



# Health Technology Assessment (HTA)

## Scoping Report

Title	The treatment of primary hypercholesterolaemia and mixed/combined hyperlipidaemia with ezetimibe-containing medicines
Author/Affiliation	Jonathan Henry Jacobsen, Royal Australasian College of Surgeons Ning Ma, Royal Australasian College of Surgeons Akwasi Ampofo, Royal Australasian College of Surgeons Virginie Gaget, Royal Australasian College of Surgeons Thomas Vreugdenburg, Royal Australasian College of Surgeons David Tivey, Royal Australasian College of Surgeons

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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

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## **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.<sup>1</sup> These diseases can lead to acute events such as myocardial infarction or stroke, which result in significant morbidity or mortality.<sup>1</sup> 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.<sup>2</sup> Overtime, the build-up of plaque causes vessels to narrow and harden, increasing the risk of thromboembolic events such as stroke, transient ischaemic attack, pulmonary embolism and ischaemic heart disease.<sup>2,3</sup> 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.<sup>2</sup> 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.<sup>4,5</sup> Specific dyslipidaemias include:

**Hypercholesterolaemia**, a sub-type of dyslipidaemia, is characterised by higher-than-normal circulating low-density lipoprotein cholesterol (LDL-c) levels.<sup>5</sup> Defined thresholds for abnormal levels are complex, and take into account age, sex, ethnicity and patient history.<sup>6</sup> 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).<sup>5, 7</sup> 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*).<sup>8</sup> 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.<sup>9</sup> Irrespective of the underlying cause of hypercholesterolaemia, the resulting high cholesterol concentration is thought to cause the accumulation of plaque in blood vessels.<sup>6</sup>

**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.<sup>10</sup>

Individuals with hypercholesterolaemia or mixed/combined hyperlipidaemia are at an increased risk of CVD, including ACS, angina and myocardial infarction, and death.<sup>6</sup> For these individuals, medications that aim to lower blood concentration of LDL-c, a lipoprotein involved in the transport of cholesterol, are often prescribed.<sup>12</sup> 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.<sup>6</sup> 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).<sup>6</sup> 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).<sup>13</sup>

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.<sup>14</sup> 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).<sup>15</sup>

To ascertain whether the dyslipidaemia is familial or non-familial, age, genetic testing, family history and blood lipid levels are considered.<sup>9 16</sup> 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.<sup>14</sup> 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 polygenic.<sup>14</sup> 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.<sup>14 17</sup> 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.<sup>14 17</sup> 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.<sup>14</sup>

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.<sup>17</sup> 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.<sup>17</sup>

**Table 1 Summary of risk categories as reported by the Arbeitsgruppe Lipide und Atherosklerose (AGLA)<sup>17</sup>**

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 <sup>a</sup> ; 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 <sup>2</sup>	<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.	No treatment target, but highly recommended for risk assessment. Use LDL-c values to determine appropriate levels.	<b>Moderate hypertriglyceridemia</b> <b>TG, 177 – 886mg/dL (2 – 10mmol/L)</b> Primary goal is to lower LDL-c and non-HDL-c to target levels. Secondary goal is to treat underlying diseases if applicable.
High risk	10-year risk > 20% <sup>b</sup> 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 <sup>2</sup>	<100mg/dL (2.6mmol/L)	<131mg/dL (3.4mmol/L)	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.		<b>Severe hypertriglyceridemia</b> <b>TG &gt;886mg/dL (&gt;10mmol/L)</b> 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.
Moderate risk	10-year risk 10-20% <sup>b</sup> Risk influenced by others risk factors	<116mg/dL (3.0mmol/L)	<147mg/dL (3.8mmol/L)			
Low risk	10-year risk <10% <sup>b</sup>	No target value: optimise lifestyle interventions	No target value			<b>Mixed hyperlipidaemia</b> <b>TC &gt;233mg/dl (6mmol/L), TG &gt;177mg/dL (2mmol/L)</b> Primary goal is to lower LDL-c and non-HDL-c to target levels. Secondary goal is to treat underlying disease.
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.<sup>18 19</sup> Specifically, high cholesterol accounts for approximately one third of all ischaemic heart disease cases worldwide.<sup>19</sup> Raised cholesterol is a major cause of disease burden in developed and developing countries and its prevalence has remained fairly constant from 1980 – 2008.<sup>19</sup>

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.<sup>20-22</sup>

#### ***High cholesterol***

Approximately 20 per cent of participants in the 2007 Swiss Health survey self-reported high cholesterol levels<sup>23</sup> with significant differences found between regions.<sup>24</sup> 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 were highest in Ticino and the western part of Switzerland (Leman) and lowest in the eastern part of Switzerland.<sup>24</sup>

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.<sup>25</sup>

#### ***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.<sup>26</sup> 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).<sup>26 27</sup>

- An evaluation of Swiss patients hospitalised with ACS determined 1.6 and 17.8 per cent had probable/definite and possible familial hypercholesterolaemia, respectively.<sup>28</sup>
- 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%).<sup>29</sup> The prevalence of familial hypercholesterolaemia due to all different genetic variants (*LDLR*, *PCSK9* and *APOB*) was 1/132 (0.7%).<sup>29</sup>
- 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).<sup>30</sup>

