin in the management of patients with familial hypercholesterolaemia. *Current Medical Research and Opinion* 2010;26(3):529-36.

103. Plans-Rubi P. The cost effectiveness of statin therapies in Spain in 2010, after the introduction of generics and reference prices. *American Journal of Cardiovascular Drugs* 2010;10(6):369-82.

104. Reckless J, Davies G, Tunceli K, et al. Projected cost-effectiveness of ezetimibe/simvastatin compared with doubling the statin dose in the United Kingdom: Findings from the INFORCE study. *Value in Health* 2010;13(6):726-34.

105. van Nooten F, Davies GM, Jukema JW, et al. Economic evaluation of ezetimibe combined with simvastatin for the treatment of primary hypercholesterolaemia. *Netherlands Heart Journal* 2011;19(2):61-67.

106. Ara R, or A, Tumur I, et al. Cost effectiveness of ezetimibe in patients with cardiovascular disease and statin intolerance or contraindications: A Markov model. *American Journal of Cardiovascular Drugs* 2008c;8(6):419-27.

107. Ara R, or A, Tumur I, et al. Estimating the health benefits and costs associated with ezetimibe coadministered with statin therapy compared with higher dose statin monotherapy in patients with established cardiovascular disease: Results of a Markov model for UK costs using data registries. *Clinical Therapeutics* 2008a;30(8):1508-23.

108. Alonso R, Fernandez de Bobadilla J, Mendez I, et al. Cost-effectiveness of managing familial hypercholesterolemia using atorvastatin-based preventive therapy. *Rev Esp Cardiol* 2008;61(4):382-93.

109. Krempf M, Simpson RJ, Ramey DR, et al. Patient and physician factors influence decision-making in hypercholesterolemia: A questionnaire-based survey. *Lipids in Health and Disease* 2015;14 (1) (no pagination)(45)

110. Kwok S, Pang J, Adam S, et al. An online questionnaire survey of UK general practitioners' knowledge and management of familial hypercholesterolaemia. *BMJ Open* 2016;6 (11) (no pagination)(e012691)

111. Setia S, Fung SSW, Waters DD. Doctors' knowledge, attitudes, and compliance with 2013 ACC/AHA guidelines for prevention of atherosclerotic cardiovascular disease in Singapore. *Vascular Health and Risk Management* 2015;11:303-10.

112. Tokgozoglu L, Ozdemir R, Altindag R, et al. Patient characteristics and statin discontinuation-related factors during treatment of hypercholesterolemia: An observational non-interventional study in patients with statin discontinuation (stay study). *Turk Kardiyoloji Dernegi Arsivi* 2016;44(1):53-64.

113. Umeda T, Hayashi A, Fujimoto G, et al. Medication adherence/persistence and demographics of japanese dyslipidemia patients on statin-ezetimibe as a separate pill combination lipid-lowering therapy: An observational pharmacy claims database study. *Circulation Journal* 2019;83(8):1689-97.

114. Wallach-Kildemoes H, Hansen EH. Sociodemographic and diagnostic characteristics of prescribing a second-line lipid-lowering medication: Ezetimibe used as initial medication, switch from statins, or add-on medication. *European Journal of Clinical Pharmacology* 2015;71(10):1245-54.

115. Greenland P, Lloyd-Jones D. Critical lessons from the ENHANCE trial. *JAMA* 2008;299(8):953-5. doi: 10.1001/jama.299.8.953.

116. Alsabbagh WM, Dagenais J, Yan L, et al. Use and misuse of ezetimibe: analysis of use and cost in Saskatchewan, a Canadian jurisdiction with broad access. *Am J Med* 2014;127(2):145-51. doi: 10.1016/j.amjmed.2013.09.027. Epub 13 Oct 15.

117. Department of Health. Post-market review of ezetimibe 2017; Available from: http://www.pbs.gov.au/info/reviews/post-market-review-ezetimibe 14 Novemeber 2019.

118. Ballantyne CM, Lipka LJ, Sager PT, et al. Long-term safety and tolerability profile of ezetimibe and atorvastatin coadministration therapy in patients with primary hypercholesterolaemia. *International Journal of Clinical Practice* 2004;58(7):653-58.

119. Ballantyne CM, Houri J, Notarbartolo A, et al. Effect of ezetimibe coadministered with atorvastatin in 628 patients with primary hypercholesterolemia: A prospective, randomized, double-blind trial. *Circulation* 2003;107(19):2409-15.

120. Hougaard M, Hansen HS, Thayssen P, et al. Influence of ezetimibe in addition to high-dose atorvastatin therapy on plaque composition in patients with ST-segment elevation myocardial infarction assessed by serial: Intravascular ultrasound with iMap: the OCTIVUS trial. *Cardiovascular Revascularization Medicine* 2017;18(2):110-17.

121. Kastelein JJ, Akdim F, Stroes ES, et al. Simvastatin with or without ezetimibe in familial hypercholesterolemia. *N Engl J Med* 2008;358(14):1431-43. doi: 10.056/NEJMoa0800742. Epub 2008 Mar 30.

122. Kouvelos GN, Arnaoutoglou EM, Matsagkas MI, et al. Effects of rosuvastatin with or without ezetimibe on clinical outcomes in patients undergoing elective vascular surgery: Results of a pilot study. *Journal of Cardiovascular Pharmacology and Therapeutics* 2013;18(1):5-12.

123. Masana L, Mata P, Gagne C, et al. Long-term safety and tolerability profiles and lipid-modifying efficacy of ezetimibe coadministered with ongoing simvastatin treatment: A multicenter, randomized, double-blind, placebo-controlled, 48-week extension study. *Clinical Therapeutics* 2005;27(2):174-84.

124. Gagne C, Gaudet D, Bruckert E. Efficacy and safety of ezetimibe coadministered with atorvastatin or simvastatin in patients with homozygous familial hypercholesterolemia. *Circulation* 2002;105(21):2469-75.

125. West AM, Anderson JD, Meyer CH, et al. The effect of ezetimibe on peripheral arterial atherosclerosis depends upon statin use at baseline. *Atherosclerosis* 2011;218(1):156-62.

126. Alvarez-Sala LA, Cachofeiro V, Masana L, et al. Effects of fluvastatin extended-release (80 mg) alone and in combination with ezetimibe (10 mg) on low-density lipoprotein cholesterol and inflammatory parameters in patients with primary hypercholesterolemia: A 12-week, multicenter, randomized, open-label, parallel-group study. *Clinical Therapeutics* 2008;30(1):84-97.

127. Ansquer JC, Bekaert I, Guy M, et al. Efficacy and safety of coadministration of fenofibrate and ezetimibe compared with each as monotherapy in patients with type IIb dyslipidemia and features of the metabolic syndrome: A prospective, randomized, double-blind, three-parallel arm, multicenter, comparative study. *American Journal of Cardiovascular Drugs* 2009;9(2):91-101.

128. Averna M, Zaninelli A, Le Grazie C, et al. Ezetimibe/simvastatin 10/20 mg versus simvastatin 40 mg in coronary heart disease patients. *Journal of Clinical Lipidology* 2010;4(4):272-78.

129. Ballantyne CM, Blazing MA, King TR, et al. Efficacy and safety of ezetimibe co-administered with simvastatin compared with atorvastatin in adults with hypercholesterolemia. *American Journal of Cardiology* 2004;93(12):1487-94.

130. Ballantyne CM, Weiss R, Moccetti T, et al. Efficacy and Safety of Rosuvastatin 40 mg Alone or in Combination With Ezetimibe in Patients at High Risk of Cardiovascular Disease (Results from the EXPLORER Study). *American Journal of Cardiology* 2007;99(5):673-80.

131. Ballantyne CM, Laufs U, Ray KK, et al. Bempedoic acid plus ezetimibe fixed-dose combination in patients with hypercholesterolemia and high CVD risk treated with maximally tolerated statin therapy. *Eur J Prev Cardiol* 2019;29(2047487319864671):2047487319864671.

132. Bardini G, Giorda CB, Pontiroli AE, et al. Ezetimibe + simvastatin versus doubling the dose of simvastatin in high cardiovascular risk diabetics: A multicenter, randomized trial (the LEAD study). *Cardiovascular Diabetology* 2010;9 (no pagination)(20)

133. Barrios V, Amabile N, Paganelli F, et al. Lipid-altering efficacy of switching from atorvastatin 10 mg/day to ezetimibe/simvastatin 10/20 mg/day compared to doubling the dose of atorvastatin in hypercholesterolaemic patients with atherosclerosis or coronary heart disease. *International journal of clinical practice* 2005;59(12):1377-86.

134. Bays HE, Ose L, Fraser N, et al. A multicenter, randomized, double-blind, placebo-controlled, factorial design study to evaluate the lipid-altering efficacy and safety profile of the ezetimibe/simvastatin tablet compared with ezetimibe and simvastatin monotherapy in patients with primary hypercholesterolemia. *Clinical Therapeutics* 2004;26(11):1758-73.

135. Bays H, Sapre A, Taggart W, et al. Long-term (48-week) safety of ezetimibe 10 mg/day coadministered with simvastatin compared to simvastatin alone in patients with primary hypercholesterolemia. *Current Medical Research and Opinion* 2008;24(10):2953-66.

136. Goldberg AC, Sapre A, Liu J, et al. Efficacy and Safety of Ezetimibe Coadministered with Simvastatin in Patients with Primary Hypercholesterolemia: A Randomized, Double-Blind, Placebo-Controlled Trial. *Mayo Clinic Proceedings* 2004;79(5):620-29.

137. Bays HE, Davidson MH, Massaad R, et al. Safety and efficacy of ezetimibe added on to rosuvastatin 5 or 10 mg versus up-titration of rosuvastatin in patients with hypercholesterolemia (the ACTE Study). *American Journal of Cardiology* 2011;108(4):523-30.

138. Bays HE, Averna M, Majul C, et al. Efficacy and safety of ezetimibe added to atorvastatin versus atorvastatin uptitration or switching to rosuvastatin in patients with primary hypercholesterolemia. *American Journal of Cardiology* 2013;112(12):1885-95.

139. Bays HE, Chen E, Tomassini JE, et al. Fixed-dose combination ezetimibe+atorvastatin lowers LDL-C equivalent to co-administered components in randomized trials: Use of a dose-response model. *Fundamental and Clinical Pharmacology* 2015;29(2):209-18.

140. Blagden MD, Chipperfield R. Efficacy and safety of ezetimibe co-administered with atorvastatin in untreated patients with primary hypercholesterolaemia and coronary heart disease. *Current Medical Research and Opinion* 2007;23(4):767-75.

141. Brohet C, Banai S, Alings AMW, et al. LDL-C goal attainment with the addition of ezetimibe to ongoing simvastatin treatment in coronary heart disease patients with hypercholesterolemia. *Current Medical Research and Opinion*;21(4):571-78.

142. Catapano AL, Davidson MH, Ballantyne CM, et al. Lipid-altering efficacy of the ezetimibe/simvastatin single tablet versus rosuvastatin in hypercholesterolemic patients. *Current Medical Research and Opinion* 2006;22(10):2041-53.

143. Chenot F, Montant PF, Marcovitch O, et al. Co-administration of ezetimibe and simvastatin in acute myocardial infarction. *European Journal of Clinical Investigation* 2007;37(5):357-63.

144. Chirinos JA, Williams MM, Bregman DB, et al. Efficacy of cholesterol uptake inhibition added to statin therapy among subjects following a low-carbohydrate diet: A randomized controlled trial. *American Heart Journal* 2010;159(5):918.e1-18.e6.

145. Conard SE, Bays HE, Leiter LA, et al. Efficacy and Safety of Ezetimibe Added on to Atorvastatin (20 mg) Versus Uptitration of Atorvastatin (to 40 mg) in Hypercholesterolemic Patients at Moderately High Risk for Coronary Heart DiseaseConflicts of interest. *American Journal of Cardiology* 2008;102(11):1489-94.

146. Cruz-Fernandez JM, Bedarida GV, Adgey J, et al. Efficacy and safety of ezetimibe co-administered with ongoing atorvastatin therapy in achieving low-density lipoprotein goal in patients with hypercholesterolemia and coronary heart disease. *International journal of clinical practice* 2005;59(6):619-27.

147. Davidson MH, McGarry T, Bettis R, et al. Ezetimibe coadministered with simvastatin in patients with primary hypercholesterolemia. *Journal of the American College of Cardiology* 2002;40(12):2125-34.

148. Davidson MH, Voogt J, Luchoomun J, et al. Inhibition of intestinal cholesterol absorption with ezetimibe increases components of reverse cholesterol transport in humans. *Atherosclerosis* 2013;230(2):322-9. doi: 10.1016/j.atherosclerosis.2013.08.006. Epub 13 Aug 13.

149. Deharo P, Pankert M, Quilici J, et al. Safety and effectiveness of the association ezetimibe-statin (E-S) versus high dose rosuvastatin after acute coronary syndrome: The SAFE-ES study. *Annales de Cardiologie et d'Angeiologie* 2014;63(4):222-27.

150. Dujovne CA, Ettinger MP, McNeer JF, et al. Efficacy and safety of a potent new selective cholesterol absorption inhibitor, ezetimibe, in patients with primary hypercholesterolemia. *American Journal of Cardiology* 2002;90(10):1092-97.

151. Farnier M, Volpe M, Massaad R, et al. Effect of co-administering ezetimibe with on-going simvastatin treatment on LDL-C goal attainment in hypercholesterolemic patients with coronary heart disease. *International Journal of Cardiology* 2005;102(2):327-32.

152. Farnier M, Freeman MW, Macdonell G, et al. Efficacy and safety of the coadministration of ezetimibe with fenofibrate in patients with mixed hyperlipidaemia. *European Heart Journal* 2005;26(9):897-905.

153. Farnier M, Roth E, Gil-Extremera B, et al. Efficacy and safety of the coadministration of ezetimibe/simvastatin with fenofibrate in patients with mixed hyperlipidemia. *American Heart Journal* 2007;153(2):335.e1-35.e8.

154. Farnier M, Averna M, Missault L, et al. Lipid-altering efficacy of ezetimibe/simvastatin 10/20 mg compared with rosuvastatin 10 mg in high-risk hypercholesterolaemic patients inadequately controlled with prior statin monotherapy - The IN-CROSS study. *Int J Clin Pract* 2009;63(4):547-59. doi: 10.1111/j.742-241.2009.02022.x. Epub 2009 Feb 16.

155. Feldman T, Koren M, Insull Jr W, et al. Treatment of high-risk patients with ezetimibe plus simvastatin co-administration versus simvastatin alone to attain National Cholesterol Education Program Adult Treatment Panel III Low-Density lipoprotein cholesterol goals. *American Journal of Cardiology* 2004;93(12):1481-86.

156. Foody JM, Brown WV, Zieve F, et al. Safety and efficacy of ezetimibe/simvastatin combination versus atorvastatin alone in adults >=65 years of age with hypercholesterolemia and with or at moderately high/high risk for coronary heart disease (the VYTELD study). *American Journal of Cardiology* 2010;106(9):1255-63.

157. Goldberg RB, Guyton JR, Mazzone T, et al. Ezetimibe/simvastatin vs atorvastatin in patients with type 2 diabetes mellitus and hypercholesterolemia: The VYTAL study. *Mayo Clinic Proceedings* 2006;81(12):1579-88.

158. Hing Ling P, Civeira F, Dan A, et al. Ezetimibe/simvastatin 10/40 mg versus atorvastatin 40 mg in high cardiovascular risk patients with primary hypercholesterolemia: A randomized, double-blind, active-controlled, multicenter study. *Lipids in Health and Disease* 2012;11 (no pagination)(18)

159. Japaridze L, Sadunishvili M. The short-term effect of atorvastatin plus ezetimibe therapy versus atorvastatin monotherapy on clinical outcome in acute coronary syndrome patients by gender. *Kardiologia Polska* 2017;75(8):770-78.

160. Jones PH, Goldberg AC, Knapp HR, et al. Efficacy and safety of fenofibric acid in combination with atorvastatin and ezetimibe in patients with mixed dyslipidemia. *American Heart Journal* 2010;160(4):759-66.

161. Knopp RH, Gitter H, Truitt T, et al. Effects of ezetimibe, a new cholesterol absorption inhibitor, on plasma lipids in patients with primary hypercholesterolemia. *Eur Heart J* 2003;24(8):729-41. doi: 10.1016/s0195-668x(02)00807-2.

162. Kosoglou T, Statkevich P, Fruchart JC, et al. Pharmacodynamic and pharmacokinetic interaction between fenofibrate and ezetimibe. *Current Medical Research and Opinion* 2004a;20(8):1197-207.

163. Kosoglou T, Statkevich P, Yang B, et al. Pharmacodynamic interaction between ezetimibe and rosuvastatin. *Current Medical Research and Opinion* 2004b;20(8):1185-95.

164. Kostapanos MS, Spyrou AT, Tellis CC, et al. Ezetimibe treatment lowers indicators of oxidative stress in hypercholesterolemic subjects with high oxidative stress. *Lipids* 2011;46(4):341-8. doi: 10.1007/s11745-011-3539-z. Epub 2011 Feb 26.

165. Krysiak R, Zmuda W, Okopien B. The effect of ezetimibe and simvastatin on hemostasis in patients with isolated hypercholesterolemia. *Fundamental and Clinical Pharmacology* 2012;26(3):424-31.

166. Krysiak R, Zmuda W, Okopien B. The effect of ezetimibe, administered alone or in combination with simvastatin, on lymphocyte cytokine release in patients with elevated cholesterol levels. *J Intern Med* 2012;271(1):32-42. doi: 10.1111/j.365-2796.011.02394.x. Epub 2011 May 30.

167. Kumar SS, Lahey KA, Day A, et al. Comparison of the efficacy of administering a combination of ezetimibe plus fenofibrate versus atorvastatin monotherapy in the treatment of dyslipidemia. *Lipids in Health and Disease* 2009;8(56)

168. Lakoski SG, Xu F, Vega GL, et al. Indices of cholesterol metabolism and relative responsiveness to ezetimibe and simvastatin. *Journal of Clinical Endocrinology and Metabolism* 2010;95(2):800-09.