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.<sup>14</sup>

### 3.4 Treatment pathway

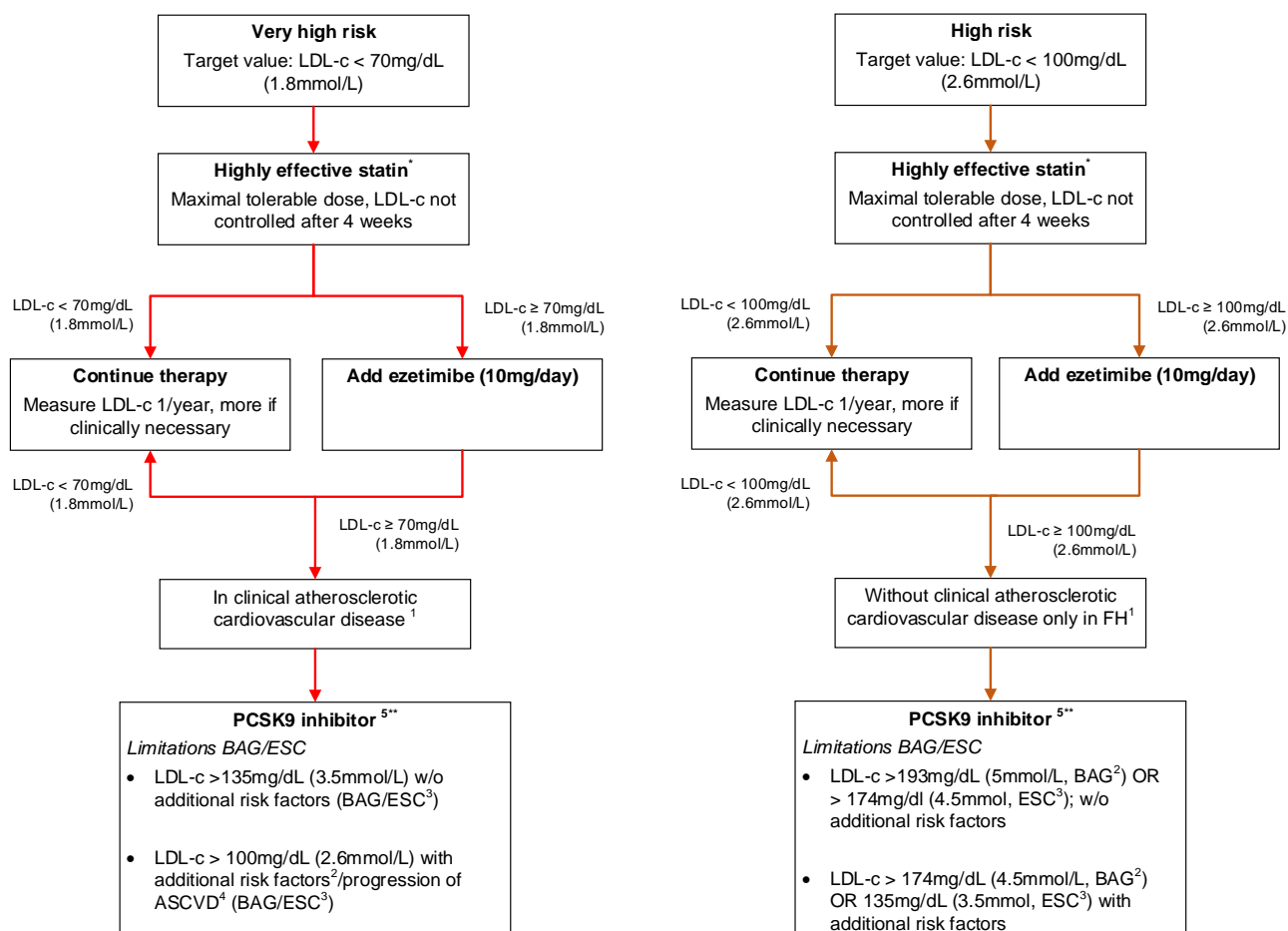
#### 3.4.1 Dyslipidaemia

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.<sup>6 14</sup> 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<sup>31</sup>). 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.<sup>6</sup> 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.<sup>6 14</sup> 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.<sup>6 14</sup> 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.<sup>14</sup> 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.<sup>6</sup> The statin initially selected should largely reflect the patient's overall cardiovascular risk and their respective treatment goals.<sup>6</sup> For patients with familial hypercholesterolaemia, LDL apheresis may additionally be considered at this stage.<sup>6 14</sup>

If patients do not reach their treatment goals, or are intolerant to statins, ezetimibe or ezetimibe-statin combination therapy is recommended.<sup>6 14</sup> 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.<sup>14</sup> 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.<sup>32</sup> 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)<sup>17</sup>**

### 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.

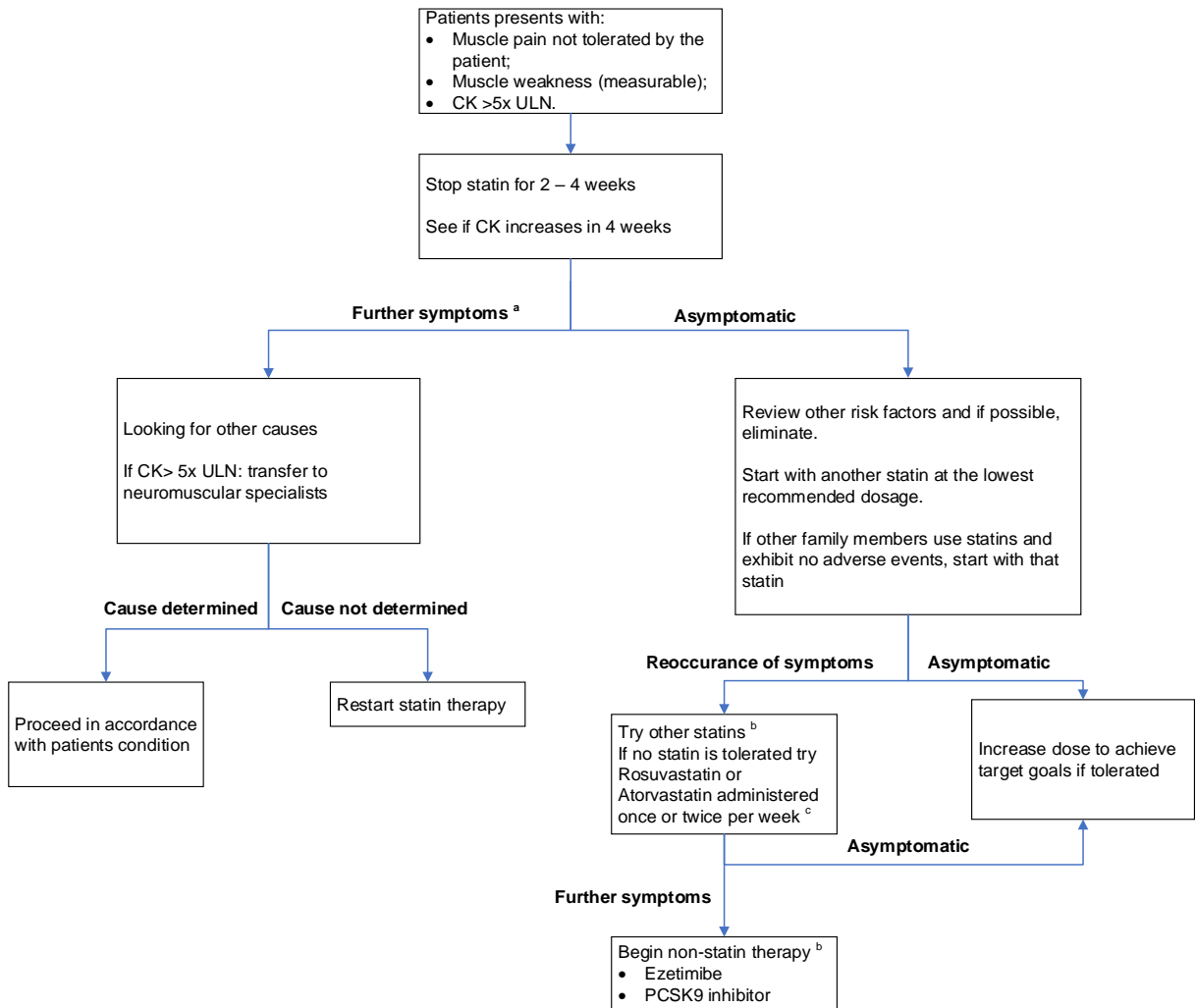
**4** = Progression according to the BAG limitation: progressive clinical atherosclerotic cardiovascular disease (repeated acute coronary syndrome, myocardial infarction, stroke, or unplanned repeated coronary revascularization within 5 years of the first cardiovascular event).

**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.<sup>33</sup> 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.<sup>34-36</sup> While there is no consensus regarding the definition of statin intolerance<sup>36</sup>, AGLA defines it as the inability to take statins due to the statin-associated myopathy, liver damage or other adverse events.<sup>14</sup> 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.<sup>14</sup>

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.<sup>14</sup> For further information regarding clinical management of statin-intolerance refer to **Figure 2**.



**Figure 2 Clinical management pathway for statin intolerance (AGLA)<sup>14</sup>**

**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).<sup>37</sup> 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.<sup>37</sup>

In Switzerland, ezetimibe exists as an individual medicine<sup>38 39</sup> or in fixed combination with statins including: simvastatin,<sup>40</sup> atorvastatin,<sup>41</sup> and rosuvastatin.<sup>42</sup> Ezetimibe is additionally licensed for free combinations with fenofibrate or other licensed statins (each drug is administered as a separate pill).<sup>38</sup> <sup>39</sup> 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).<sup>35</sup> 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.<sup>14</sup> 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
<i>Ezetimibe</i>				
Ezetrol®, Ezetimibe MSD® (Merck Sharp & Dohme)	Ezetimibe (10mg) Available as a tablet taken once daily at any time regardless of food intake.	Primary hetero- and homozygous familial and primary non-familial hypercholesterolaemia	Contraindicated in patients with hypersensitivity to ezetimibe or active liver disease.	No limitations
Ezetimib Zentiva® (Helvepharm AG)	The patient should follow a lipid-lowering diet while taking the medication.	Mixed/combined hyperlipidaemia	Not recommended in children under 10 years.	
Ezetimib Spirig HC® (Spirig HealthCare AG)	Can be taken with a statin or fenofibrate	Homozygous sitosterolemia (phytosterolemia) <sup>a</sup>		