169. Leiter LA, Bays H, Conard S, et al. Efficacy and Safety of Ezetimibe Added on to Atorvastatin (40 mg) Compared With Uptitration of Atorvastatin (to 80 mg) in Hypercholesterolemic Patients at High Risk of Coronary Heart Disease. *American Journal of Cardiology* 2008;102(11):1495-501.

170. McCormack T, Harvey P, Gaunt R, et al. Incremental cholesterol reduction with ezetimibe/simvastatin, atorvastatin and rosuvastatin in UK General Practice (IN-PRACTICE): Randomised controlled trial of achievement of Joint British Societies (JBS-2) cholesterol targets. *International Journal of Clinical Practice* 2010;64(8):1052-61.

171. McKenney JM, Jones PH, Bays HE, et al. Comparative effects on lipid levels of combination therapy with a statin and extended-release niacin or ezetimibe versus a statin alone (the COMPELL study). *Atherosclerosis* 2007;192(2):432-37.

172. McKenney JM, Farnier M, Lo KW, et al. Safety and Efficacy of Long-Term Co-Administration of Fenofibrate and Ezetimibe in Patients With Mixed Hyperlipidemia. *Journal of the American College of Cardiology* 2006;47(8):1584-87.

173. Melani L, Mills R, Hassman D, et al. Efficacy and safety of ezetimibe coadministered with pravastatin in patients with primary hypercholesterolemia: A prospective, randomized, double-blind trial. *European Heart Journal* 2003;24(8):717-28.

174. Moutzouri E, Liberopoulos E, Mikhailidis DP, et al. Comparison of the effects of simvastatin vs. rosuvastatin vs. simvastatin/ezetimibe on parameters of insulin resistance. *International Journal of Clinical Practice* 2011;65(11):1141-48.

175. Nicholls SJ, Ray KK, Ballantyne CM, et al. Comparative effects of cholesteryl ester transfer protein inhibition, statin or ezetimibe on lipid factors: The ACCENTUATE trial. *Atherosclerosis* 2017;261:12-18.

176. Ose L, Johnson-Levonas A, Reyes R, et al. A multi-centre, randomised, double-blind 14-week extension study examining the long-term safety and efficacy profile of the ezetimibe/simvastatin combination tablet. *International Journal of Clinical Practice* 2007;61(9):1469-80.

177. Ostad MA, Eggeling S, Tschentscher P, et al. Flow-mediated dilation in patients with coronary artery disease is enhanced by high dose atorvastatin compared to combined low dose atorvastatin and ezetimibe: Results of the CEZAR study. *Atherosclerosis* 2009;205(1):227-32.

178. Pandey AS, Bissonnette S, Boukas S, et al. Effectiveness and tolerability of ezetimibe co-administered with statins versus statin dose-doubling in high-risk patients with persistent hyperlipidemia: The EZE(STAT)2 trial. *Archives of Medical Science* 2011;7(5):767-75.

179. Patel JV, Hughes EA. Efficacy, safety and LDL-C goal attainment of ezetimibe 10 mg-simvastatin 20 mg vs. placebo-simvastatin 20 mg in UK-based adults with coronary heart disease and hypercholesterolaemia. *Int J Clin Pract* 2006;60(8):914-21. doi: 10.1111/j.742-241.2006.01023.x.

180. Pearson GJ, Francis GA, Romney JS, et al. The clinical effect and tolerability of ezetimibe in high-risk patients managed in a specialty cardiovascular risk reduction clinic. *Canadian Journal of Cardiology* 2006;22(11):939-45.

181. Reckless JPD, Henry P, Pomykaj T, et al. Lipid-altering efficacy of ezetimibe/simvastatin 10/40 mg compared with doubling the statin dose in patients admitted to the hospital for a recent coronary event: The INFORCE study. *International Journal of Clinical Practice* 2008;62(4):539-54.

182. Robinson JG, Ballantyne CM, Grundy SM, et al. Lipid-Altering Efficacy and Safety of Ezetimibe/Simvastatin Versus Atorvastatin in Patients With Hypercholesterolemia and the Metabolic Syndrome (from the VYMET Study). *American Journal of Cardiology* 2009;103(12):1694-702.

183. Roeters Van Lennep HWO, An HL, Dunselman PHJM, et al. The efficacy of statin monotherapy uptitration versus switching to ezetimibe/simvastatin: Results of the EASEGO study. *Current Medical Research and Opinion* 2008;24(3):685-94.

184. Rosen JB, Jimenez JG, Pirags V, et al. A comparison of efficacy and safety of an ezetimibe/simvastatin combination compared with other intensified lipid-lowering treatment strategies in diabetic patients with symptomatic cardiovascular disease. *Diabetes and Vascular Disease Research* 2013;10(3):277-86.

185. Ruggenenti P, Cattaneo D, Rota S, et al. Effects of combined ezetimibe and simvastatin therapy as compared with simvastatin alone in patients with type 2 diabetes: a prospective randomized double-blind clinical trial. *Diabetes Care* 2010;33(9):1954-6. doi: 10.2337/dc10-0320. Epub 2010 Jun 21.

186. Stein E, Stender S, Mata P, et al. Achieving lipoprotein goals in patients at high risk with severe hypercholesterolemia: efficacy and safety of ezetimibe co-administered with atorvastatin. *Am Heart J* 2004;148(3):447-55. doi: 10.1016/j.ahj.2004.03.052.

187. Stojakovic T, De Campo A, Scharnagl H, et al. Differential effects of fluvastatin alone or in combination with ezetimibe on lipoprotein subfractions in patients at high risk of coronary events. *European Journal of Clinical Investigation* 2010;40(3):187-94.

188. Strony J, Yang B, Hanson ME, et al. Long-term safety and tolerability of ezetimibe coadministered with simvastatin in hypercholesterolemic patients: A randomized, 12-month double-blind extension study. *Current Medical Research and Opinion* 2008;24(11):3149-57.

189. Sudhop T, Lutjohann D, Kodal A, et al. Inhibition of intestinal cholesterol absorption by ezetimibe in humans. *Circulation* 2002;106(15):1943-8. doi: 10.161/01.cir.0000034044.95911.dc.

190. Sudhop T, Reber M, Tribble D, et al. Changes in cholesterol absorption and cholesterol synthesis caused by ezetimibe and/or simvastatin in men. *Journal of Lipid Research* 2009;50(10):2117-23.

12 Appendix A: Sources of Literature (databases)

Table 11 Databases searched and number of search results

Source	Location	Search results
PubMed	https://www.ncbi.nlm.nih.gov	2616
Embase	https://www.embase.com/	8285
The Cochrane Library (inc. CENTRAL)	https://www.cochranelibrary.com/	1696
CINAHL	https://www.ebscohost.com/nursing/products/cinahl-databases/cinahl-complete	1339
York CRD (inc. HTA, NHS EED, DARE)	https://www.crd.york.ac.uk/CRDWeb/	40
CEA Registry	http://healtheconomics.tuftsmedicalcenter.org/cear4/home.aspx	15
Econlit	https://www.aeaweb.org/econlit/	1
ETHMED	http://www.ethicsweb.eu/search_ets	10
	Total	**14002**

Table 12 Search strategy – Ovid/Embase [Inception to 31st December 2019]

Number	Query	Results
1	Ezetimib*.mp.	10963
2	Ezetrol.mp.	254
3	Zetia.mp.	387
4	SCH?58235.mp.	5
5	'58235, SCH'.mp.	5
6	SCH58235.mp.	0
7	'Niemann Pick C1 like 1 protein inhibitor'.mp.	3
8	'NPC1L1 inhibitor'.mp.	27
9	Atozet.mp.	5
10	Inegy.mp.	96
11	Vytorin.mp.	467
12	ezetimibe/	9645
13	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12	10979
14	limit 13 to human	9671
15	limit 14 to (conference abstracts and conference abstract status and conference abstract)	1093
16	limit 14 to conference paper	188
17	limit 14 to conference review	5
18	14 not (15 or 16 or 17)	8385

Table 13 Search strategy – Medline [Inception to 31st December 2019]

Number	Query	Results
1	Ezetimib*	3362
2	Ezetrol	3356
3	Zetia	3359
4	SCH?58235	3356
5	'58235, SCH'	1
6	SCH58235	3355
7	Niemann Pick C1-like 1 protein inhibitor	87
8	NPC1L1 inhibitor	113
9	Atozet	1
10	Inegy	549
11	Vytorin	575
12	Ezetimibe[Mesh]	2062
13	((((((((((Ezetimib*) OR Ezetrol) OR Zetia) OR SCH?58235) OR '58235, SCH') OR SCH58235) OR Niemann–Pick C1-like 1 protein inhibitor) OR NPC1L1 inhibitor) OR Atozet) OR Inegy) OR Vytorin) OR Ezetimibe[Mesh]	3384
14	Filters human	2616

Table 14 Search Strategy – Cochrane [Inception to 31st December 2019]

Number	Query	Results
1	Ezetimib*	1686
2	Ezetrol	37
3	Zetia	28
4	SCH?58235	2
5	'58235, SCH'	16
6	SCH58235	3
7	'Niemann pick C1 like 1 protein inhibitor'	3
8	'NPC1L1 inhibitor'	5
9	Atozet	0
10	Inegy	13
11	Vytorin	96
12	MeSH descriptor: [Ezetimibe] explode all trees	737
13	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12	1696

Table 15 Search strategy – CINAHL [Inception to 31st December 2019]

Number	Query	Results
1	Ezetimib*	1086
2	Ezetrol	4
3	Zetia	18
4	SCH?58235	0
5	'58235, SCH'	3
6	SCH58235	429
7	'Niemann pick C1-like 1 protein inhibitor'	296
8	'NPC1L1 inhibitor'	3
9	Atozet	0
10	Inegy	3
11	Vytorin	71
12	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11	1339

Table 16 Search Strategy – York CRD (including DARE, NHS EED, HTA) [Inception to 31st December 2019]

Number	Query	Results
1	Ezetimibe	35
2	Ezetrol	3
3	Zetia	1
4	SCH?58235	0
5	58235, SCH	0
6	SCH58235	0
7	Niemann Pick C1-like 1 protein inhibitor	0
8	NPC1L1 inhibitor	0
9	Atozet	0
10	Inegy	1
11	Vytorin	0
	Total	40

Table 17 Search strategy – Ethicsweb [Inception to 9th November 2019]

No.	Query	Results
1	Ezetimibe	8
2	Ezetrol	1
3	Zetia	1
4	SCH?58235	0
5	'58235, SCH'	0
6	SCH58235	0
9	Atozet	0
10	Inegy	0
11	Vytorin	0
	Total	10

Table 18 Search strategy – CEA Registry [Inception to 23rd September 2019]

Number	Query	Results
1	Ezetimibe	14
2	Ezetrol	0
3	Zetia	0
4	SCH?58235	0
5	58235, SCH	0
6	SCH58235	0
7	Niemann–Pick C1-like 1 protein inhibitor	0
8	NPC1L1 inhibitor	0
9	Atozet	0
10	Inegy	0
11	Vytorin	1
	Total	15

Table 19 Search strategy – Econlit [Inception to 23rd September 2019]

Number	Query	Results
1	Ezetimibe	1
2	Ezetrol	0
3	Zetia	0
4	SCH?58235	0
5	'58235, SCH'	0
6	SCH58235	0
7	'Niemann–Pick C1-like 1 protein inhibitor'	0
8	NPC1L1 inhibitor	0
9	Atozet	0
10	Inegy	0
11	Vytorin	0
12	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11	1

Table 20 HTA agency websites

HTA Websites	
International	
National Information Centre of Health Services Research and Health Care Technology (NICHSR)	https://www.nlm.nih.gov/nichsr/db.html
National Library of Medicine Health Services/Technology Assessment Texts (HSTAT)	https://www.ncbi.nlm.nih.gov/books/NPBK16710/
International Information Network on New and Emerging Health Technologies (EuroScan International Network)	https://www.euroscan-network.global/index.php/en/47-public-features/761-database-home
Australia	
Adelaide Health Technology Assessment (AHTA)	https://www.adelaide.edu.au/ahta/pubs/
Centre for Clinical Effectiveness, Monash University	http://monashhealth.org/health-professionals/cce/
Centre for Health Economics, Monash University	https://www.monash.edu/business/che
National Health and Medical Research Council	https://www.nhmrc.gov.au/
Australian Safety and Efficacy Register of New Interventional Procedures—Surgical (ASERNIP-S)	https://www.surgeons.org/research-audit/research-evaluation-inc-asernips
Australia & New Zealand	
Health Technology Reference Group (HTRG)	http://www.coagcouncil.gov.au/
Austria	
Institute of Technology Assessment / HTA unit	https://www.oeaw.ac.at/ita/publikationen/
Ludwig Boltzmann Institute for Health Technology Assessment (LBI-HTA)	https://hta.lbg.ac.at/page/publikationen/en
Gesunheit Österreich GmbH (GÖG)	http://www.goeg.at
Hauptverband der Österreichischen Sozialversicherungsträger (HVB)	http://www.sozialversicherung.at
University for Health Sciences, Medical Informatics and Technology	https://www.umit.at
Argentina	
Institute for Clinical Effectiveness and Health Policy (IECS)	http://www.iecs.org.ar
Belgium	
Scientific Institute of Public Health (IPH)	https://www.wiv-isp.be/en
Belgian Health Care Knowledge Centre (KCE)	http://kce.fgov.be
Rijksinstituut voor Ziekte- en Invaliditeitsverzekering (RIZIV-INAMI)	https://www.inami.fgov.be/
Bulgaria	
National Center of Public Health Analyses (NCPHA)	https://www.ncpha.government.bg
Brazil	
National Committee for Technology Incorporation (CONITEC)	http://www.conitec.gov.br/
Canada	
Institute of Health Economics (IHE)	http://www.ihe.ca
Institut National d'Excellence en Santé et en Services (INESSS)	https://www.inesss.qc.ca/en/home.html
Alberta Heritage Foundation for Medical Research (AHFMR)	http://www.ahfmr.ab.ca/
Alberta Institute of Health Economics	http://www.ihe.ca/

The Canadian Agency for Drugs And Technologies in Health (CADTH)	http://www.cadth.ca/
The Canadian Association for Health Services and Policy Research (CAHSPR)	https://www.cahspr.ca/
Centre for Health Economics and Policy Analysis (CHEPA), McMaster University	http://www.chepa.org/
Centre for Health Services and Policy Research (CHSPR), University of British Columbia	http://www.chspr.ubc.ca/
Institute for Clinical and Evaluative Studies (ICES)	http://www.ices.on.ca/
Saskatchewan Health Quality Council (Canada)	http://www.hqc.sk.ca/
Evidence Development and Standards Branch (HQO)	http://www.hqontario.ca
Croatia	
Ministry of Health of the Republic of Croatia (MIZ)	https://www.miz.hr
Croatian Health Insurance Fund (CHIF)	https://www.hzzo.hr
Croatian Institute of Public Health (CIPH)	https://www.hzjz.hr/english/
Colombia	
Instituto de Evaluación Tecnológica en Salud (IETS)	http://www.iets.org.co
Cyprus	
Ministry of Health Cyprus (MoH Cyprus)	https://www.eunethta.eu/moh-cyprus
Czech Republic	
Ministry of Health Czech Republic (MoH Czech)	https://www.mzcr.cz/en
State Institute for Drug Control (SUKL)	https://www.sukl.eu
Denmark	
Danish National Institute of Public Health	https://www.sdu.dk/en/sif/forskning
Social & Health Services and Labour Market (DEFACTUM)	http://www.defactum.net
Estonia	
Institute of Family Medicine and Public Health (UTA)	https://www.tervis.ut.ee
Finland	
Finnish National Institute for Health and Welfare	https://thl.fi/en/web/thlfi-en/publications
Finnish Coordinating Center for Health Technology Assessment (FinCCHTA)	http://www.fincchta.fi
Finnish Medicines Agency (FIMEA)	http://www.fimea.fi
National Institute for Health and Welfare (THL)	https://www.thl.fi
France	
French National Authority for Health (Haute Autorité de Santé; HAS)	https://www.has-sante.fr/
Comité d'Evaluation et de Diffusion des Innovations Technologiques (CEDIT)	info.cedit@sap.aphp.fr
Germany	
German Institute for Medical Documentation and Information (DIMDI)	https://www.dimdi.de/
Institute for Quality and Efficiency in Health Care (IQWiG)	http://www.iqwig.de
Federal Joint Committee (Gemeinsamer Bundesausschuss; G-BA)	http://www.g-ba.de
Greece	

Institute of Pharmaceutical Research and Technology (IFET)	http://www.ifet.gr/english_site/
National and Kapodistrian University of Athens (EKAPTY-NKUA)	http://www.phs.uoa.gr/
National Evaluation Centre of Quality and Technology in S.A-EKAPTY	http://www.ekapty.gr/
National Organization for Medicines (EOF)	http://www.eof.gr
National Organisation for Healthcare Provision (EOPYY)	http://www.eopyy.gov.gr
Onassis Cardiac Surgery Centre (OCSC)	http://www.onasseio.gr/
Hungary	
Health Services Management Training Center (SU)	http://www.semmelweis.hu/emk/en/
National Institute of Pharmacy and Nutrition (NIPN)	http://www.ogyei.gov.hu/main_page/
Ireland	
Health Information and Quality Authority (HIQA)	http://www.hiqa.ie
National Centre for Pharmacoeconomics, St James Hospital (NCPE)	http://www.ncpe.ie
Korea	
National Evidence-based healthcare Collaborating Agency (NECA)	www.neca.re.kr/eng
Luxembourg	
Inspection Générale de la Sécurité Sociale (IGSS), Cellule d'Expertise Médicale (CEM)	http://www.mss.public.lu/publications/index.html
Malaysia	
Health Technology Assessment Section, Ministry of Health Malaysia (MaHTAS)	http://www.moh.gov.my
Malta	
Directorate for Pharmaceutical Affairs (DPA/MoH Malta)	http://www.health.gov.mt/en/pharmaceutical/Pages/pharmaceutical-affairs.aspx
Mexico	
Centro Nacional de Excelencia Tecnológica en Salud (CENETEC)	www.cenetec.gob.mx
Norway	
Norwegian Knowledge Centre for the Health Services	https://www.fhi.no/sys/ks/
Norwegian Institute of Public Health (NIPH)	http://www.fhi.no
The Netherlands	
Erasmus Universiteit Rotterdam (EUR)	http://www.eur.nl/
Health Council of the Netherlands (Gezondheidsraad)	https://www.gezondheidsraad.nl/
The Netherlands Organisation for Health Research and Development (ZonMw)	http://www.zonmw.nl
Zorginstituut Nederland (ZIN)	https://www.zorginstituutnederland.nl/
Utrecht University (UU)	http://www.uu.nl
Norway	
The Norwegian Institute of Public Health (NIPHNO)	http://www.fhi.no/
Norwegian Directorate of Health (Hdir)	http://helsedirektoratet.no/english
Norwegian Medicines Agency (NOMA)	http://www.legemiddelverket.no
Poland	