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.			
<i>Ezetimibe + simvastatin</i>				
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
<i>Ezetimibe + atorvastatin</i>				
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
	<p>diet while taking the medication.</p> <p>The dosage is based on the individual's baseline LDL-c levels, treatment goals and response to therapy.</p>		<p>adolescent under 18 years.</p> <p>Should be used with caution in elderly patients (&gt;65 years).</p>	<p>mmol/l] at high risk) were not reached under maximum tolerated statin therapy.</p>
<i>Ezetimibe + rosuvastatin</i>				
<p>Ezetimib-Rosuvastatin Mepha (Mepha Pharma AG)</p>	<p>Ezetimibe (10mg) + rosuvastatin (10 or 20mg)</p> <p>Available as a tablet taken once daily at the same time of day regardless of food intake.</p> <p>The patient should follow a lipid-lowering diet while taking the medication.</p> <p>The dosage is based on the individuals baseline LDL-c levels, treatment goals and response to therapy.</p>	<p>Indicated as a replacement therapy in adults receiving ezetimibe and rosuvastatin as separate tablets.</p>	<p>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.</p> <p>Not recommended for children or adolescent under 18 years.</p> <p>In the elderly (&gt;65 years), fixed dose combination is not suitable as initial therapy.</p>	<p>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.</p>

**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.<sup>38 40-42</sup> For combination treatments the dose of the statin varies from 10 to 80mg for simvastatin and atorvastatin<sup>40 41</sup> and 10 to 20mg for rosuvastatin.<sup>42</sup> 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.<sup>43</sup>

Once consumed, ezetimibe is rapidly absorbed and metabolised to its active form ezetimibe-glucuronide, which has a half-life of approximately 22 hours.<sup>37 44</sup> There are no significant effects of sex or race on the pharmacokinetics of ezetimibe;<sup>44</sup> 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.<sup>40 42</sup> 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.<sup>41 42</sup>

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.<sup>45</sup>

### **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.<sup>38</sup> Uncommon adverse effects include but are not limited to: dyspepsia, cough, body aches, back pain, chest pain, joint pain, fatigue and weakness.<sup>38 40</sup> Early reports observed an increased incidence of cancer associated with ezetimibe use<sup>46</sup>; however, pooled data from three clinical trials noted the incidence of cancer was similar between ezetimibe and placebo.<sup>47</sup>

There are two contraindications for ezetimibe: patients should not take the drug if they are hypersensitive to ezetimibe or have active liver disease.<sup>38</sup> 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.<sup>40-42</sup>

## 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.<sup>48 49</sup> 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,<sup>50 51</sup> however, there is limited evidence supporting the remaining supplements.<sup>6 52</sup>

### 4.2.2 Statins

In addition to lifestyle changes, statins are often considered first-line treatment for primary dyslipidaemia and secondary prevention.<sup>6 14</sup> 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.<sup>6 53</sup> 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
<i>Atorvastatin</i> <sup>54</sup> 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
<p><i>Fluvastatin</i><sup>55</sup> Mepha Pharma AG and Novartis Pharma Schweiz AG, Sandoz Pharmaceuticals AG</p>	<p>Fluvastatinum 20, 40 or 80mg/day Oral</p>	<p>Adults with coronary heart disease, mixed dyslipidaemia or primary hypercholesterolaemia who have failed dietary interventions.</p> <p>Males (9 – 16 years), and post-menarche females (10 – 16 years) with familial hypercholesterolaemia.</p>	<p>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.</p>
<p><i>Pitavastatin</i><sup>56</sup> Recordati AG</p>	<p>Pitavastatinum 1, 2 or 4mg/day Oral</p>	<p>Adults with mixed dyslipidaemia and primary hypercholesterolaemia who have failed dietary and other non-pharmacological interventions.</p>	<p>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.</p> <p>It is not recommended for individuals under 18 years.</p>
<p><i>Pravastatin</i><sup>57</sup> 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</p>	<p>Pravastatinum natriicum 10, 20 or 40mg/day Oral</p>	<p>Individuals with primary hypercholesterolaemia, combined hyperlipidaemia, coronary heart disease, angina pectoris or post-myocardial infarction.</p>	<p>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.</p> <p>It is not recommended in children under the age of 8</p>
<p><i>Rosuvastatin</i><sup>58</sup> AstraZeneca AG Axapharm AG, Drossapharm AG Helvepharm, Sandoz Pharmaceuticals AG, Spirig HealthCare AG, and Mepha Pharma AG</p>	<p>Rosuvastatinum 5, 10 or 20mg/day Oral</p>	<p>Adults with mixed dyslipidaemia, primary hypercholesterolaemia or who are at high cardiovascular risk</p>	<p>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.</p> <p>It is not recommended in children under the age of 10.</p>

Name/ manufacturer(s)	Active ingredient/ dose/ administration	Indications/applications	Contraindications/ recommendations
<i>Simvastatin</i> <sup>59</sup> 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.<sup>60 61</sup> Fibrates are agonists of the PPAR- $\alpha$  and regulate steps involved with lipid and lipoprotein metabolism. Consequently, fibrates lower lipoprotein levels, triglycerides and triglyceride-rich lipoprotein remnant particles.<sup>60 61</sup>

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

- 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.<sup>63</sup> 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 cholesteryl ester transfer protein inhibitors.<sup>6 14</sup> Bile acid sequestrants, mipomersen, nicotinic acid and cholesteryl ester transfer protein inhibitors, lomitapide and PCSK9 are either not widely used in Switzerland, have limited efficacy or are considered third-line treatments.<sup>6 14 64</sup> 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.<sup>35</sup> 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.<sup>40-42</sup> Further, the pharmacokinetics of these drugs differ in the elderly (> 65 years) compared to younger patients.<sup>38</sup> 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.<sup>34 35</sup> These two populations have different cardiovascular risk profiles and require different treatment management strategies and respond differently to lipid-lowering medication.<sup>36</sup> 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.<sup>17</sup> 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).<sup>65 66</sup> 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.<sup>14 38</sup> 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.<sup>40-42</sup> 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.<sup>67</sup> 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.<sup>6</sup> 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.<sup>6 14</sup> PCSK9 inhibitors are the last-line treatment for primary and secondary prevention and strictly limited in reimbursement.<sup>14 64</sup> 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.<sup>68</sup> There is no standardised definition of MACE and different definitions can lead to different conclusions.<sup>69</sup> In this instance, the EMAs recommendation for MACE will be utilised which encompasses cardiovascular mortality, non-fatal stroke and non-fatal myocardial infarction.<sup>68</sup> 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-assess 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.<sup>70-72</sup>

#### 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<sup>14</sup>, European<sup>6</sup> and American guidelines<sup>73</sup> 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<sup>6</sup>, a lipoprotein involved in lipid deposition and the progression of atherosclerotic plaques.<sup>2</sup> Multiple studies have demonstrated a relationship between changes in LDL-c and cardiovascular risk and mortality.<sup>74 75</sup> Consequently, most clinical guidelines used LDL-c levels as a measure to determine overall cardiovascular risk and set treatment goals.<sup>6 31</sup> For example, AGLA recommends target goals for very high, high and moderate risk groups are 70, 100 and 115mg/dL, respectively.<sup>14 76</sup> 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.<sup>77-</sup>  
<sup>79</sup> 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.<sup>68</sup>

**HDL** is a measure of a variety of lipoproteins (most notable ApoA) and cholesterol.<sup>6</sup> HDL is involved in reverse cholesterol transport and is therefore thought to play an important role in prevention of atherosclerosis.<sup>80</sup> HDL is inversely associated with cardiovascular risk however, a causal relationship between HDL and atherosclerosis has not been established.<sup>6</sup> 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.<sup>68</sup>

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

**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.<sup>31 85 86</sup> 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 imaging techniques such as intravascular ultrasound (IVUS) and magnetic resonance imaging.<sup>68</sup> 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;<sup>87</sup> 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.<sup>88</sup> 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<sup>89</sup> 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.<sup>82</sup> 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.<sup>90</sup>

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**

<b>P:</b>	<ol style="list-style-type: none"> <li>1. Patients who have primary (hetero- and homozygous familial and non-familial) hypercholesterolaemia with or without pre-existing ASCVD.</li> <li>2. Patients who have mixed/combined hyperlipidaemia with or without pre-existing ASCVD.</li> </ol> <p><b>Sub-groups:</b> <i>Children and adolescents, elderly (&gt; 65 years), sex and individuals with diabetes, metabolic syndrome or statin-intolerance, AGLA risk categories, primary and secondary prevention populations.</i></p> <p><b>Exclusion:</b> <i>Predominantly Asian, African and Latin-American populations.</i></p>
<b>I &amp; C:</b>	<ol style="list-style-type: none"> <li>1. Intervention: Ezetimibe monotherapy Comparator: Placebo, statin or fenofibrate</li> <li>2. Intervention: Ezetimibe in combination with any statin licensed in Switzerland (fixed or free) Comparator: Statin, statin plus placebo</li> <li>3. Intervention: Ezetimibe in combination with fenofibrate (fixed or free) Comparator: Fenofibrate, fenofibrate plus placebo</li> </ol> <p><b>Sub-groups for intervention:</b> <i>ezetimibe in combination with atorvastatin, fluvastatin, pitavastatin, pravastatin, simvastatin or rosuvastatin.</i></p> <p><b>Sub-groups for comparators:</b> <i>atorvastatin, fluvastatin, pitavastatin, pravastatin, simvastatin or rosuvastatin.</i></p> <p><b>Exclusion criteria:</b> <i>niacin, n-3 fatty acids, bile sequestrants, cholesteryl ester transfer protein inhibitors, LDL apheresis, lomitapide and mipomersen, PCSK9 inhibitor.</i></p>
<b>O:</b>	<p><b>Efficacy/effectiveness<sup>a</sup>:</b></p> <p><i>Critical outcomes</i></p> <ul style="list-style-type: none"> <li>• Major adverse cardiovascular events (defined as non-fatal stroke, non-fatal myocardial infarction and cardiovascular mortality) <ul style="list-style-type: none"> <li>○ Non-fatal myocardial infarction<sup>b</sup></li> <li>○ Non-fatal ischaemic stroke</li> <li>○ Cardiovascular mortality</li> </ul> </li> <li>• Non-cardiovascular mortality</li> <li>• Coronary revascularisation</li> <li>• Hospitalisation for unstable angina</li> <li>• Health-related quality of life</li> </ul>