Agency for Health Technology Assessment and Tariff System (AOTMiT)	http://www.aotm.gov.pl
Portugal	
Administração Central do Sistema de Saúde, I.P. (ACSS IP)	http://www.acss.min-saude.pt
National Authority of Medicines and Health Products (INFARMED)	http://www.infarmed.pt
Republic of China, Taiwan	
Center for Drug Evaluation (CDE)	http://www.cde.org.tw
Romania	
Babes-bolayi University, Cluj School of Public Health (UBB)	http://publichealth.ro/
Institutu National De Sanatate Publica (INSP/NIPHB)	http://www.inspo.gov.ro
National School of Public Health, Management and Professional Development (NSPHMPDB)	http://www.snspms.ro
Singapore	
Agency for Care Effectiveness (ACE)	http://www.ace-hta.gov.sg/
Slovakia	
Comenius University in Bratslava (UniBA FOF)	https://uniba.sk/en/
Ministry of Health of the Slovak Republic (MoH Slovak Republic)	http://www.health.gov.sk
Slovenia	
Ministry of Health of the Republic of Slovenia (MoH Slovenia)	http://www.mz.gov.si/en/
National institute of Public Health (NIJZ)	http://www.nijz.si
Public Agency of the Republic of Slovenia for Medical Products and Medical Devices (JAZMP)	http://www.jazmp.si/en/
South Africa	
Charlotte Maxeke Research Consortium (CmeRC)	http://www.cmerc.org
Spain	
Agencia Española de Medicamentos y Productos Sanitarios (AEMPS)	http://www.aemps.gob.es
Agencia de Evaluación de Tecnologias Sanitarias, Instituto de Salud “Carlos III”I / Health Technology Assessment Agency (AETS)	http://publicaciones.isciii.es/
Agency for Health Quality and Assessment of Catalonia (AquAS)	http://aquas.gencat.cat
Andalusian HTA Agency	http://www.aetsa.org/
Basque Foundation for Health Innovation and Research (BIOEF)	http://www.bioef.org/
Basque Office for Health Technology Assessment (OSTEBA)	http://www.euskadi.eus/web01-a2ikeost/en/
Catalan Agency for Health Technology Assessment (CAHTA)	http://www.gencat.cat
Directorate General for Pharmacy and Health Care Products (DGFPS MSPSI)	website not provided
Evaluation AND Planning Unit – Directorate of the Canary Islands Health Service (SESCS)	http://www.sescs.es
Fundación Canaria de Investigación Sanitaria (Funcanis)	http://www.funcanis.org/
Fundacion Profesor Novoa Santos (AVALIA FNS)	http://www.fundacionprofesornovoasantos.org/es/
Fundación Pública Andaluza Progreso y Salud (FPS)	http://www.juntadeandalucia.es/fundacionprogresoysalud/
Galician Agency for Health Technology Assessment (AVALIA-T)	http://acis.sergas.es

Health Sciences Institute in Aragon (IACS)	http://www.iacs.es/
The Instituto De Salud Carlos III (AETS-ISCIIIS)	http://www.eng.isciii.es
Sweden	
Center for Medical Health Technology Assessment	http://www.cmt.liu.se/?l=en&sc=true
Dental and Pharmaceutical Benefits Agency (TLV)	http://www.tlv.se
Medical Products Agency (MPA)	http://www.lakemedelsverket.se
Swedish Council on Technology Assessment in Health Care (SBU)	http://www.sbu.se/en/
Switzerland	
Swiss Federal Office of Public Health (SFOPH)	http://www.bag.admin.ch/hta
Swiss Network on Health Technology Assessment (SNHTA)	http://www.snhta.ch/
Tunisia	
INEAS – National Authority for Assessment and Accreditation in Healthcare, TUNISIA	http://www.ineas.tn/fr
United Kingdom	
All Wales Therapeutics and Toxicity Centre (AWTTC)	http://awttc.org
Health Information Quality Authority (HIQA)	http://www.higa.ie
Healthcare Improvement Scotland (HIS)	http://www.healthcareimprovementscotland.org
National Health Service Health Technology Assessment (UK) / National Coordinating Centre for Health Technology Assessment (NCCHTA)	https://www.nihr.ac.uk/funding-and-support/funding-for-research-studies/funding-programmes/health-technology-assessment/
NHS Quality Improvement Scotland	http://www.nhshealthquality.org/
National Institute for Clinical Excellence (NICE)	http://www.nice.org.uk/
Health Technology Wales (HTW)	http://www.healthtechnology.wales
National Institute for Health Research (NIHR), including HTA programme	http://www.nets.nihr.ac.uk/programmes/hta
United States	
Agency for Healthcare Research and Quality (AHRQ)	https://www.ahrq.gov/research/findings/index.html
Harvard School of Public Health	http://www.hsph.harvard.edu/
Institute for Clinical and Economic Review (ICER)	http://www.icer-review.org/
Institute for Clinical Systems Improvement (ICSI)	http://www.icsi.org
Minnesota Department of Health (US)	http://www.health.state.mn.us/
Office of Health Technology Assessment Archive (US)	http://ota.fas.org/
U.S. Blue Cross / Blue Shield Association Technology Evaluation Center (Tec)	https://www.bcbs.com/news/press-releases/blue-cross-blue-shield-association-launches-evidence-street-website-streamline
Veteran's Affairs Research and Development Technology Assessment Program (US)	http://www.research.va.gov/default.cfm
Ukraine	
Department of HTA at the State Expert Centre of the Ministry of Health (SEC)	website not provided
Uruguay	
Health Assessment Division, Ministry of Public Health, (HAD)	http://www.msp.gub.uy

Table 21 Patient/social and ethical databases

Clinical trial registries	
Psychinfo	https://www.apa.org/pubs/databases/psycinfo/
ETHMED	http://www.ethicsweb.eu/search_ets

Table 22 Clinical trial registries

Clinical trial registries	
ClinicalTrials.gov	https://clinicaltrials.gov/
Cochrane Central Register of Controlled Trials	https://www.cochranelibrary.com/central
EU Clinical Trials Registry	https://www.clinicaltrialsregister.eu/ctr-search/search
WHO International Clinical Trials Registry Platform (ICTRP)	http://www.who.int/ictrp/en/
Australian New Zealand Clinical Trials Registry	http://www.anzctr.org.au/

Table 23 Legal websites

Legal aspects	
Case law database of the European Court of Justice	http://curia.europa.eu/juris/recherche.jsf?language=en
Case law database of the European Court of Human Rights	https://hudoc.echr.coe.int/eng#
Council of Europe	https://www.coe.int/en/web/cm
EudraLex – Volume 1: The rules governing medicinal products in the European Union	https://ec.europa.eu/health/documents/eudralex/vol-1_en
EU law and other public EU documents	https://eur-lex.europa.eu/homepage.html?locale=en
EUR-Lex	http://eur-lex.europa.eu/n-lex/index_en
European Medicines Agency's Human medicines regulatory information	https://www.ema.europa.eu/en/human-medicines-regulatory-information
Non-binding ISO standards related to health	https://www.iso.org/caring-about-health-and-safety.html
79itte database	http://www.tress-network.org/

Table 24 Organisational websites

Organisational aspects	
ERIC (Education Recourses Information Center)	https://eric.ed.gov/

Table 25 Specialty websites

Specialty websites	
Geneva Medical Association	https://www.amge.ch/
Arbeitsgruppe Lipide und Atherosklerose	https://www.agla.ch/familiare-hypercholesterinamie/therapie-bei-erwachsenen
Swiss Stroke Society	https://congrex.com/client/shg-sss/
European Society of Cardiology	https://www.escardio.org/
European Heart Network	http://www.ehnheart.org/about-us/overview.html
World Heart Federation	https://www.world-heart-federation.org/
UEMS Section and Board of Vascular Surgery	https://uemsvascular.com/national-societies/
European Society of Vascular Surgery	https://www.esvs.org
The Familial Hypercholesterolaemia Network	https://www.fheurope.org
European Stroke Organisation	https://www.eso-stroke.org
Stroke Alliance for Europe	https://www.safestroke.eu
American Stroke Association	https://www.stroke.org
Heart and Stroke Association of Canada	https://www.heartandstroke.ca/stroke
Stroke Association UK	https://www.stroke.org.uk
Stroke foundation – Australia	https://www.strokefoundation.org.au
The Heart Foundation – Australia	https://www.heartfoundation.org.au

Table 26 Clinical practice guideline websites

Clinical practice guidelines	
Guidelines International Network (GIN)	https://www.g-i-n.net/library/international-guidelines-library
Association of Scientific Medical Societies (AWMF)	https://www.awmf.org/awmf-online-das-portal-der-wissenschaftlichen-medizin/awmf-aktuell.html
National Guideline Clearinghouse	https://www.ahrq.gov/gam/index.html
Scottish Intercollegiate Guidelines Network	http://www.sign.ac.uk/guidelines/published/
Swiss Medical Weekly	https://smw.ch/en/
European Society of Cardiology	https://www.escardio.org/Guidelines/Clinical-Practice-Guidelines

13 Appendix B: Characteristics of included trials

13.1 Efficacy studies

Table 27 List of included studies for efficacy-related outcomes

Author; year; country; trial name	Inclusion criteria; Sample size	Design; Setting; Follow-up	Intervention; Comparator	Relevant efficacy outcomes
Ballantyne 2004a[118] USA NCT00525824	Primary hypercholesterolaemia LDL-c: 145 – 250mg/dL Triglycerides: ≤ 350mg/dL n = 246	RCT , double-blind, extension study[119] Multicentre 12 months	Atorvastatin (10mg) + Ezetimibe (10mg) Atorvastatin (10mg) + Placebo	• LDL-c, HDL, triglycerides, total cholesterol • Cardiovascular and non-cardiovascular mortality
Cannon 2015[45] NR NCT00202878	Acute coronary syndrome LDL: >125 and 100 for patients receiving and not receiving treatment Triglycerides: NR n = 18114	RCT, double-blind International, multicentre 7 years	Simvastatin (40mg) + Ezetimibe (10mg) Simvastatin (40mg) + Placebo	• LDL-c, HDL, triglycerides, total cholesterol • MACE, stroke, coronary intervention, myocardial infarction, cardiovascular mortality • Non-cardiovascular mortality
Hougaard 2017[120] Denmark NCT01385631	ST-segment elevation myocardial infarction LDL-c: NR Triglycerides: NR n = 87	RCT, double-blind Single-centre 12 months	Atorvastatin (80mg) + Ezetimibe (10mg) Atorvastatin (80mg) + Placebo	• LDL-c, HDL, total cholesterol • Cardiovascular and non-cardiovascular mortality • Vascular damage (IVUS)
Kastelein 2008[121] America, Africa and Europe [a] NCT00552097	Familial hypocholesterolaemia LDL-c: >210mg/dL; or <210mg/dL + existing lipid lowering therapy Triglycerides: NR n = 720	RCT, double blind International, multicentre 24 months	Simvastatin (80mg) + Ezetimibe (10mg) Simvastatin (80mg) + Placebo	• LDL-c, HDL, triglycerides, total cholesterol • MACE, stroke, coronary intervention, myocardial infarction, cardiovascular mortality • Vascular damage (cIMT)
Kouvelos 2013[122] Greece NR	Elective vascular surgery LDL-c: NR Triglycerides: NR n = 262	RCT, blinding NR Centres NR 12 months	Rosuvastatin (10mg) Rosuvastatin (10mg) + Ezetimibe (10mg)	• LDL-c, HDL, triglycerides, total cholesterol • MACE, stroke, myocardial infarction, cardiovascular mortality

Author; year; country; trial name	Inclusion criteria; Sample size	Design; Setting; Follow-up	Intervention; Comparator	Relevant efficacy outcomes
Masana 2005[123] NR NR	Primary hypocholesteraemia LDL-c > 160mg/dL + 1 risk factor LDL-c > 130mg/dL + 2 risk factor LDL-c > 100mg/dL + coronary heart disease Triglycerides: NR n = 433	RCT, double-blind, extension study[124] Multicentre 48 weeks	Simvastatin (10, 20, 40, 80mg) + Ezetimibe (10mg) Simvastatin (10, 20, 40, 80mg) + Placebo	• LDL-c, HDL, triglycerides, total cholesterol • Non-cardiovascular mortality
West 2011[125] USA NCT00587678	Peripheral artery disease, ABI 0.4 – 0.9 LDL-c: NR Triglycerides: NR n = 87	RCT, double-blind Single-centre 12 months	Simvastatin (40mg) Simvastatin (40mg) + Ezetimibe (10mg)	• LDL-c, HDL, triglycerides, total cholesterol • MACE • Non-cardiovascular mortality • Vascular damage (MRI)

Abbreviations

ABI = ankle brachial index, **ALT** = alanine aminotransferase, **AST** = aspartate aminotransferase, **CK** = creatine kinase, **cMIT** = carotid intima–media thickness (ultrasound), **IVUS** = intravascular ultrasound, **LDL-c** = low density lipoprotein-cholesterol, **mg** = milligrams, **MRI** = magnetic resonance imaging, **n** = number of participants, **NR** = not reported, **RCT** = randomised controlled trial.

Notes:

a = USA, Canada, South Africa, Spain, Denmark, Norway, Sweden, The Netherlands.

13.2 Safety studies

Table 28 List of included studies for safety-related outcomes

Author; year; country; trial ID	Inclusion criteria; Sample size	Design; Setting; Follow-up	Intervention; Comparator	Safety outcomes
Alvarez-Sala 2008[126] Spain NR	Hypercholesterolaemia LDL-c: ≥130mg/dL Triglycerides: ≤400mg/dL n = 89	RCT, open-label Multicentre 12 weeks	Fluvastatin (80mg) Fluvastatin (80mg) + ezetimibe (10mg)	• Withdrawal • Adverse events • ALT, AST, CK
Ansquer 2009[127] Belgium, Germany, France NCT00349284	Type IIb dyslipidaemia with metabolic syndrome (NCEP-ATP III definition) LDL-c: ≥160mg/dL Triglycerides: 150 – 405mg/dL n = 60	RCT, double-blind International, multicentre 12 weeks	Ezetimibe (10mg) Fenofibrate (145mg) Fenofibrate (145mg) + ezetimibe (10mg)	• Withdrawal • Adverse events • ALT, AST, CK
Averna 2010[128] Italy NCT00423579	Primary hypercholesterolaemia with CHD LDL-c: 100 – 160mg/dL despite treatment Triglycerides: ≤350mg/dL n = 120	RCT, double-blind Multicentre 6 weeks	Simvastatin (40mg) + ezetimibe (10mg) Simvastatin (40mg) + placebo	• Withdrawal • Adverse events • ALT, AST, CK • Compliance
Ballantyne 2003[119] USA NR	Primary hypercholesterolaemia LDL-c: 145 – 250mg/dL Triglycerides: ≤350mg/dL n = 628	RCT, double-blind Multicentre 12 weeks	Atorvastatin (10, 20, 40 or 80mg) Atorvastatin (10, 20, 40 or 80mg) + ezetimibe (10mg) Ezetimibe (10mg) Placebo	• Withdrawal • Adverse events • ALT, AST, CK • Compliance
Ballantyne 2004a[118] USA NCT00525824	Primary hypercholesterolaemia LDL-c: 145 – 250mg/dL Triglycerides: ≤ 350mg/dL n = 246	RCT , double-blind, extension study[119] Multicentre 12 months	Ezetimibe (10mg) + Atorvastatin (10mg) Atorvastatin (10mg) + Placebo	• Withdrawal • Adverse events • ALT, AST, CK
Ballantyne 2004b[129] USA	Primary hypercholesterolaemia	RCT, double-blind Multicentre	Atorvastatin (10mg titered to 80mg)	• Withdrawal • Adverse events

Author; year; country; trial ID	Inclusion criteria; Sample size	Design; Setting; Follow-up	Intervention; Comparator	Safety outcomes
NR	LDL-c > NCEP-ATP III guidelines Triglycerides: ≤350mg/dL n = 788	24 weeks	Simvastatin (10mg titered to 80mg) + ezetimibe (10mg) Simvastatin (20mg tittered to 80mg) + ezetimibe (10mg)	• ALT, AST, CK
Ballantyne 2007[130] Austria, Germany, Switzerland, South Africa, USA D3569C00006	Hypercholesterolaemia with CHD LDL-c: 160 – 250mg/dL Triglycerides: ≤400mg/dL n = 469	RCT, open-label International, multicentre 6 weeks	Rosuvastatin (40mg) Rosuvastatin (40mg) + ezetimibe (10mg)	• Withdrawal • Adverse events • ALT, AST, CK • Compliance
Ballantyne 2019[131] USA NCT03337308	High-risk of CVD with LDL-c ≥100mg/dL or ASCVD and/or HeFH and multiple CVD risk factors with LDL-c ≥130mg/dL despite treatment n = 382	RCT, double-blind Multicentre 12 weeks	Ezetimibe (10mg) Placebo	• Withdrawal • Adverse events • ALT, AST, CK
Bardini 2010[132] Italy Protocol 04037	Type 2 diabetes with CHD LDL-c: 100 – 160mg/dL Triglyceride: ≤350mg/dL n = 93	RCT, double-blind Multicentre 6 weeks	Simvastatin (20mg) Simvastatin (20mg) + ezetimibe (10mg)	• Withdrawal • Adverse events • ALT, AST, CK • Compliance
Barrios 2005[133] Asia and Europe [a] NR	Hypercholesterolaemia with CHD LDL-c: 100 – 160mg/dL Triglycerides: ≤350mg/dL n = 435	RCT, double-blind International, multicentre 6 weeks	Atorvastatin (20mg) Simvastatin (20mg) + ezetimibe (10mg)	• Withdrawal • Adverse events • ALT, AST, CK • Compliance
Bays 2004[134] USA + 22 countries [b] NR	Primary hypercholesterolaemia LDL-c: 145 – 250mg/dL Triglycerides: ≤350mg/dL n = 1528	RCT, double-blind International, multicentre 12 weeks	Ezetimibe (10mg) Simvastatin (10, 20, 40 or 80mg) Simvastatin (10, 20, 40 or 80mg) + ezetimibe (10mg) Placebo	• Withdrawal • Adverse events • ALT, AST, CK • Compliance