*Important outcomes*

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

**Safety<sup>c</sup>:**

*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.<sup>91-93</sup> 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 (ClinicalTrials.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

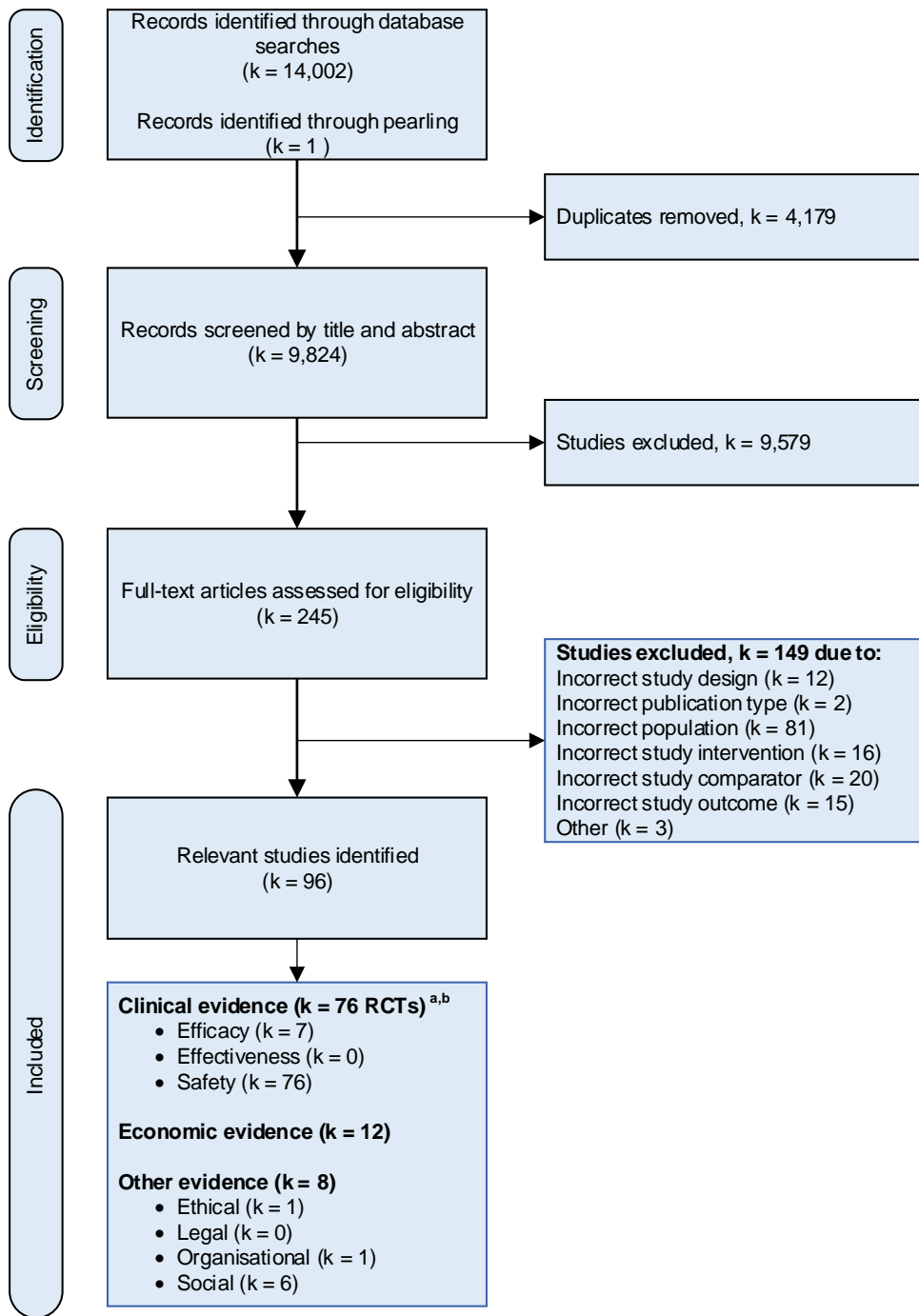
The results of the systematic literature searches are presented in **Figure 3**. Databases searches and pearling of relevant studies identified 14,003 studies. After removal of duplicates, 9,824 studies were reviewed by title and abstract, of which 245 were reviewed by full-text. A total of 96 studies 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<sup>94</sup>, adolescents<sup>95</sup> and individuals aged greater than 65 years.<sup>96</sup> 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**

<b>Outcome</b>	<b>All populations Median (range)</b>
<i>Efficacy</i>	
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)
<i>Safety</i>	
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 as 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.<sup>91-93</sup> 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<sup>106 107</sup> and 10 compared ezetimibe (as a monotherapy or in combination with a statin) to a statin.<sup>97-105 108</sup> 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.<sup>100 107</sup>