Author; year; country; trial ID	Inclusion criteria; Sample size	Design; Setting; Follow-up	Intervention; Comparator	Safety outcomes
Bays 2008 [135] USA, 22 other countries [b] NR	Primary hypercholesterolaemia LDL-c: 145 – 250mg/dL Triglycerides: ≤350mg/dL n = 768	RCT, double-blind, extension study[136] International, multicentre 48 weeks	Simvastatin (10, 20, 40 or 80mg) Simvastatin (10, 20, 40 or 80mg) + ezetimibe (10mg)	• Withdrawal • Adverse events • ALT, AST, CK
Bays 2011[137] America, Europe [c] NCT00783263	Hypercholesterolaemia with high risk of CHD or ASCVD LDL-c : > NCEP-ATP III guidelines Triglycerides: ≤350mg/dL n = 440	RCT, double-blind International, multicentre 6 weeks	Rosuvastatin (40mg) Rosuvastatin (40mg) + ezetimibe (10mg)	• Withdrawal • Adverse events • ALT, AST, CK • Compliance
Bays 2013[138] America and Europe [d] NCT01154036	Primary hypercholesterolaemia with high risk of CVD LDL-c: 166 – 190md/dL Triglycerides: NR n = 1547	RCT, double-blind International, multicentre 12 weeks	Atorvastatin (20mg) Atorvastatin (10mg) + ezetimibe (10mg) Rosuvastatin (10mg)	• Withdrawal • Adverse events • ALT, AST, CK • Compliance
Bays 2015[139] Australia, America and Europe [e] NCT01730040	Primary hypercholesterolaemia with high risk of CVD LDL-c: >70mg/dL high risk CVD; >100mg/dL with diabetes/kidney disease despite therapy Triglycerides: NR n = 355	RCT, double-blind International, multicentre 24 weeks	Atorvastatin (40mg) Atorvastatin (20mg) + ezetimibe (10mg) Rosuvastatin (40mg)	• Withdrawal • Adverse events • ALT, AST, CK • Compliance
Blagden 2007[140] UK NR	Primary hypercholesterolaemia with CHD LDL-c: 130 – 209mg/dL Triglycerides: ≤368mg/dL n = 148	RCT, double-blind Multicentre 6 weeks	Atorvastatin (10mg) + ezetimibe (10mg) Atorvastatin (10mg) + Placebo	• Withdrawal • Adverse events • ALT, AST, CK • Compliance
Brohet 2005[141] Europe [f]	CHD	RCT, double-blind	Simvastatin (10 or 20mg)	• Withdrawal • Adverse event • ALT, AST, CK

Author; year; country; trial ID	Inclusion criteria; Sample size	Design; Setting; Follow-up	Intervention; Comparator	Safety outcomes
NR	LDL-c: 100 – 160mg/dL n = 418	International, multicentre 6 weeks	Simvastatin (10 or 20mg) + ezetimibe (10mg)	• Compliance
Cannon 2015[45] NR NCT00202878	Acute coronary syndrome LDL: >125 and 100 for patients receiving and not receiving treatment Triglycerides: NR n = 18114	RCT, double-blind International, multicentre 7 years	Simvastatin (40mg) + ezetimibe (10mg) Simvastatin (40mg) + Placebo	• Withdrawal • Adverse events • ALT, AST, CK
Catapano 2006[142] USA Protocol 058	Hypercholesterolaemia with risk of CHD LDL-c: 145 – 250mg/dL Triglycerides: ≤350mg/dL n = 2959	RCT, double-blind, extension study Multicentre 6 weeks	Rosuvastatin (10, 20 and 40mg) Simvastatin (20, 40 or 80mg) + ezetimibe (10mg)	• Withdrawal • Adverse events • ALT, AST, CK
Chenot 2007[143] Belgium NR	Acute myocardial infarction LDL-c: >90mg/dL Triglycerides: NR n = 60	RCT, blinding NR Centres NR 1 week	No drugs Simvastatin (40mg) Simvastatin (40mg) + ezetimibe (10mg)	• Adverse events
Chirinos 2010[144] USA NCT00566267	Elevated LDL-c LDL-c: 130 – 190mg/dL Triglycerides: <400mg/dL n = 58	RCT, single-blind Single-centre 8 weeks	Simvastatin (20mg) Simvastatin (20mg) + ezetimibe (10mg)	• Withdrawal • Adverse events
Conard 2008[145] Austria, Canada, Costa Rica, USA Protocol 079	Hypercholesterolaemia with CAD LDL-c: 100 – 160mg/dL Triglyceride ≤350mg/dL n = 196	RCT, double-blind International, multicentre 6 weeks	Atorvastatin (40mg) Atorvastatin (20mg) + ezetimibe (10mg)	• Withdrawal • Adverse events • ALT, AST, CK
Cruz-Fernandez 2005[146] Europe, North America [9] Protocol 803/4	CHD LDL-c: 101 – 160mg/dL Triglycerides: ≤350mg/dL n = 450	RCT, double-blind International, multicentre 6 weeks	Atorvastatin (10 or 20mg) + ezetimibe (10mg) Atorvastatin (10 or 20mg) + Placebo	• Withdrawal • Adverse events • ALT, AST, CK • Compliance

Author; year; country; trial ID	Inclusion criteria; Sample size	Design; Setting; Follow-up	Intervention; Comparator	Safety outcomes
Davidson 2002[147] USA NR	Primary hypercholesterolaemia LDL-c: 145 – 250mg/dL Triglycerides: ≤350mg/dL n = 668	RCT, double-blind Multicentre 12 weeks	Ezetimibe (10mg) Simvastatin (10, 20, 40 or 80mg) Simvastatin (10, 20, 40 or 80mg) + ezetimibe (10mg) Placebo	• Withdrawal • Adverse events • ALT, AST, CK • Compliance
Davidson 2013[148] USA NCT00701727	Hypercholesterolaemia LDL-c: 130 – 200mg/dL Triglycerides: <350mg/dL n = 26	RCT, double-blind, cross-over Single-centre 14 weeks	Ezetimibe (10mg) Placebo	• Withdrawal • Adverse events
Deharo 2014[149] France SAFE-SE	Acute coronary syndrome LDL-c: ≥100mg/dL Triglycerides: NR n = 128	RCT, open-label Single-centre 4 weeks	Rosuvastatin (20mg) Simvastatin (40mg) + ezetimibe (10mg)	• Withdrawal • Adverse events • ALT, AST, CK • Compliance
Dujovne 2002[150] USA Protocol P00474	Primary hypercholesterolaemia LDL-c: 130 – 200mg/dL Triglycerides: ≤350mg/dL n = 892	RCT, double-blind Multicentre 20 weeks	Ezetimibe (10mg) Placebo	• Withdrawal • Adverse events • ALT, AST, CK • Compliance
Farnier 2005a[151] Asia, Europe [h] Protocol 802	Hypercholesterolaemia with CHD LDL-c: 100 – 162mg/dL Triglycerides: ≤354mg/dL n = 372	RCT, double-blind International, multicentre 6 weeks	Simvastatin (10 or 20mg) + ezetimibe (10mg) Simvastatin (10 or 20mg) + placebo	• Withdrawal • Adverse events • ALT, AST, CK • Compliance
Farnier 2005b[152] NR NCT00092573	Mixed hyperlipidaemia LDL-c: 131 – 220mg/dL Triglycerides: 203 – 504mg/dL n = 559	RCT, double-blind International, multicentre 12 weeks	Ezetimibe (10mg) Fenofibrate (160mg) Fenofibrate (160mg) + ezetimibe (10mg) Placebo	• Withdrawal • Adverse events • ALT, AST, CK • Compliance
Farnier 2007[153] NR	Mixed hyperlipidaemia	RCT, double-blind	Fenofibrate (160mg)	• Withdrawal • Adverse events • ALT, AST, CK

Author; year; country; trial ID	Inclusion criteria; Sample size	Design; Setting; Follow-up	Intervention; Comparator	Safety outcomes
NCT00093899	LDL-c: 130 – 220mg/dL Triglycerides: 150 – 500mg/dL n = 265	International, multicentre 12 weeks	Simvastatin (20mg) + ezetimibe (10mg) Simvastatin (20mg) + ezetimibe (10mg) + Fenofibrate (160mg) Placebo	• Compliance
Farnier 2009[154] Europe [i] NCT00479713	Hypercholesterolaemia with high risk of CVD LDL-c: 100 – 190mg/dL Triglycerides: ≤350mg/dL n = 618	RCT, double-blind International, multicentre 8 weeks	Rosuvastatin (20mg) Simvastatin (40mg) + ezetimibe (10mg)	• Withdrawal • Adverse events • ALT, AST, CK • Compliance
Feldman 2004[155] USA NR	CHD or CHD risk equivalent LDL-c: ≥130mg/dL Triglycerides: ≤350mg/dL n = 710	RCT, double-blind Multicentre 23 weeks	Simvastatin (10mg) Simvastatin (10, 20 or 40mg) + ezetimibe (10mg)	• Withdrawal • Adverse events • ALT, AST, CK
Foody 2010[156] USA NCT00535405	Hyperlipidaemia with high risk of CHD LDL-c: ≥130mg/dL Triglycerides: ≤350mg/dL n = 1289	RCT, double-blind Multicentre 12 weeks	Atorvastatin (10, 20 or 40mg) Simvastatin (20 or 40mg) + ezetimibe (10mg)	• Withdrawal • Adverse events • ALT, AST, CK • Compliance
Gagne 2002[124] NR NR	Primary hypercholesterolaemia LDL-c: ≥160mg/dL + 1 risk or LDL-c: ≥130mg/dL + 2 risk factors or LDL-c: ≥100mg/dL + coronary heart disease Triglycerides: NR n = 769	RCT, double-blind Multicentre 15 weeks	Statin + ezetimibe (10mg) Statin + placebo [j]	• Withdrawal • Adverse events • ALT, AST, CK

Author; year; country; trial ID	Inclusion criteria; Sample size	Design; Setting; Follow-up	Intervention; Comparator	Safety outcomes
Goldberg 2004[136] USA + 22 countries [b] NR	Primary hypercholesterolaemia LDL-c: ≥145 – 250mg/dL Triglycerides ≤350mg/dL n = 887	RCT, double-blind International, multicentre 12 weeks	Ezetimibe (10mg) Simvastatin (10, 20, 40 or 80mg) Simvastatin (10, 20, 40 or 80mg) + ezetimibe (10mg) Placebo	• Withdrawal • Adverse events • ALT, AST, CK
Goldberg 2006[157] USA NCT00110435	Primary hypercholesterolaemia with type 2 diabetes LDL-c: ≥100mg/dL Triglycerides: ≤400mg/dL n = 1229	RCT, double-blind Multicentre 6 weeks	Atorvastatin (10 or 20mg) Simvastatin (20mg) + ezetimibe (10mg)	• Withdrawal • Adverse events • ALT, AST, CK
Hing Ling 2012[158] Asia, Europe, South America [k] NCT00782184	Primary hypercholesterolaemia with high risk of CHD LDL-c: 100 – 160mg/dL Triglycerides: ⩽ 400mg/dL n = 250	RCT, double-blind International, multicentre 6 weeks	Atorvastatin (40mg) Simvastatin (20mg) + ezetimibe (10mg)	• Withdrawal • Adverse events • ALT, AST, CK
Hougaard 2017[120] Denmark NCT01385631	ST-segment elevation myocardial infarction LDL-c: NR Triglycerides: NR n = 87	RCT, double-blind Single-centre 12 months	Atorvastatin (80mg) + ezetimibe (10mg) Atorvastatin (80mg) + Placebo	• Withdrawal • Adverse events • ALT, AST, CK
Japaridze 2017[159] Georgia NR	Acute coronary syndrome LDL-c: ≥70mg/dL despite treatment Triglycerides: NR n = 292	RCT, open-label Single-centre 16 weeks	Atorvastatin (40mg) Atorvastatin (20mg) + ezetimibe (10mg)	• Withdrawal • Adverse events • ALT, AST, CK
Jones 2010[160] USA NCT00639158	Dyslipidaemia defined as fasting: LDL-c: ≥130mg/dL Triglyceride: 150 – 400 mg/dL HDL: <40mg/dL (male) and <50mg/dL (female) n = 543	RCT, double-blind Multicentre 12 weeks	Atorvastatin (40mg) + ezetimibe (10mg) Atorvastatin (40mg) + ezetimibe (10mg) + fenofibric acid (135mg)	• Withdrawal • Adverse events • ALT, AST, CK
Kastelein 2008[121]	Familial hypocholesterolaemia	RCT, double blind	Simvastatin (80mg) + ezetimibe (10mg)	• Withdrawal • Adverse events

Author; year; country; trial ID	Inclusion criteria; Sample size	Design; Setting; Follow-up	Intervention; Comparator	Safety outcomes
America, Africa and Europe [I] NCT00552097	LDL-c: >210mg/dL; or <210mg/dL + existing lipid lowering therapy Triglycerides: NR n = 720	International, multicentre 24 months	Simvastatin (80mg) + placebo	• ALT, AST, CK • Compliance
Knopp 2003[161] USA NR	Primary hypercholesterolaemia LDL-c: ≥130mg/dL Triglycerides: ≤250mg/dL n = 827	RCT, double-blind Multicentre 12 weeks	Ezetimibe (10mg) Placebo	• Withdrawal • Adverse events • ALT, AST, CK
Kosoglou 2004a[162] France NR	Primary hypercholesterolaemia LDL-c: ≥130mg/dL n = 33	RCT, single-blind Single-centre 2 weeks	Ezetimibe (10mg) Fenofibrate (200mg) Fenofibrate (200mg) + ezetimibe (10mg) Placebo	• Withdrawal • Adverse events
Kosoglou 2004b[163] France NR	Hypercholesterolaemia LDL-c: ≥130mg/dL Triglycerides: ≤400mg/dL n = 40	RCT, single-blind Single-centre 2 weeks	Ezetimibe (10mg) + placebo Rosuvastatin (10mg) + ezetimibe (10mg) Rosuvastatin (10mg) + Placebo Placebo + placebo	• Withdrawal • Adverse events • ALT, AST, CK
Kouvelos 2013[122] Greece NR	Elective vascular surgery LDL-c: NR Triglycerides: NR n = 262	RCT, blinding NR Centres NR 12 months	Rosuvastatin (10mg) Rosuvastatin (10mg) + ezetimibe (10mg)	• Withdrawal • Adverse events • ALT, AST, CK
Krysiak 2012a[165] Poland NR	Primary hypercholesterolaemia with LDL-c: 130mg/dL Triglycerides: <150mg/dL n = 104	RCT, double-blind Multicentre 12 weeks	Ezetimibe (10mg) Simvastatin (40mg) Simvastatin (40mg) + ezetimibe (10mg) Placebo	• Withdrawal • Adverse events • Compliance
Krysiak 2012b[166] Poland NR	Hypercholesterolaemia	RCT, double-blind Multicentre 12 weeks	Ezetimibe (10mg) Simvastatin (40mg)	• Withdrawal • Adverse events • Compliance

Author; year; country; trial ID	Inclusion criteria; Sample size	Design; Setting; Follow-up	Intervention; Comparator	Safety outcomes
	LDL-c: 130mg/dL Triglycerides: <150mg/dL n = 178		Simvastatin (40mg) + ezetimibe (10mg) Placebo	
Kumar 2009[167] Canada NR	Hypercholesterolaemia LDL-c: NR Triglycerides: NR n = 43	RCT, open-label, cross over Centre NR 6 weeks	Atorvastatin (10mg) Fenofibrate (160mg) + ezetimibe (10mg)	• Withdrawal • Adverse events • ALT, AST, CK
Kusters 2015[94] Europe, North America [m] NCT00867165	Familial hypercholesterolaemia or nonfamilial hypercholesterolaemia LDL-c dependent on family history Children n = 138	RCT, double-blind International, multicentre 12 weeks	Ezetimibe (10mg) Placebo	• Withdrawal • Adverse events • ALT, AST, CK • Compliance
Lakoski 2010[168] USA NR	Elevated LDL LDL-c: 130 – 175mg/dL Triglycerides: ≤250mg/dL n = 215	RCT double-blind, cross-over Single-centre 6 weeks	Ezetimibe (10mg) Simvastatin (10mg/dl) Simvastatin (10mg) + ezetimibe (10mg) Placebo	• Withdrawal • Adverse events • Compliance
Leiter 2008[169] Canada, USA Protocol 090	Hypercholesterolaemia LDL-c: 70 – 160mg/dL Triglycerides: ≤350mg/dL n = 579	RCT, double-blind International, multicentre 6 weeks	Atorvastatin (80mg) Atorvastatin (40mg) + ezetimibe (10mg)	• Withdrawal • Adverse events • ALT, AST, CK
Masana 2005[123] NR NR	Primary hypocholesteraemia LDL-c > 160mg/dL + 1 risk factor LDL-c > 130mg/dL + 2 risk factor LDL-c > 100mg/dL + coronary heart disease Triglycerides: NR n = 433	RCT, double-blind, extension study[124] Multicentre 48 weeks	Simvastatin (10, 20, 40, 80mg) + ezetimibe (10mg) Simvastatin (10, 20, 40, 80mg) + placebo	• Withdrawal • Adverse events • ALT, AST, CK • Compliance
McCormack 2010[170]	CVD or high-risk CVD	RCT, double-blind	Atorvastatin (40mg)	• Withdrawal • Adverse events

Author; year; country; trial ID	Inclusion criteria; Sample size	Design; Setting; Follow-up	Intervention; Comparator	Safety outcomes
UK NCT00462748	LDL-c: 77 – 162mg/dL Triglycerides: <328mg/dL n = 786	Multicentre 6 weeks	Rosuvastatin (5 or 10mg) Simvastatin (40mg) + ezetimibe (10mg)	• Compliance
McKenney 2007[171] USA NCT00079638	Elevated LDL-c with risk for or established CHD LDL-c: ≥190mg/dL with 0 – 1 risk factors LDL-c: ≥160mg/dL with 2 risk factors LDL-c: ≥130mg/dL with CHD Triglycerides: NR n = 293	RCT, blinding NR Multicentre 12 weeks	Rosuvastatin (10 titrated to 40mg) Simvastatin (20 titrated to 40mg) + ezetimibe (10mg)	• Withdrawal • Adverse events • ALT, AST, CK
McKenney 2006[172] NR NCT00092573	Mixed hyperlipidaemia LDL-c: 130 – 220mg/dL Triglycerides: 200 - 500mg/dL n = 576	RCT, double-blind, extension study [152] International, multicentre 48 weeks	Fenofibrate (160mg) Fenofibrate (106mg) + ezetimibe (10mg)	• Withdrawal • Adverse events • ALT, AST, CK
Melani 2003[173] USA NCT00079638	Primary hypercholesterolaemia LDL-c: 155 – 251mg/dL Triglycerides: ≤354mg/dL n = 538	RCT, double-blind Multicentre 12 weeks	Placebo Pravastatin (10, 20 or 40mg) Pravastatin (10, 20 or 40mg) + ezetimibe (10mg)	• Withdrawal • Adverse events • ALT, AST, CK • Compliance
Moutzouri 2011[174] Greece NR	Primary hypercholesterolaemia LDL-c: ≥NCEP-ATP III guidelines Triglycerides: < 500mg/dL n = 153	RCT, open-label Single-centre 12 weeks	Rosuvastatin (10mg) Simvastatin (40mg) Simvastatin (10mg) + ezetimibe (10mg)	• Withdrawal • ALT, AST, CK • Compliance
Nicholls 2017[175] USA NCT02227784	ASCVD with/without diabetes LDL-c: ≥70mg/dL Triglycerides: ≤400mg/dL n = 366	RCT, double-blind Multicentre 12 weeks	Atorvastatin (40mg) Atorvastatin (80mg) Atorvastatin (40mg) + ezetimibe (10mg)	• Withdrawal • Adverse events • ALT, AST, CK

Author; year; country; trial ID	Inclusion criteria; Sample size	Design; Setting; Follow-up	Intervention; Comparator	Safety outcomes
Ose 2007[176] USA + 24 countries [b] Protocol 038-10	Primary hypercholesterolaemia LDL-c: 145 – 250mg/dL Triglycerides: ≤350mg/dL n = 1104	RCT, double-blind, extension study[134] International, multicentre 14 weeks	Simvastatin (10, 20, 40 or 80mg) + ezetimibe (10mg) Simvastatin (10, 20, 40 or 80mg)	• Withdrawal • Adverse events • ALT, AST, CK
Ostad 2009[177] Germany ISRCTN34110682	CAD LDL-c: ≥100mg/dL Triglycerides: NR n = 58	RCT, double-blind Single-centre 8 weeks	Atorvastatin (80mg) Atorvastatin (10mg) + ezetimibe (10mg)	• Withdrawal • Adverse events • ALT, AST, CK
Pandey 2011[178] Canada NCT00652847	Primary hypercholesterolaemia with high CAD risk LDL-c: 96mg/dL despite treatment Triglycerides: NR n = 936	RCT, open-label Multicentre 6 weeks	Statin + ezetimibe Statin + statin	• Withdrawal • Adverse events
Patel 2006[179] UK Protocol P00680	Primary hypercholesterolaemia LDL-c: ≥127 mg/dL Triglycerides: ≤350mg/dL n = 153	RCT, double-blind Multicentre 6 weeks	Simvastatin (20mg) + ezetimibe (10mg) Simvastatin (20mg) + placebo	• Withdrawal • Adverse events • ALT, AST, CK • Compliance
Pearson 2006[180] USA NR	Hypercholesterolaemia LDL-c: >NCEP-ATP III guidelines Triglycerides: ≤350mg/dL n = 3030	RCT, double-blind Multicentre 6 weeks	Statin + ezetimibe (10mg) Statin + placebo	• Withdrawal • Adverse events • ALT, AST, CK
Reckless 2008[181] Asia, Europe [n] NCT00132717	Hospitalised for coronary event LDL-c: NR Triglycerides: ⩽ 350mg/dL n = 424	RCT, open-label International, multicentre 12 weeks	Double Statin dose Simvastatin (40mg) + ezetimibe (10mg)	• Withdrawal • Adverse events • ALT, AST, CK • Compliance
Robinson 2009[182] USA NCT00409773	Hypercholesterolaemia at risk of CHD with metabolic syndrome LDL-c: ≥70mg/dL with ASCVD;	RCT, double-blind Multicentre 6 weeks	Atorvastatin (10mg) Atorvastatin (20mg) Atorvastatin (40mg)	• Withdrawal • Adverse events • ALT, AST, CK

Author; year; country; trial ID	Inclusion criteria; Sample size	Design; Setting; Follow-up	Intervention; Comparator	Safety outcomes
	≥100mg/dL without ASCVD Triglycerides: NR n = 1143		Simvastatin (20mg) + ezetimibe (10mg) Simvastatin (40mg) + ezetimibe (10mg)	
Roeters 2008[183] The Netherlands EASEGO	CHD with/without Type 2 diabetes LDL-c: 96 – 193mg/dL despite treatment Triglycerides: <350mg/dL n = 367	RCT, open-label Multicentre 14 weeks	Double Statin dose Simvastatin (20mg) + ezetimibe (10mg)	• Withdrawal • Adverse events • ALT, AST, CK
Rosen 2013[184] Europe, North and South America [o] NR	CVD with Type 1 or 2 diabetes LDL-c: 70 – 160mg/dL despite treatment Triglycerides: ⩽ 400mg/dL n = 808	RCT, double-blind International, multicentre 6 weeks	Double Statin dose Rosuvastatin (10mg) Simvastatin (20mg) + ezetimibe (10mg)	• Withdrawal • Adverse events • ALT, AST, CK
Ruggenenti 2010[185] Italy NCT00157482	Elevated LDL-c with type 2 diabetes LDL-c ≥135mg/dL despite lipid-lowering therapy n = 108	RCT, double-blind Multicentre 8 weeks	Simvastatin (40mg) + ezetimibe (10mg) Simvastatin (40mg) + Placebo	• Withdrawal • Adverse events • ALT, AST, CK
Stein 2004[186] 21 countries [b] NR	Primary hypercholesterolaemia with CHD and 2 cardiovascular risk factors or HeFH with LDL-c ≥130mg/dL despite treatment n = 621	RCT, double-blind International, multicentre 14 weeks	Atorvastatin (20mg) Atorvastatin (10mg) + ezetimibe (10mg)	• Withdrawal • Adverse events • ALT, AST, CK
Stojakovic 2010[187] Germany NCT00814723	With or at high-risk of CHD LDL-c: 100 – 160mg/dL Triglycerides: NR n = 84	RCT, single-blind Single-centre 12 weeks	Fluvastatin (80mg) Fluvastatin (80mg) + ezetimibe (10mg)	• ALT, AST, CK
Strony 2008[188] USA NR	Primary hypercholesterolaemia	RCT, double-blind, extension study[147] Multicentre	Simvastatin (10, 20, 40 or 80mg) + ezetimibe (10mg)	• Withdrawal • Adverse events • ALT, AST, CK • Compliance

Author; year; country; trial ID	Inclusion criteria; Sample size	Design; Setting; Follow-up	Intervention; Comparator	Safety outcomes
	LDL-c: 145 – 250mg/dl Triglycerides: <350mg/dL n = 109	12 months	Simvastatin (10, 20, 40 or 80mg) + Placebo	
Sudhop 2002[189] Germany NR	Hypercholesterolaemia LDL-c: 130 – 180mg/dL Triglycerides: <250mg/dL n = 18	RCT, double-blind, cross-over Single-centre 6 weeks	Ezetimibe (10mg) Placebo	• Adverse events • ALT, AST, CK
Sudhop 2009[190] NR NCT00652301	Hypercholesterolaemia LDL-c: 130 – 180mg/dL Triglycerides: <250mg/dL n = 41	RCT, double-blind, cross-over Centres NR 28 weeks	Ezetimibe (10mg) Simvastatin (20mg) Simvastatin (20mg) + Ezetimibe (10mg) Placebo	• Withdrawal • Adverse events • ALT, AST, CK
van der Graff 2008[95] The Netherlands NCT00129402	Familial hypercholesterolaemia LDL-c value based on genotype Triglyceride: ≤ 350mg/dL Adolescents n = 248	RCT, double-blind/open label [p] Multicentre 52 weeks	Simvastatin (10, 20 or 40mg) + ezetimibe (10mg) Simvastatin (10, 20 or 40mg) + placebo	• Withdrawal • Adverse events • ALT, AST, CK
West 2011[125] USA NCT00587678	Peripheral artery disease, ABI 0.4 – 0.9 LDL-c: NR Triglycerides: NR n = 87	RCT, double-blind Single-centre 24 months	Simvastatin (40mg) Simvastatin (40mg) + ezetimibe (10mg)	• Withdrawal • Adverse events • ALT, AST, CK • Compliance
Zieve 2010[96] America and Europe [q] NCT00418834	High-risk of CHD with/without ASCVD LDL-c: 70 – 160mg/dL established CHD; 100 – 190mg/dL high-risk of CHD Triglycerides: ≤350mg/dL Patients ≥ 65 years	RCT, double-blind International, multicentre 12 weeks	Atorvastatin (20mg titrated to 40mg) Atorvastatin (10mg) + ezetimibe (10mg)	• Withdrawal • Adverse events • ALT, AST, CK

Author; year; country; trial ID	Inclusion criteria; Sample size	Design; Setting; Follow-up	Intervention; Comparator	Safety outcomes
	n = 1053			

Abbreviations:
ALT = alanine aminotransferase, **ASCVD** = atherosclerotic cardiovascular disease, **AST** = aspartate aminotransferase, **CAD** = coronary artery disease, **CHD** = coronary heart disease, **CVD** = cardiovascular disease, **CK** = creatine kinase, **HeFH** = Heterozygous familial hypercholesterolaemia, **LDL-c** = low density lipoprotein-cholesterol, **mg** = milligrams, **n** = number of participants, **NCEP ATP** = national cholesterol education adult treatment panel, **NR** = not reported, **RCT** = randomised controlled trial.

Notes
a = Estonia, France, Latvia, The Netherlands, Slovenia, Spain, Taiwan.
b = Remaining countries not reported.
c = Canada, Columbia, Croatia, Denmark, Finland, Hungary, Peru, Poland, Puerto Rico, USA.
d = Argentina, Belgium, Bulgaria, Canada, Chile, Columbia, Croatia, Czech Republic, Denmark, Estonia, Finland, France, Germany, Hungary, Israel, Italy, Lithuania, Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, Turkey, United Kingdom and USA.
e = Australia, Canada, France, Germany, Italy, Mexico, Spain, UK, USA.
f = Belgium, Germany, Greece, Hungary, Israel, Netherlands, Norway, Portugal, Romania, Slovenia, Sweden, and Switzerland.
g = Canada, Czech Republic, Germany, Greece, Hungary, Italy, The Netherlands, Norway, Spain, UK.
h = Croatia, Czech Republic, Egypt, France, Italy, Lebanon, Russia, Saudi Arabia, Spain, Turkey and United Arab Emirates.
i = Belgium, Czech Republic, Estonia, France, Greece, Italy, Latvia, Lithuania, the Netherlands and Portugal.
j = Statins include: Simvastatin, Atorvastatin or another Statin.
k = Costa Rica, Estonia, Guatemala, Hungary, Israel, Latvia, Malaysia, Peru, Poland, Romania and Spain.
l = USA, Canada, South Africa, Spain, Denmark, Norway, Sweden, The Netherlands.
m = Canada, Columbia, France, Greece, Israel, Italy, Norway, Netherlands and USA.
n = Australia, Austria, Belgium, Chile, Croatia, France, Germany, Hong Kong, Italy, Jordan, Malaysia, Singapore, Switzerland, UK.
o = Austria, Bulgaria, Chile, Costa Rica, Croatia, Egypt, Estonia, Germany, Greece, Hungary, Italy, Latvia, Lithuania, Peru, Portugal, United States.
p = open-label extension from week 33 to 57.
q = Canada, Poland, Romania, Russia, Ukraine, USA.

*NCEP-ATP III guidelines = < 100mg/dL for moderately high/high-risk subjects without atherosclerotic vascular disease or 70mg/dL for high-risk subjects with atherosclerotic vascular disease.

14 Appendix C: Economic evaluation study extraction

Table 29 Evidence table for the included studies on health economic evaluations

Study Characteristics								Health Economic Evaluation Summary						
Study	**Country**	**Drug regimen combinations**	**Costing Year**	**Time horizon**	**Study Perspective**	**Patient characteristics**	**Subgroup patient**	**Model**	**Health State**	**Sensitivity Analysis**	**Discount rate**	**Source**	**QoL Measure**	**Evaluation Outcome**
Alonso 2007[108]	Spain	**Intervention** • A40 + E10 • A80 + E10 **Comparators** • A (10, 20, 30, 40, 50, 60, 80) • C (0.2, 0.4, 0.6, 0.8) • F (20, 40) • L (10, 20, 40, 60, 80, 120) • P (10, 20, 40, 60, 80) • S (10, 20, 30, 40, 50, 60, 80, 120)	2005	Lifetime	Government	• 18 to 82 years old • Genetic FH patients, 44% Men	Variation in age and gender cohorts	Life-table	6 based on CVD events; • MI • Other ischemic heart disease • Heart failure • Ictus • CVD death • Non-CVD death	Scenario analysis • best case scenario: upper limit of SMR and management costs <10% • worst case scenario: lower limit of SMR and management • Costs> 10% • Revision of discount rate to 6%	3% of Effects 6% of cost	Spanish FH Registry (1999-2002)	NR	Cost per LYG from PYLL
Ara 2008a[107]	UK	**Intervention** • Simvastatin (NOS) + Ezetimibe (NOS) • Atorvastatin (NOS) + Ezetimibe (NOS) **Comparators** • Simvastatin (NOS) • Atorvastatin (NOS)	2006	• 5 years • 10 years • 20 years • Lifetime	Government	• Men • 55-year old • History of CVD • LDL-c (116mg/dL [3.0 mmol/l])	NR	Markov model	6 based on CHD History; • No CHD • Non-fatal CVD • Recurrent CVD • Healthy secondary prevention • Fatal CVD from stroke and CHD • Non-CVD death	• Variations in baseline parameters • Health state utility variation ±20% • Health state cost ±50% • PSA	3.5%	• British National Formulary • Nottingham Heart Attack Register. • South London Stroke Register • 12 weeks of treatment	EQ-5D	Cost per QALY gained

Study Characteristics								Health Economic Evaluation Summary						
Study	**Country**	**Drug regimen combinations**	**Costing Year**	**Time horizon**	**Study Perspective**	**Patient characteristics**	**Subgroup patient**	**Model**	**Health State**	**Sensitivity Analysis**	**Discount rate**	**Source**	**QoL Measure**	**Evaluation Outcome**
Ara 2008b[97]	UK	**Intervention** • Ezetimibe (10) • A (10, 20, 40) + E10 • S (10, 20, 40, 80) + E10 • P (10, 20, 40) + E10 **Comparators** • A (10, 20, 40, 80) • S (10, 20, 40) • R (10, 20, 40) • No treatment	2006	• 20 years • Lifetime	• Healthcare payer	• ≥ 18 years • LDL-c 129.93 – 251.35 mg/dL (3.36–6.50 mmol/l) • FH patients • Statin intolerant	• CHD or non-CHD diabetic patients • Different ethnic groups • HeFH and non-HeFH patients • Different LDL-c levels; 96.67, 116 and 135.34mg/dL (2.5, 3.0 and 3.5 mmol/l)	Markov model	9 based on CHD History • Stable angina • unstable angina • Non-fatal MI • Non-fatal stroke • TIA • CHD-death • Fatal stroke • Fatal TIA • Non-CHD death	• Variations in baseline parameters	3.5%	• Review of existing studies • Expert opinion • ScHARR economic analysis of statin therapy	EQ-5D	• Cost per QALY gained • Cost per LYG
Ara 2008c[106]	UK	**Intervention** • Ezetimibe (NOS) **Comparators** No treatment	2006	• 2 years • 5 years • 20 years • 45 years (Lifetime)	Government	• Male CVD patients • Statin intolerant or contraindications • 55 years • LDL-c 154.68mg/dL (4.0 mmol/)l	Variation in gender and age cohort (75)	Markov Model	6 based on CHD History; • No CHD • Non-fatal CVD • Recurrent CVD • Healthy secondary prevention • Fatal CVD from stroke and CHD • Non-CVD death	• Variation in drug cost • Variation in LDL-c. • Variation in effectiveness rate of Ezetimibe • Variation in relative risk of CVD events • PSA	3.5%	• Published studies • British Heart Foundation • Nottingham Heart Attack Register. • South London Stroke Register	EQ-5D	Cost per QALY gained