**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.<sup>98 100 104 107</sup>

**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,<sup>98-101 104 105 107</sup> with one study requiring patients to be hospitalised due to an ACS event.<sup>104</sup> Two studies investigated patients who were statin intolerant or contraindicated to statins as the eligibility to ezetimibe.<sup>97 106</sup> 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.<sup>103</sup> The remaining studies (k = 2) did not have specific eligibility requirements.<sup>102 108</sup> 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<sup>99</sup> and in 2015.<sup>101</sup> 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)<sup>103</sup>, 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.<sup>106 107 100 98 97</sup>

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.<sup>103 108</sup> One study performed the economic evaluation using actuarial methodologies only targeting survived patients.<sup>108</sup> 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.<sup>103</sup> 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**

<b>Model type</b>	CUA and CEA
<b>Modelling techniques</b>	State transition Markov models
<b>Common health state</b>	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
<b>Quality of life measures</b>	Commonly by EQ-5D, but some not specified
<b>Primary outcomes</b>	Incremental cost per quality of life gained for CUA Incremental cost per life year gained for CEA
<b>Sensitivity analysis</b>	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.<sup>105-107</sup>

### ***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,<sup>97 99-102 104-107</sup> of which EQ-5D was the quality of life measure in five.<sup>97 99 105-107</sup> 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;<sup>97 98 100 101 103 108</sup> two of these examined the cost per life year gained as their exclusive economic outcomes without considering quality of life measures.<sup>98 108</sup> 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.<sup>103</sup>

### ***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.<sup>45</sup>

## 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
<i>Patient and social issues</i>		
Krempf 2015 <sup>109</sup> 29 countries	Survey of physicians	Factors affecting physician's treatment recommendations for hypercholesterolaemia.
Kwok 2016 <sup>110</sup> United Kingdom	Survey of physicians	Knowledge and adherence of guidelines and treatment recommendation for familial hypercholesterolaemia.
Setia 2015 <sup>111</sup> Singapore	Survey of physicians	Knowledge and adherence of guidelines and treatment recommendation for atherosclerotic cardiovascular disease.
Tokgozoglu 2016 <sup>112</sup> Turkey	Survey of patients	Identification of factors that influence adherence and discontinuation of lipid-lowering therapy.
Umeda 2019 <sup>113</sup> Japan	Analysis of national pharmacy claims database	Identification of patient demographic factors that influence adherence and discontinuation of lipid-lowering therapy.
Wallach-Kildemoes 2015 <sup>114</sup> Denmark	Analysis of national prescription registry	Identification of patient demographic factors that influence the utilisation of lipid-lowering therapies.
<i>Ethical issues</i>		
Greenland 2008 <sup>115</sup>	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<sup>109-111</sup> and three studies aimed to identify sociodemographic factors influencing the initiation, adherence and discontinuation of ezetimibe.<sup>112 113 114</sup>

### Ethical issues

One commentary was identified highlighting ethical issues associated with publication, media interpretation and perceived conflicts of interest associated with the ENHANCE trial.<sup>115</sup> 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 <sup>116</sup>	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.<sup>116</sup> 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 ensure 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 a 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.<sup>117</sup> 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 <sup>a</sup>	Non-inferior <sup>b</sup>	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 <sup>a</sup>	Health forgone possible: need other supportive factors	?	?	? Likely CEA/CUA
	Non-inferior <sup>b</sup>	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.

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## 12 Appendix A: Sources of Literature (databases)

**Table 11 Databases searched and number of search results**

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

**Table 12 Search strategy – Ovid/Embase [Inception to 31<sup>st</sup> 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 31<sup>st</sup> 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 31<sup>st</sup> 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 31<sup>st</sup> 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 31<sup>st</sup> 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 9<sup>th</sup> 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 23<sup>rd</sup> 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 23<sup>rd</sup> 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**