Study Characteristics								Health Economic Evaluation Summary						
Study	**Country**	**Drug regimen combinations**	**Costing Year**	**Time horizon**	**Study Perspective**	**Patient characteristics**	**Subgroup patient**	**Model**	**Health State**	**Sensitivity Analysis**	**Discount rate**	**Source**	**QoL Measure**	**Evaluation Outcome**
Cook 2004[98]	Germany Norway Spain	**Intervention** • S (10, 20, 40, 80) + E10 • A (10, 20, 40, 80) + E10 **Comparators** • A (10, 20, 40, 80) • S (10, 20, 40, 80)	• 2004	• 5 years • Lifetime	Germany: Healthcare payer Norway and Spain: Government	• CHD or non- • CHD diabetic patients • Patients prescribed atorvastatin or simvastatin • Germany and Spain: LDL-c ≥100mg/dL • Norway: -LDL-c 193.55mg/dL (≥5.0 mmol/l)	CHD or non-CHD diabetic patients	Markov Model	4 based on CHD History; • No CHD • MI • Angina • CHD death • Non-CHD death	• 10% & 20% relative reduction in the annual CHD risk • 25% & 50% reduction in the daily cost of atorvastatin and simvastatin • 0% & 6% discount rate • 5-year duration of ezetimibe coadministration	3%	• German REALITY Study • 12 months of treatment	NR	Cost per LYG
Davies 2017[99]	US	**Intervention** • A (10, 20, 40, 80) + E10 • S (10, 20, 40, 80) + E10 • R (5,10, 20, 40, 80) + E10 **Comparator** • A (10, 20, 40, 80) • S (10, 20, 40, 80) • R (5, 10, 20, 40, 80)	2013	100 years	Healthcare payer	35 -74 years old History of CHD and/or stroke LDL-c ≥70mg/dL	LDL-c levels ≥100mg/dL Diabetic patients with LDL-c levels ≥70mg/dL	Markov model	28 health state based on CVD History; No history of CVD prior to CHD prior to stroke prior to CVD. CVD death Non-CVD death	• Variations in LDL-c level lowering efficacy • CVD event rate reductions • Utility weights • Baseline risk • Allocation of CVD death • Percent price reduction of ezetimibe.	3%	• IMS • Health's PharMetrics Plus Health Plan Claims database (PMTX+) • Electronic Medical Record (EMR)	EQ-5D	Cost per QALY gained

Study Characteristics								Health Economic Evaluation Summary						
Study	**Country**	**Drug regimen combinations**	**Costing Year**	**Time horizon**	**Study Perspective**	**Patient characteristics**	**Subgroup patient**	**Model**	**Health State**	**Sensitivity Analysis**	**Discount rate**	**Source**	**QoL Measure**	**Evaluation Outcome**
Kohli 2006[100]	Canada	**Intervention** • A (10, 20, 40) + E10 **Comparators** • A (10, 20, 40)	2002	• 2 years • Lifetime	Government	• 65-year-old patients • high risk CAD patients • Patients prescribed atorvastatin • LDL-c levels of 119.88 or 139.2mg/dL (3.1 or 3.6 mmol/L)	NR	Markov Model (Cook model)	Stage one 4 based on CHD History; • No CHD • Stroke • MI • Angina Stage two 4 based on CAD events; • -Non-fatal MI • - Non-fatal Angina • -CAD death • Non-CAD death	• Variation in drug cost by 20% • Management cost for post-MI and Angina • Removal of 7% drug acquisition cost mark-up • Removal of 1-year lag time before benefit of treatment. • Variation in utility for individuals in MI and angina. • Variation in age 45-55	5%	• Ontario Drug Benefit Formulary • Various Clinical trials	NR	• Cost per QALY gained • Cost per LYG
Laires 2015[101]	Portugal	**Intervention** • A10+E10 • A20+E10 **Comparators** • R10 • R20	2015	100 years	Healthcare payer	• High cardiovascular risk patients • History of CHD and/or diabetes • LDL- C ≥100mg/dL (2.5 mmol/L) • 49% Men	• CHD only • Diabetes only • Both diabetes and CHD	Markov model	7 based on CHD History; • No CHD • Non-fatal MI • Angina pectoris • Subsequent year CHD • Healthy secondary prevention • Fatal CHD • Non-CHD death.	Discount rate to 0% and 7%	5%	• DYSIS • National Authority of Medicines and Health Products (INFARMED) • National Institute of Statistics	NR	• Cost per QALY gained • Cost per LYG

Study Characteristics								Health Economic Evaluation Summary						
Study	**Country**	**Drug regimen combinations**	**Costing Year**	**Time horizon**	**Study Perspective**	**Patient characteristics**	**Subgroup patient**	**Model**	**Health State**	**Sensitivity Analysis**	**Discount rate**	**Source**	**QoL Measure**	**Evaluation Outcome**
Nherera 2010[102]	UK	**Intervention** • S40+E10 • S80+E10 **Comparators** • A80 • S40 • R20 • R40	2008-2009	100 years	Healthcare payer	• FH patients • 20 and 70 years old	Different age cohorts; • 20-39 • 40-59 • ≥60	Markov model	9 based on CHD History; • No event • MI • Stroke • Peripheral artery disease • Heart failure • Revascularisation • Unstable angina • CVD death • Non-CVD death	• Variation in treatment effect • Variation in age • Variation in risk of death from Non-CVD	3.5%	• UK Prescription Pricing Authority • Various study sources for QoL data	NR	Cost per QALY gained
Plans-Rubio 2010[103]	Spain	**Intervention** Each comparator + E10 **Comparators** • A (10, 20, 40, 80) • F (20, 40, 80) • L (20, 40) • P (10, 20, 40) • R (5, 10, 20) • S (10, 20, 40)	2010	NR	Healthcare payer	• Failed statin at highest dose • ≥45 years for men • ≥55 years for women • LDL- C ≥130mg/dL	• CHD Patients LDL- C ≥130mg/dL • LDL- C ≥160mg/dL • LDL- C ≥190mg/dL	Treat-to-Target= Drug cost/ Max % LDL-c reduction	NR	Variation in ICER computation with changes in • dominance • quality of therapies	NR	Meta-Analysis • 16 weeks of treatment • 2 months of dietary treatment before drug therapy	NR	• Cost per LYG • ICER
Reckless 2010[104]	UK	**Intervention** S40 + E10 **Comparators** • A20 • A40 • S40	2009	100 years	Government	• Hospitalised ACS patients • On a stable (≥6 weeks) statin dose before admission	3 Strata of statin dose/potency; • low • Medium • high	Markov model	5 based on CHD History; • no event • MI • angina pectoris • CHD death • non–CHD death.	• Equating prices of generic atorvastatin to generic simvastatin	3.5%	INFORCE trial 12- week follow up	NR	-Cost per QALY gained

Study Characteristics								Health Economic Evaluation Summary						
Study	**Country**	**Drug regimen combinations**	**Costing Year**	**Time horizon**	**Study Perspective**	**Patient characteristics**	**Subgroup patient**	**Model**	**Health State**	**Sensitivity Analysis**	**Discount rate**	**Source**	**QoL Measure**	**Evaluation Outcome**
Van Nooten 2011[105]	Netherlands	**Intervention** • S20 + E10 • S40 + E10 **Comparators** • A20 • A40 • S40	2008	100 years	Healthcare payer	• CHD patients on a stable (≥4 weeks) statin dose (S20 or A10) • LDL-c >96.67mg/dL (2.5 mmol/l) • Female 24.3%	NR	Markov model	6 based on CHD History; • No CHD • Non-fatal CVD • Recurrent CVD • Healthy secondary prevention • Fatal CVD. • Non-CVD death	PSA output as CEAC with variation in WTP threshold	1.5% of Effects 4% of cost	• Dutch EASEGO • 2006 Dutch Guideline on Cardiovascular Risk Management • 2008 Dutch Healthcare Performance Report	EQ-5D	Cost per QALY gained

Abbreviations:

ACER = Average cost-effectiveness ratios, **CAD** =coronary artery disease, **CEAC** = Cost-Effectiveness Acceptability Curves, **CEAF** =cost-effectiveness acceptability frontier, **CHD** = coronary heart disease, **CKD** = chronic kidney disease, **CVD** = cardiovascular disease, **DM** = Diabetes Mellitus, **EVPI** = Expected Value of Perfect Information, **EQ-5D** = EuroQol-5D, **EQ-5D HRQoL**= EuroQol-5D health related quality of life, **EVPPI** = Expected Value of Perfect Information for Parameters, **FH** = Familial hypercholesterolaemia, **HeFH** = heterozygous familial hypercholesterolaemia, **IMS =** Intercontinental Medical Statistics, **IS** = ischaemic stroke (IS), **LDL-c**= low-density lipoprotein cholesterol, **MI** = myocardial infarction, **NOS** = no otherwise specific, **PSA** = Probabilistic sensitivity analysis, **PYLL** =potential years of life lost, **QALY** = quality-adjusted life year, **SMR** = standardized mortality rate, **TIA** = transient ischemic attack, **VAS** = visual analogue scale, **WTP** = willingness to pay.

Notes: Drug are abbreviated with the first letter of various statins and Ezetimibe, and their regimens. **E** is for Ezetimibe and others are for statins therapy. A = Atorvastatin, C = Cerivastatin, F = Fluvastatin, C = Cerivastatin, L = Lovastatin, P = Pravastatin, R = Rosuvastatin, S = Simvastatin. The regimens are 5mg, 10mg, 20mg, 30mg, 40mg, 50mg, 60mg, 80mg, 120mg. For example, 20mg Atorvastatin drug is written as A20. This is consistent for all except Cerivastatin which has regimens of 0.2mg, 0.4mg, 0.6mg, 0.8mg.

15 Appendix D: List of ongoing clinical trials

Table 30 Ongoing clinical trials fitting the inclusion criteria

Trial registry ID	Indication; Target sample size	Design	Intervention	Comparator	Primary outcomes	Status
EU Clinical Trials Register						
2014-001069-28	Hypercholesterolemia and high-risk cardiovascular patients with hypertriglyceridemia n = 13,000	RCT, single-blind, multicentre	OMEGA-3 (800mg) Statin + Ezetimibe Statin	Placebo	MACE	Ongoing
2011-001055-36	Diabetes and cardiovascular event Hypercholesteremia n = 28	RCT, double-blind, centre NR	Simvastatin Atorvastatin Rosuvastatin Ezetimibe	Fluvastatin Sodium Pravastatin Sodium	Cost-effectiveness in prescribing leads, determined by initial LDL-c	Ongoing
2006-006557-28	Type II Diabetic and hyperlipidaemia n = 480	RCT, open-label, multicentre	Fenofibrate (160mg)/ Pravastatin (40mg) OR Fenofibrate (160mg)/ Pravastatin (40mg) + Ezetimibe (10mg)	Simvastatin (20mg) OR Simvastatin (20mg) + Ezetimibe (10mg)	Change in plasma non-HDL-c	Ongoing
2016-004556-30	Patients with Primary Hypercholesterolaemia n = 758	RCT, double-blind, multi centre	Rosuvastatin (10mg) + ezetimibe (10mg) Rosuvastatin (20mg) + ezetimibe (10mg) Rosuvastatin (40mg) + ezetimibe (10mg)	Rosuvastatin (10mg) Rosuvastatin (20mg) Rosuvastatin (40mg)	Change in LDL-c	Ongoing
2004-004416-22	Diabetes mellitus type 2, without or with renal impairment n = 100	RCT, double-blind, single centre	Simvastatin (40mg) + Ezetimibe (10mg)	Simvastatin (40mg)	To compare drug effectiveness	Ongoing
2008-003908-61	Metabolic syndrome patients n = 1080	RCT, double-blind, multi centre	Simvastatin (10mg) + ezetimibe (10mg)	Simvastatin (80 mg)	Postprandial arterial endothelial function	Ongoing

2009-013622-17	Suspected stable CAD candidates to PCI n = 1080	RCT, double-blind, multi centre	Rosuvastatin (40mg)	Ezetimibe (10mg)	Reduction in the extent of peri-procedural MI	Ongoing
2008-000824-20	Type 2 diabetes mellitus n = 16	RCT, double-blind, single centre	Simvastatin (10mg) + ezetimibe (10mg)	Simvastatin (20mg)	postprandial lipemia	Ongoing
Clinicaltrials.gov						
NCT03169985	Coronary Artery Disease n = 280	RCT, single-blind, single centre	Rosuvastatin (10mg) + ezetimibe (10mg)	Rosuvastatin (20mg)	Change in percent atheroma volume (PAV)	Recruiting
NCT03044665	Cardiovascular diseases n = 3780	RCT, open-label, single centre	Rosuvastatin (10mg) + ezetimibe (10mg)	Rosuvastatin (20mg)	Composite of cardiovascular death Composite of nonfatal stroke Major cardiovascular event	Recruiting
NCT03434613	Non-alcoholic Fatty Liver Disease Hyperlipidaemia LDL-c > 130mg/dL with less than 1 major risk factor LDL-c > 100mg/dL with 2 or more risk factors LDL-c > 70mg/dL with carotid stenosis > 50% abdominal aortic aneurysm and diabetes mellitus n = 70	RCT, open-label, single centre	Rosuvastatin 5 mg + ezetimibe (10mg)	Rosuvastatin 5 mg	Change in liver fat	Recruiting
NCT03771053	Coronary Heart Disease n = 240	RCT, double-blind, single Centre	Simvastatin (40mg) + Ezetimibe (10mg)	Simvastatin (40mg)	Change from Baseline coronary plaque volume percentage (PAV)	Recruiting
NCT03597412	Atherosclerotic cardiovascular disease Type 2 Diabetes Mellitus n = 244	RCT, Open Label, Single centre	Rosuvastatin (10mg) + ezetimibe (10mg)	Rosuvastatin (20mg)	Change in LDL-c	Recruiting
NCT03403556	Atherosclerotic Cardiovascular Disease Type 2 Diabetes n = 140	RCT, Open Label, Multi-centre	Rosuvastatin (10mg) + ezetimibe (10mg)	Rosuvastatin (20mg)	Change in LDL-c	Recruiting

NCT03768427	Hypercholesterolemia n = 450	RCT, double-blind, single centre	Atorvastatin (10mg) + Atorvastatin (10mg) Atorvastatin (20mg) + ezetimibe (10mg)	Atorvastatin (10mg) Atorvastatin (20mg)	Change in LDL-c	Recruiting
NCT04074551	Hypertension Dyslipidaemias[a] n = 129	RCT, double-blind, single centre	Rosuvastatin (mg NR) + ezetimibe (mg NR)	HCP1701 (mg NR) Losartan (mg NR) Amlodipine (mg NR)	Change in LDL-c	Recruiting
NCT03510884	Hypercholesterolaemia n = 150	RCT, triple-blind, multi centre	Ezetimibe (mg NR)	Rosuvastatin (mg NR) Atorvastatin (mg NR) Simvastatin (mg NR) Pravastatin (mg NR) Lovastatin (mg NR) Fluvastatin (mg NR) Cholestyramine (mg NR) Nicotinic acid Fenofibrate Omega-3 fatty acids Placebo	Change in LDL-c	Recruiting

Abbreviations

HDL-c = high density lipoprotein, **LDL-c** = low density lipoprotein-cholesterol, **mg** = milligrams, **n** = number of patients, **NR** = not reported, **RCT** = randomised controlled trial.

Notes

a = dyslipidaemia not defined.

16 Appendix E: List of excluded trials at full text

Wrong study design

Blazing MA, Giugliano RP, de Lemos JA, et al. On-treatment analysis of the Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT). *American Heart Journal* 2016;182:89-96.

Bohula EA, Giugliano RP, Cannon CP, et al. Achievement of dual low-density lipoprotein cholesterol and high-sensitivity c-reactive protein targets more frequent with the addition of ezetimibe to simvastatin and associated with better outcomes in IMPROVE-IT. *Circulation* 2015;132(13):1224-33.

Charles Z, Pugh E, Barnett D. Ezetimibe for the treatment of primary (heterozygous-familial and non-familial) hypercholesterolaemia: NICE technology appraisal guidance. *Heart* 2008;94(5):642-3.

Dujovne CA, Suresh R, McCrary Sisk C, et al. Safety and efficacy of ezetimibe monotherapy in 1624 primary hypercholesterolaemic patients for up to 2 years. *International Journal of Clinical Practice* 2008;62(9):1332-36.

Gryskiewicz KA, Coleman CI, Gillespie EL, et al. Cost-effectiveness analysis of combination statin/ezetimibe therapy for the treatment of elevated low-density lipoprotein cholesterol. *Hospital Pharmacy* 2005;40(8):687-92.

Haynes R, Lewis D, Emberson J, et al. Effects of lowering LDL cholesterol on progression of kidney disease. *Journal of the American Society of Nephrology* 2014;25(8):1825-33.

Pokharel Y, Chinnakondepalli K, Vilain K, et al. Impact of Ezetimibe on the Rate of Cardiovascular-Related Hospitalizations and Associated Costs Among Patients With a Recent Acute Coronary Syndrome: Results From the IMPROVE-IT Trial (Improved Reduction of Outcomes: Vytorin Efficacy International Trial). *Circ Cardiovasc Qual Outcomes* 2017;10(5).

Robinson JG, Ballantyne CM, Hsueh W, et al. Achievement of specified low-density lipoprotein cholesterol, non-high-density lipoprotein cholesterol apolipoprotein B, and high-sensitivity C-reactive protein levels with ezetimibe/simvastatin or atorvastatin in metabolic syndrome patients with and without atherosclerotic vascular disease (from the VYMET study). *Journal of Clinical Lipidology* 2011;5(6):474-82.

Rossebo AB, Pedersen TR, Boman K, et al. Intensive lipid lowering with simvastatin and ezetimibe in aortic stenosis. *BMJ* 2008;337:10.1136/bmj.a493.

Soini EJ, Davies G, Martikainen JA, et al. Population-based health-economic evaluation of the secondary prevention of coronary heart disease in Finland. *Curr Med Res Opin* 2010;26(1):25-36.

Steg PG, Verdier JC, Carre F, et al. A randomised trial of three counselling strategies for lifestyle changes in patients with hypercholesterolemia treated with ezetimibe on top of statin therapy (TWICE). *Archives of Cardiovascular Diseases* 2008;101(11):723-35.

Strony J, Hoffman R, Hanson M, et al. Tolerability and effects on lipids of ezetimibe coadministered with pravastatin or simvastatin for twelve months: Results from two open-label extension studies in hypercholesterolemic patients. *Clinical Therapeutics* 2008;30(12):2280-97.

Wrong population (includes country and patient demographics)

Ahmed S, Ullah E, Ahmed M, et al. Efficacy of combination of ezetimibe and simvastatin versus atorvastatin in reducing low density lipoprotein-cholesterol in male patients of hypercholesterolemia, at Bahawalpur. *Medical Forum Monthly* 2008;19(5):3-9.

Araujo DB, Bertolami MC, Ferreira WP, et al. Pleiotropic effects with equivalent low-density lipoprotein cholesterol reduction: Comparative study between simvastatin and simvastatin/ezetimibe coadministration. *Journal of Cardiovascular Pharmacology* 2010;55(1):1-5.

Arimura T, Miura SI, Ike A, et al. Comparison of the efficacy and safety of statin and statin/ezetimibe therapy after coronary stent implantation in patients with stable angina. *Journal of Cardiology* 2012;60(2):111-18.

Azar M, Valentin E, Badaoui G, et al. Comparison of the effects of combination atorvastatin (40 mg) + ezetimibe (10 mg) versus atorvastatin (40 mg) alone on secretory phospholipase A2 activity in patients with stable coronary artery disease or coronary artery disease equivalent. *American Journal of Cardiology* 2011;107(11):1571-74.

Azar RR, Badaoui G, Sarkis A, et al. Effect of ezetimibe/atorvastatin combination on oxidized low density lipoprotein cholesterol in patients with coronary artery disease or coronary artery disease equivalent. *American Journal of Cardiology* 2010;106(2):193-97.

Baigent C, ray M, Reith C, et al. Study of Heart and Renal Protection (SHARP): Randomized trial to assess the effects of lowering low-density lipoprotein cholesterol among 9,438 patients with chronic kidney disease. *American Heart Journal* 2011;160(5):785-94.

Baigent C, ray MJ, Reith C, et al. The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): A randomised placebo-controlled trial. *The Lancet* 2010;377(9784):2181-92.

Barbosa SP, Lins LC, Fonseca FA, et al. Effects of ezetimibe on markers of synthesis and absorption of cholesterol in high-risk patients with elevated C-reactive protein. *Life Sciences* 2013;92(14):845-51.

Briseno GG, Mino-Leon D. Cost-effectiveness of rosuvastatin versus ezetimibe/simvastatin in managing dyslipidemic patients in Mexico. *Current Medical Research and Opinion* 2010;26(5):1075-81.

Chow D, Chen H, Glesby MJ, et al. Short-term ezetimibe is well tolerated and effective in combination with statin therapy to treat elevated LDL cholesterol in HIV-infected patients. *AIDS* (London, England) 2009;23(16):2133-41.

Cno YK, Hur SH, Han CD, et al. Comparison of ezetimibe/simvastatin 10/20 mg versus atorvastatin 20 mg in achieving a target low density lipoprotein-cholesterol goal for patients with very high risk. Korean *Circulation Journal* 2011;41(3):149-53.

Coll B, Aragones G, Parra S, et al. Ezetimibe effectively decreases LDL-cholesterol in HIV-infected patients. *Aids* 2006;20(12):1675-77.

Constance C, Westphal S, Chung N, et al. Efficacy of ezetimibe/simvastatin 10/20 and 10/40 mg compared with atorvastatin 20 mg in patients with type 2 diabetes mellitus. *Diabetes, Obesity and Metabolism* 2007;9(4):575-84.

El-Tamalawy MM, Ibrahim OM, Hassan TM, et al. Effect of Combination Therapy of Ezetimibe and Atorvastatin on Remnant Lipoprotein Versus Double Atorvastatin Dose in Egyptian Diabetic Patients. *Journal of Clinical Pharmacology* 2018;58(1):34-41.

Gonzalez-Ortiz M, Martinez-Abundis E, Kam-Ramos AM, et al. Effect of ezetimibe on insulin sensitivity and lipid profile in obese and dyslipidaemic patients. *Cardiovascular Drugs and Therapy* 2006;20(2):143-46.

Grandi AM, Nicolini E, Rizzi L, et al. Dyslipidemia in HIV-positive patients: A randomized, controlled, prospective study on ezetimibe+fenofibrate versus pravastatin monotherapy. *Journal of the International AIDS Society* 2014;17(19004)

Hagiwara N, Kawada-Watanabe E, Koyanagi R, et al. Low-density lipoprotein cholesterol targeting with pitavastatin 1 ezetimibe for patients with acute coronary syndrome and dyslipidaemia: The HIJ-PROPER study, a prospective, open-label, randomized trial. *European Heart Journal* 2017;38(29):2264-75.

Hamdan R, Hajj F, Kadry Z, et al. Benefit and tolerability of the coadministration of ezetimibe and atorvastatin in acute coronary syndrome patients. *Journal Medical Libanais* 2011;59(2):65-69.

Her AY, Kim JY, Kang SM, et al. Effects of atorvastatin 20 mg, rosuvastatin 10 mg, and atorvastatin/ ezetimibe 5 mg/5 mg on lipoproteins and glucose metabolism. *Journal of Cardiovascular Pharmacology* and Therapeutics 2010;15(2):167-74.

Hibi K, Sonoda S, Kawasaki M, et al. Effects of ezetimibe-statin combination therapy on coronary atherosclerosis in acute coronary syndrome. *Circulation Journal* 2018;82(3):757-66.

Hong SJ, Jeong HS, Ahn JC, et al. A Phase III, Multicenter, Randomized, Double-blind, Active Comparator Clinical Trial to Compare the Efficacy and Safety of Combination Therapy With Ezetimibe and Rosuvastatin Versus Rosuvastatin Monotherapy in Patients With Hypercholesterolemia: I-ROSETTE (Ildong Rosuvastatin & Ezetimibe for Hypercholesterolemia) Randomized Controlled Trial. *Clinical Therapeutics* 2018;40(2):226-41.e4.

Ishimitsu T, Ohno E, Ueno Y, et al. Effects of atorvastatin and ezetimibe on endothelial function in dyslipidemic patients with chronic kidney disease. *Clinical and Experimental Nephrology* 2014;18(5):704-10.

Joshi S, Sharma R, Rao HK, et al. Efficacy of combination therapy of rosuvastatin and ezetimibe vs rosuvastatin monotherapy on lipid profile of patients with coronary artery disease. *Journal of Clinical and Diagnostic Research* 2017;11(12):OC28-OC31.

Kanat M, Serin E, Tunckale A, et al. A multi-center, open label, crossover designed prospective study evaluating the effects of lipid lowering treatment on steroid synthesis in patients with type 2 diabetes (MODEST Study). *Journal of Endocrinological Investigation* 2009;32(10):852-56.

Kasmas SH, Izar MC, Franca CN, et al. Differences in synthesis and absorption of cholesterol of two effective lipid-lowering therapies. *Brazilian Journal of Medical and Biological Research* 2012;45(11):1095-101.

Kater ALA, Batista MC, Ferreira SRG. Synergistic effect of simvastatin and ezetimibe on lipid and pro-inflammatory profiles in pre-diabetic subjects. *Diabetology and Metabolic Syndrome* 2010;2(34).

Kawashiri Ma, Nohara A, Noguchi T, et al. Efficacy and Safety of Coadministration of Rosuvastatin, Ezetimibe, and Colestimide in Heterozygous Familial Hypercholesterolemia. *American Journal of Cardiology* 2012.

Kikuchi K, Nezu U, Inazumi K, et al. Double-blind randomized clinical trial of the effects of ezetimibe on postprandial hyperlipidaemia and hyperglycaemia. *Journal of Atherosclerosis and Thrombosis* 2012;19(12):1093-101.

Kim KJ, Kim SH, Yoon YW, et al. Effect of fixed-dose combinations of ezetimibe plus rosuvastatin in patients with primary hypercholesterolemia: MRS-ROZE (Multicenter Randomized Study of ROsuvastatin and eZEtimibe). *Cardiovascular Therapeutics* 2016;34(5):371-82.

Kim W, Yoon YE, Shin SH, et al. Efficacy and Safety of Ezetimibe and Rosuvastatin Combination Therapy Versus Those of Rosuvastatin Monotherapy in Patients With Primary Hypercholesterolemia. *Clinical Therapeutics* 2018;40(6):993-1013.

Kinouchi K, Ichihara A, Bokuda K, et al. Effects of adding ezetimibe to fluvastatin on kidney function in patients with hypercholesterolemia: A randomized control trial. *Journal of Atherosclerosis and Thrombosis* 2013;20(3):245-56.

Koh KK, Oh PC, Sakuma I, et al. Vascular and metabolic effects of ezetimibe combined with simvastatin in patients with hypercholesterolemia. *International Journal of Cardiology* 2015;199:126-31.

Kosoglou T, Statkevich P, Meyer I, et al. Effects of ezetimibe on the pharmacodynamics and pharmacokinetics of lovastatin. *Current Medical Research and Opinion* 2004;20(6):955-65.

Landray M, Baigent C, Leaper C, et al. The second United Kingdom Heart and Renal Protection (UK-HARP-II) study: A randomized controlled study of the biochemical safety and efficacy of adding ezetimibe to simvastatin as initial therapy among patients with CKD. *American Journal of Kidney Diseases* 2006;47(3):385-95.

Lee CJ, Choi S, Cheon DH, et al. Effect of two lipid-lowering strategies on high-density lipoprotein function and some HDL-related proteins: a randomized clinical trial. *Lipids in Health and Disease* 2017;16(49)

Lee JH, Kang HJ, Kim HS, et al. Effects of ezetimibe/simvastatin 10/20 mg vs. Atorvastatin 20 mg on apolipoprotein b/apolipoprotein a1 in korean patients with type 2 diabetes mellitus: Results of a randomized controlled trial. *American Journal of Cardiovascular Drugs* 2013;13(5):343-51.

Lee JH, Shin DH, Kim BK, et al. Early effects of intensive lipid-lowering treatment on plaque characteristics assessed by virtual histology intravascular ultrasound. *Yonsei Medical Journal* 2016;57(5):1087-94.

Lee SH, Kang SM, Park S, et al. The effects of statin monotherapy and low-dose statin/ezetimibe on lipoprotein-associated phospholipase A2. *Clinical Cardiology* 2011;34(2):108-12.

Lee SH, Park S, Kang SM, et al. Effect of atorvastatin monotherapy and low-dose atorvastatin/ezetimibe combination on fasting and postprandial triglycerides in combined hyperlipedemia. *Journal of Cardiovascular Pharmacology and Therapeutics* 2012;17(1):65-71.

Lin H, Zhang YM. The effect of Ezetimibe and Simvastatin Combination Therapy on percutaneous coronary intervention patients. *International Journal of Cardiology* 2017;242:1-3.

Liu B, Che W, Yan H, et al. Effects of rosuvastatin vs. Simvastatin/ezetimibe on arterial wall stiffness in patients with coronary artery disease. *Internal Medicine* 2013;52(24):2715-19.

Liu Z, Hao H, Yin C, et al. Therapeutic effects of atorvastatin and ezetimibe compared with double-dose atorvastatin in very elderly patients with acute coronary syndrome. *Oncotarget* 2017;8(25):41582-89.

Malina DMT, Fonseca FA, Barbosa SA, et al. Additive effects of plant sterols supplementation in addition to different lipid-lowering regimens. *Journal of Clinical Lipidology* 2015;9(4):542-52.

Masuda J, Tanigawa T, Yamada T, et al. Effect of Combination therapy of Ezetimibe and Rosuvastatin on Regression of Coronary Atherosclerosis in Patients with Coronary Artery Disease. *International Heart Journal* 2015;56(3):278-85.

Matsue Y, Matsumura A, Suzuki M, et al. Differences in action of atorvastatin and ezetimibe in lowering low-density lipoprotein cholesterol and effect on endothelial function - Randomized controlled trial. *Circulation Journal* 2013;77(7):1791-98.

Mihaylova B, Schlackow I, Herrington W, et al. Cost-effectiveness of Simvastatin plus Ezetimibe for Cardiovascular Prevention in CKD: Results of the Study of Heart and Renal Protection (SHARP). *Am J Kidney Dis* 2016;67(4):576-84.

Oikawa S, Yamashita S, Nakaya N, et al. Efficacy and safety of long-term coadministration of fenofibrate and ezetimibe in patients with combined hyperlipidemia: Results of the EFECTL study. *Journal of Atherosclerosis and Thrombosis* 2017;24(1):77-94.

Okada K, Iwahashi N, Endo T, et al. Long-term effects of ezetimibe-plus-statin therapy on low-density lipoprotein cholesterol levels as compared with double-dose statin therapy in patients with coronary artery disease. *Atherosclerosis* 2012;224(2):454-56.

Okada K, Kimura K, Iwahashi N, et al. Clinical usefulness of additional treatment with ezetimibe in patients with coronary artery disease on statin therapy: From the viewpoint of cholesterol metabolism. *Circulation Journal* 2011;75(10):2496-504.

Ouchi Y, Sasaki J, Arai H, et al. Ezetimibe Lipid-Lowering Trial on Prevention of Atherosclerotic Cardiovascular Disease in 75 or Older (EWTOPIA 75): A Randomized Controlled Trial. *Circulation* 2019;22

Padhy BM, Yadav R, Gupta YK. Hypolipidaemic and anti-inflammatory effects of fixed dose combination of atorvastatin plus ezetimibe in Indian patients with dyslipidaemia. *Singapore Medical Journal* 2013;54(2):90-95.

Ran D, Nie HJ, Gao YL, et al. A randomized, controlled comparison of different intensive lipid-lowering therapies in Chinese patients with non-ST-elevation acute coronary syndrome (NSTE-ACS): Ezetimibe and rosuvastatin versus high-dose rosuvastatin. *International Journal of Cardiology* 2011;235:49-55.

Ren Y, Zhu H, Fan Z, et al. Comparison of the effect of rosuvastatin versus rosuvastatin/ezetimibe on markers of inflammation in patients with acute myocardial infarction. *Experimental and Therapeutic Medicine* 2017;14(5):4942-50.

Rodney RA, Sugimoto D, Wagman B, et al. Efficacy and safety of coadministration of ezetimibe and simvastatin in African-American patients with primary hypercholesterolemia. *Journal of the National Medical Association* 2006;98(5):772-78.

Saeedi R, Johns K, Frohlich J, et al. Lipid lowering efficacy and safety of Ezetimibe combined with rosuvastatin compared with titrating rosuvastatin monotherapy in HIV-positive patients. *Lipids in Health and Disease* 2015;14(57)

Saito I, Azuma K, Kakikawa T, et al. A randomized, double-blind, placebo-controlled study of the effect of ezetimibe on glucose metabolism in subjects with type 2 diabetes mellitus and hypercholesterolemia. *Lipids in Health and Disease* 2015;14(40)

Sakamoto K, Kawamura M, Kohro T, et al. Effect of ezetimibe on LDL-C lowering and atherogenic lipoprotein profiles in type 2 diabetic patients poorly controlled by statins. *PLoS ONE* 2017;10

Sakamoto K, Kawamura M, Watanabe T, et al. Effect of ezetimibe add-on therapy over 52 weeks extension analysis of prospective randomized trial (RESEARCH study) in type 2 diabetes subjects. *Lipids in Health and Disease* 2015;16(122)

Sasaki J, Otonari T, Sawayama Y, et al. Double-dose pravastatin versus add-on ezetimibe with low-dose pravastatin - effects on LDL cholesterol, cholesterol absorption, and cholesterol synthesis in japanese patients with hypercholesterolemia (PEAS study). *Journal of Atherosclerosis and Thrombosis* 2012;19(5):485-93.

Schlackow I, Kent S, Herrington W, et al. Cost-effectiveness of lipid lowering with statins and ezetimibe in chronic kidney disease. *Kidney Int* 2019;96(1):170-79.

Shankar PK, Bhat R, Prabhu M, et al. Efficacy and tolerability of fixed-dose combination of simvastatin plus ezetimibe in patients with primary hypercholesterolemia: Results of a multicentric trial from India. *Journal of Clinical Lipidology* 2007;1(4):264-70.

Shaw SM, Chaggar P, Ritchie J, et al. The efficacy and tolerability of ezetimibe in cardiac transplant recipients taking cyclosporin. *Transplantation* 2009;87(5):771-75.

Stein E A, Ballantyne C M, Windler E, et al. Efficacy and Tolerability of Fluvastatin XL 80 mg Alone, Ezetimibe Alone, and the Combination of Fluvastatin XL 80 mg With Ezetimibe in Patients With a History of Muscle-Related Side Effects With Other Statins. *American Journal of Cardiology* 2008; 101(4):490-6.

Sugiyama S, Jinnouchi H, Hieshima K, et al. A pilot study of ezetimibe vs. atorvastatin for improving peripheral microvascular endothelial function in stable patients with type 2 diabetes mellitus. *Lipids in Health and Disease* 2015;14(37)

Takase S, Matoba T, Nakashiro S, et al. Ezetimibe in combination with statins ameliorates endothelial dysfunction in coronary arteries after stenting: the CuVIC trial (effect of cholesterol absorption inhibitor usage on target vessel dysfunction after coronary stenting), a multicenter randomized controlled trial. *Arteriosclerosis, Thrombosis, and Vascular Biology* 2017;37(2):350-58.

Teramoto T, Sawada T, Iwamoto K, et al. Clinical Efficacy and Tolerability of Ezetimibe in Combination With Atorvastatin in Japanese Patients With Hypercholesterolemia-Ezetimibe Phase IV Randomized Controlled Trial in Patients With Hypercholesterolemia. *Current Therapeutic Research - Clinical and Experimental* 2012;73(1):16-40.

Torimoto K, Okada Y, Mori H, et al. Efficacy of combination of Ezetimibe 10 mg and rosuvastatin 2.5 mg versus rosuvastatin 5 mg monotherapy for hypercholesterolemia in patients with type 2 diabetes. *Lipids in Health and Disease* 2013;12(137)

Tsujita K, Sugiyama S, Sumida H, et al. Impact of dual lipid-lowering strategy with ezetimibe and atorvastatin on coronary plaque regression in patients with percutaneous coronary intervention: The multicenter randomized controlled PRECISE-IVUS trial. *Journal of the American College of Cardiology* 2015;66(5):495-507.

Uemura Y, Watarai M, Ishii H, et al. Atorvastatin 10 mg plus ezetimibe 10 mg compared with atorvastatin 20 mg: Impact on the lipid profile in Japanese patients with abnormal glucose tolerance and coronary artery disease. *Journal of Cardiology* 2012

Villegas-Rivera G, Roman-Pintos LM, Cardona-Munoz EG, et al. Effects of ezetimibe/simvastatin and rosuvastatin on oxidative stress in diabetic neuropathy: A randomized, double-blind, placebo-controlled clinical trial. *Oxidative Medicine and Cellular Longevity* 2015;2015(756294)

Wang J, Ai XB, Wang F, et al. Efficacy of ezetimibe combined with atorvastatin in the treatment of carotid artery plaque in patients with type 2 diabetes mellitus complicated with coronary heart disease. *International Angiology* 2017;36(5):467-73.

Wang X, Zhao X, Li L, et al. Effects of Combination of Ezetimibe and Rosuvastatin on Coronary Artery Plaque in Patients with Coronary Heart Disease. *Heart Lung and Circulation* 2016;25(5):459-65.

Watanabe E, Yamaguchi J, Arashi H, et al. Effects of statin versus the combination of ezetimibe plus statin on serum lipid absorption markers in patients with acute coronary syndrome. *Journal of Lipids* 2015;2015(109158)

Wu NQ, Guo YL, Zhu CG, et al. Comparison of statin plus ezetimibe with double-dose statin on lipid profiles and inflammation markers 11 Medical and Health Sciences 1103 Clinical Sciences. *Lipids in Health and Disease* 2018;17(265)

Yamazaki D, Ishida M, Watanabe H, et al. Comparison of anti-inflammatory effects and high-density lipoprotein cholesterol levels between therapy with quadruple-dose rosuvastatin and rosuvastatin combined with ezetimibe. *Lipids in Health and Disease* 2013;12(9)

Yang L, Zhao P, Zhao J, et al. Effects of ezetimibe and anticoagulant combined therapy on progressing stroke: a randomized, placebo-controlled study. *Journal of Neurology* 2016;263(12):2438-45.

Yang YJ, Kim BS, Cho YK, et al. Combination Therapy of Rosuvastatin and Ezetimibe in Patients with High Cardiovascular Risk. *Clinical Therapeutics* 2017;39(1):107-17.

Yoon HS, Kim SH, Kim JK, et al. Comparison of effects of morning versus evening administration of ezetimibe/simvastatin on serum cholesterol in patients with primary hypercholesterolemia. *Annals of Pharmacotherapy* 2011;45(7):841-49.

Yu CC, Lai WT, Shih KC, et al. Efficacy, safety and tolerability of ongoing statin plus ezetimibe versus doubling the ongoing statin dose in hypercholesterolemic Taiwanese patients: an open-label, randomized clinical trial. *BMC research notes* 2012;5:251.

Zhang J, Long M, Yu Y. The effects of additional ezetimibe treatment to baseline rosuvastatin on circulating PCSK9 among patients with stable angina. *Journal of Thoracic Disease* 2017;9(5):1226-33.

Zubaid M, Shakir DK, Bazargani N, et al. Effect of ezetimibe coadministration with simvastatin in a Middle Eastern population: A prospective, multicentre, randomized, double-blind, placebo-controlled trial. *Journal of Cardiovascular Medicine* 2008;9(7):688-93.

Wrong outcomes

Bozzetto L, Annuzzi G, Corte GD, et al. Ezetimibe beneficially influences fasting and postprandial triglyceride-rich lipoproteins in type 2 diabetes. *Atherosclerosis* 2011;217(1):142-48.

Florentin M, Liberopoulos EN, Moutzouri E, et al. The effect of simvastatin alone versus simvastatin plus ezetimibe on the concentration of small dense low-density lipoprotein cholesterol in subjects with primary hypercholesterolemia. *Current Medical Research and Opinion* 2011;27(3):685-92.

Garcia MMO, Varela CG, Silva PF, et al. Endothelial effect of statin therapy at a high dose versus low dose associated with ezetimibe. *Arquivos Brasileiros de Cardiologia* 2016;106(4):279-88.

Gounari P, Tousoulis D, Antoniades C, et al. Rosuvastatin but not ezetimibe improves endothelial function in patients with heart failure, by mechanisms independent of lipid lowering. *International Journal of Cardiology* 2010;142(1):87-91.

Grigore L, Raselli S, Garlaschelli K, et al. Effect of treatment with pravastatin or ezetimibe on endothelial function in patients with moderate hypercholesterolemia. *European Journal of Clinical Pharmacology* 2013;69(3):341-46.

Hajer GR, Dallinga-Thie GM, van Vark - van der Zee LC, et al. The effect of statin alone or in combination with ezetimibe on postprandial lipoprotein composition in obese metabolic syndrome patients. *Atherosclerosis* 2009;202(1):216-24.

Hernandez-Mijares A, Banuls C, Rovira-Llopis S, et al. Effects of simvastatin, ezetimibe and simvastatin/ezetimibe on mitochondrial function and leukocyte/endothelial cell interactions in patients with hypercholesterolemia. *Atherosclerosis* 2016;247:40-47.

Olijhoek JK, Hajer GR, Graaf YVD, et al. The effects of low-dose simvastatin and ezetimibe compared to high-dose simvastatin alone on post-fat load endothelial function in patients with metabolic syndrome: A randomized double-blind crossover trial. *Journal of Cardiovascular Pharmacology* 2008;52(2):145-50.

Perkerson KA, Gillespie EL, Coleman CI. Cost-effectiveness of statin monotherapy and combination therapy with ezetimibe. *Conn Med* 2005;69(1):19-22.

Pesaro AEP, Serrano CV, Katz M, et al. Increasing doses of simvastatin versus combined ezetimibe/simvastatin: Effect on circulating endothelial progenitor cells. *Journal of Cardiovascular Pharmacology and Therapeutics* 2012;18(5):447-52.

Pesaro AEP, Serrano Jr CV, Fern, et al. Pleiotropic effects of ezetimibe/simvastatin vs. high dose simvastatin. *International Journal of Cardiology* 2005;158(3):400-04.

Piorkowski M, Fischer S, Stellbaum C, et al. Treatment With Ezetimibe Plus Low-Dose Atorvastatin Compared With Higher-Dose Atorvastatin Alone. Is Sufficient Cholesterol-Lowering Enough to Inhibit Platelets? *Journal of the American College of Cardiology* 2-13;49(10):1035-42.

Settergren M, Bohm F, Ryden L, et al. Cholesterol lowering is more important than pleiotropic effects of statins for endothelial function in patients with dysglycaemia and coronary artery disease. *European Heart Journal* 2008;29(14):1753-60.

Settergren M, Bohm F, Ryden L, et al. Lipid lowering versus pleiotropic effects of statins on skin microvascular function in patients with dysglycaemia and coronary artery disease. *Journal of Internal Medicine* 2009;266(5):492-98.

Tremblay AJ, Lamarche B, Hogue JC, et al. Effects of ezetimibe and simvastatin on apolipoprotein B metabolism in males with mixed hyperlipidemia. *Journal of Lipid Research* 2009;50(7):1463-71.

Wrong Intervention

Arbel R, Hammerman A, Azuri J. Usefulness of Ezetimibe Versus Evolocumab as Add-On Therapy for Secondary Prevention of Cardiovascular Events in Patients With Type 2 Diabetes Mellitus. *Am J Cardiol* 2019;123(8):1273-76.

Ballantyne CM, Hoogeveen RC, Raya JL, et al. Efficacy, safety and effect on biomarkers related to cholesterol and lipoprotein metabolism of rosuvastatin 10 or 20mg plus ezetimibe 10mg vs. simvastatin 40 or 80mg plus ezetimibe 10mg in high-risk patients: Results of the GRAVITY randomized study. *Atherosclerosis* 2014;232(1):86-93.

Cannon CP, Cariou B, Blom D, et al. Efficacy and safety of alirocumab in high cardiovascular risk patients with inadequately controlled hypercholesterolaemia on maximally tolerated doses of statins: The ODYSSEY COMBO II randomized controlled trial. *European Heart Journal* 2015;36(19):1186-94.

Farnier M, Jones P, Severance R, et al. Efficacy and safety of adding alirocumab to rosuvastatin versus adding ezetimibe or doubling the rosuvastatin dose in high cardiovascular-risk patients: The ODYSSEY OPTIONS II randomized trial. *Atherosclerosis* 2016;244:138-46.

Gaudiani LM, Lewin A, Meneghini L, et al. Efficacy and safety of ezetimibe co-administered with simvastatin in thiazolidinedione-treated type 2 diabetic patients. *Diabetes, Obesity and Metabolism* 2004;7(1):88-97.

Kazi DS, Moran AE, Coxson PG, et al. Cost-effectiveness of PCSK9 Inhibitor Therapy in Patients With Heterozygous Familial Hypercholesterolemia or Atherosclerotic Cardiovascular Disease. *JAMA* 2016;316(7):743-53.

Kazi DS, Penko J, Coxson PG, et al. Cost-Effectiveness of Alirocumab: A Just-in-Time Analysis Based on the ODYSSEY Outcomes Trial. *Ann Intern Med* 2019;170(4):221-29.

Korman M, Wisloff T. Modelling the cost-effectiveness of PCSK9 inhibitors vs. ezetimibe through LDL-C reductions in a Norwegian setting. Eur Heart J Cardiovasc *Pharmacother* 2018;4(1):15-22.

Lin X, Racette SB, Lefevre M, et al. Combined effects of ezetimibe and phytosterols on cholesterol metabolism a randomized, controlled feeding study in humans. *Circulation* 2011;124(5):596-601.

Mallya UG, Boklage SH, Koren A, et al. Budget Impact Analysis of PCSK9 Inhibitors for the Management of Adult Patients with Heterozygous Familial Hypercholesterolemia or Clinical Atherosclerotic Cardiovascular Disease. *Pharmacoeconomics* 2018;36(1):115-26.

Olry de Labry Lima A, Gimeno Ballester V, Sierra Sanchez JF, et al. Cost-effectiveness and Budget Impact of Treatment with Evolocumab Versus Statins and Ezetimibe for Hypercholesterolemia in Spain. *Rev Esp Cardiol* 2018;71(12):1027-35.

Ramos SC, Fonseca FA, Kasmas SH, et al. The role of soluble fiber intake in patients under highly effective lipid-lowering therapy. *Nutrition Journal* 2011;10(80)

Robinson JG, Nedergaard BS, Rogers WJ, et al. Effect of evolocumab or ezetimibe added to moderate- Or high-intensity statin therapy on LDL-C lowering in patients with hypercholesterolemia: The LAPLACE-2 randomized clinical trial. *JAMA - Journal of the American Medical Association* 2014;311(18):1870-82.

Roth EM, McKenney JM. ODYSSEY MONO: Effect of alirocumab 75 mg subcutaneously every 2 weeks as monotherapy versus ezetimibe over 24 weeks. *Future Cardiology* 2015;11(1):27-37.

Roth EM, Taskinen MR, Ginsberg HN, et al. Monotherapy with the PCSK9 inhibitor alirocumab versus ezetimibe in patients with hypercholesterolemia: Results of a 24 week, double-blind, randomized Phase 3 trial. *International Journal of Cardiology* 2015;176(1):55-61.

Suh DC, Griggs SK, Henderson ER, et al. Comparative effectiveness of lipid-lowering treatments to reduce cardiovascular disease. *Expert Rev Pharmacoecon Outcomes Res* 2018;18(1):51-69.

Wrong comparator

Baruch L, Agarwal S, Gupta B, et al. Effect on Serum Lipid Levels of Switching Dose of Ezetimibe from 10 to 5 mg. *American Journal of Cardiology* 2009;103(11):1568-71.

Baruch L, Gupta B, Haynos A, et al. Efficacy of ezetimibe 2.5 mg with a novel tablet-splitting strategy. *American Journal of Pharmacy Benefits* 2010;2(4):261-66.

Blom DJ, Hala T, Bolognese M, et al. A 52-week placebo-controlled trial of evolocumab in hyperlipidemia. *New England Journal of Medicine* 2014;370(19):1809-19.

El Shahawy M, Cannon CP, Blom DJ, et al. Efficacy and Safety of Alirocumab Versus Ezetimibe Over 2 Years (from ODYSSEY COMBO II). *American Journal of Cardiology* 2017;120(6):931-39.

Farnier M, Retterstol K, Steinmetz A, et al. Comparative efficacy and safety of fenofibrate/pravastatin plus ezetimibe triple therapy and simvastatin/ezetimibe dual therapy in type 2 diabetic patients with mixed hyperlipidaemia and cardiovascular disease. *Diabetes and Vascular Disease Research* 2012;9(3):205-15.

Fazio S, Guyton JR, Polis AB, et al. Long-Term Safety and Efficacy of Triple Combination Ezetimibe/Simvastatin Plus Extended-Release Niacin in Patients With Hyperlipidemia. *American Journal of Cardiology* 2010;105(4):487-94.

Gomes GB, Zazula AD, Shigueoka LS, et al. A Randomized Open-Label Trial to Assess the Effect of Plant Sterols Associated with Ezetimibe in Low-Density Lipoprotein Levels in Patients with Coronary Artery Disease on Statin Therapy. *Journal of Medicinal Food* 2017;20(1):30-36.

Guyton JR, Brown BG, Fazio S, et al. Lipid-Altering Efficacy and Safety of Ezetimibe/Simvastatin Coadministered With Extended-Release Niacin in Patients With Type IIa or Type IIb Hyperlipidemia. *Journal of the American College of Cardiology* 2008;51(16):1564-72.

Jakulj L, Trip MD, Sudhop T, et al. Inhibition of cholesterol absorption by the combination of dietary plant sterols and ezetimibe: Effects on plasma lipid levels. *Journal of Lipid Research* 2005;46(12):2692-98.

Kerzner B, Corbelli J, Sharp S, et al. Efficacy and safety of ezetimibe coadministered with lovastatin in primary hypercholesterolemia. *American Journal of Cardiology* 2003;91(4):418-24.

Koren MJ, Lundqvist P, Bolognese M, et al. Anti-PCSK9 monotherapy for hypercholesterolemia: The MENDEL-2 randomized, controlled phase III clinical trial of evolocumab. *Journal of the American College of Cardiology* 2014;63(23):2531-40.

Koren MJ, Scott R, Kim JB, et al. Efficacy, safety, and tolerability of a monoclonal antibody to proprotein convertase subtilisin/kexin type 9 as monotherapy in patients with hypercholesterolaemia (MENDEL): A randomised, double-blind, placebo-controlled, phase 2 study. *The Lancet* 2012;380(9858):1995-2006.

Kostapanos MS, Spyrou AT, Tellis CC, et al. Ezetimibe treatment lowers indicators of oxidative stress in hypercholesterolemic subjects with high oxidative stress. *Lipids* 2011;46(4):341-8. doi: 10.1007/s11745-011-3539-z. Epub 2011 Feb 26.

Meaney A, Ceballos G, Asbun J, et al. The vytorin on carotid intima-media thickness and overall arterial rigidity (VYCTOR) study. *Journal of Clinical Pharmacology* 2009;49(7):838-47.

Moriarty PM, Thompson PD, Cannon CP, et al. Efficacy and safety of alirocumab vs ezetimibe in statin-intolerant patients, with a statin rechallenge arm: The ODYSSEY ALTERNATIVE randomized trial. *Journal of Clinical Lipidology* 2015;9(6):758-69.

Nissen SE, Stroes E, Dent-Acosta RE, et al. Efficacy and tolerability of evolocumab vs ezetimibe in patients with muscle-related statin intolerance: The GAUSS-3 randomized clinical trial. *JAMA - Journal of the American Medical Association* 2016;315(15):1580-90.

Stroes E, Colquhoun D, Sullivan D, et al. Anti-PCSK9 antibody effectively lowers cholesterol in patients with statin intolerance: the GAUSS-2 randomized, placebo-controlled phase 3 clinical trial of evolocumab. *Journal of the American College of Cardiology* 2014;63(23):2541-48.

Sullivan D, Olsson AG, Scott R, et al. Effect of a monoclonal antibody to PCSK9 on low-density lipoprotein cholesterol levels in statin-intolerant patients: The GAUSS randomized trial. *JAMA - Journal of the American Medical Association* 2012;308(23):2497-506.

Taylor AJ, Villines TC, Stanek EJ, et al. Extended-release niacin or ezetimibe and carotid intima-media thickness. *New England Journal of Medicine* 2009;361(22):2113-22.

Villines TC, Stanek EJ, Devine PJ, et al. The ARBITER 6-HALTS Trial (Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol 6-HDL and LDL Treatment Strategies in Atherosclerosis). Final Results and the Impact of Medication Adherence, Dose, and Treatment Duration. *Journal of the American College of Cardiology* 2010;55(24):2721-26.

Wrong publication type

Anonymous. Ezetimibe: The French authorities gradually confirm the lack of benefit. *Prescrire International* 2010.

Milani, R. V. and Lavie, C. J. Lipid control in the modern era: An orphan's tale of rags to riches. *Journal of the American College of Cardiology* 2013; 10;62(23):2185-7.

Other (Could not be retrieved)

Hernández-Mijares A., Bañuls C., Bellod L., Jover A., Solá E., Víctor V.M., Rocha M. Study of lipoprotein subfractions following treatment with simvastatin and ezetimibe administred alone and in combination in hyperlipidemic patients. *Clinica e Investigacion en Arteriosclerosis* 2012; 24(5):217-225.

de Araujo DB, Bertolami MC, Ferreira WP, et al. Simvastain 80 mg and coadministration of simvastatin 10 mg and ezetimibe 10 mg: Effects on LDL(-) and anti-LDL(-) antibodies. *International Journal of Atherosclerosis* 2007;2(4):272-78.

Sager PT, Melani L, Lipka L, et al. Effect of coadministration of ezetimibe and simvastatin on high-sensitivity C-reactive protein. *American Journal of Cardiology* 2003;92(12):1414-18.