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

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

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

Agency for Health Technology Assessment and Tariff System (AOTMiT)	<a href="http://www.aotm.gov.pl">http://www.aotm.gov.pl</a>
<b>Portugal</b>	
Administração Central do Sistema de Saúde, I.P. (ACSS IP)	<a href="http://www.acss.min-saude.pt">http://www.acss.min-saude.pt</a>
National Authority of Medicines and Health Products (INFARMED)	<a href="http://www.infarmed.pt">http://www.infarmed.pt</a>
<b>Republic of China, Taiwan</b>	
Center for Drug Evaluation (CDE)	<a href="http://www.cde.org.tw">http://www.cde.org.tw</a>
<b>Romania</b>	
Babes-bolayi University, Cluj School of Public Health (UBB)	<a href="http://publichealth.ro/">http://publichealth.ro/</a>
Institutu National De Sanatate Publica (INSP/NIPHB)	<a href="http://www.inspo.gov.ro">http://www.inspo.gov.ro</a>
National School of Public Health, Management and Professional Development (NSPHMPDB)	<a href="http://www.snspsms.ro">http://www.snspsms.ro</a>
<b>Singapore</b>	
Agency for Care Effectiveness (ACE)	<a href="http://www.ace-hta.gov.sg/">http://www.ace-hta.gov.sg/</a>
<b>Slovakia</b>	
Comenius University in Bratislava (UniBA FOF)	<a href="https://uniba.sk/en/">https://uniba.sk/en/</a>
Ministry of Health of the Slovak Republic (MoH Slovak Republic)	<a href="http://www.health.gov.sk">http://www.health.gov.sk</a>
<b>Slovenia</b>	
Ministry of Health of the Republic of Slovenia (MoH Slovenia)	<a href="http://www.mz.gov.si/en/">http://www.mz.gov.si/en/</a>
National institute of Public Health (NIJZ)	<a href="http://www.nijz.si">http://www.nijz.si</a>
Public Agency of the Republic of Slovenia for Medical Products and Medical Devices (JAZMP)	<a href="http://www.jazmp.si/en/">http://www.jazmp.si/en/</a>
<b>South Africa</b>	
Charlotte Maxeke Research Consortium (CmeRC)	<a href="http://www.cmerc.org">http://www.cmerc.org</a>
<b>Spain</b>	
Agencia Española de Medicamentos y Productos Sanitarios (AEMPS)	<a href="http://www.aemps.gob.es">http://www.aemps.gob.es</a>
Agencia de Evaluación de Tecnologías Sanitarias, Instituto de Salud "Carlos III" / Health Technology Assessment Agency (AETS)	<a href="http://publicaciones.isciii.es/">http://publicaciones.isciii.es/</a>
Agency for Health Quality and Assessment of Catalonia (AquAS)	<a href="http://aquas.gencat.cat">http://aquas.gencat.cat</a>
Andalusian HTA Agency	<a href="http://www.aetsa.org/">http://www.aetsa.org/</a>
Basque Foundation for Health Innovation and Research (BIOEF)	<a href="http://www.bioef.org/">http://www.bioef.org/</a>
Basque Office for Health Technology Assessment (OSTEBA)	<a href="http://www.euskadi.eus/web01-a2ikeost/en/">http://www.euskadi.eus/web01-a2ikeost/en/</a>
Catalan Agency for Health Technology Assessment (CAHTA)	<a href="http://www.gencat.cat">http://www.gencat.cat</a>
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)	<a href="http://www.sescs.es">http://www.sescs.es</a>
Fundación Canaria de Investigación Sanitaria (Funcanis)	<a href="http://www.funcanis.org/">http://www.funcanis.org/</a>
Fundacion Profesor Novoa Santos (AVALIA FNS)	<a href="http://www.fundacionprofesorновоasantos.org/es/">http://www.fundacionprofesorновоasantos.org/es/</a>
Fundación Pública Andaluza Progreso y Salud (FPS)	<a href="http://www.juntadeandalucia.es/fundacionprogresoysalud/">http://www.juntadeandalucia.es/fundacionprogresoysalud/</a>
Galician Agency for Health Technology Assessment (AVALIA-T)	<a href="http://acis.sergas.es">http://acis.sergas.es</a>

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

**Table 21 Patient/social and ethical databases**

Clinical trial registries	
Psychinfo	<a href="https://www.apa.org/pubs/databases/psycinfo/">https://www.apa.org/pubs/databases/psycinfo/</a>
ETHMED	<a href="http://www.ethicsweb.eu/search_ets">http://www.ethicsweb.eu/search_ets</a>

**Table 22 Clinical trial registries**

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

**Table 23 Legal websites**

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

**Table 24 Organisational websites**

Organisational aspects	
ERIC (Education Recourses Information Center)	<a href="https://eric.ed.gov/">https://eric.ed.gov/</a>

**Table 25 Specialty websites**

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

**Table 26 Clinical practice guideline websites**

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



## 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 <sup>118</sup>  USA  NCT00525824	Primary hypercholesterolaemia  LDL-c: 145 – 250mg/dL Triglycerides: ≤ 350mg/dL  n = 246	RCT, double-blind, extension study <sup>119</sup>  Multicentre  12 months	Atorvastatin (10mg) + Ezetimibe (10mg)  Atorvastatin (10mg) + Placebo	<ul style="list-style-type: none"> <li>• LDL-c, HDL, triglycerides, total cholesterol</li> <li>• Cardiovascular and non-cardiovascular mortality</li> </ul>
Cannon 2015 <sup>45</sup>  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	<ul style="list-style-type: none"> <li>• LDL-c, HDL, triglycerides, total cholesterol</li> <li>• MACE, stroke, coronary intervention, myocardial infarction, cardiovascular mortality</li> <li>• Non-cardiovascular mortality</li> </ul>
Hougaard 2017 <sup>120</sup>  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	<ul style="list-style-type: none"> <li>• LDL-c, HDL, total cholesterol</li> <li>• Cardiovascular and non-cardiovascular mortality</li> <li>• Vascular damage (IVUS)</li> </ul>
Kastelein 2008 <sup>121</sup>  America, Africa and Europe <sup>a</sup>  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	<ul style="list-style-type: none"> <li>• LDL-c, HDL, triglycerides, total cholesterol</li> <li>• MACE, stroke, coronary intervention, myocardial infarction, cardiovascular mortality</li> <li>• Vascular damage (cIMT)</li> </ul>
Kouvelos 2013 <sup>122</sup>  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)	<ul style="list-style-type: none"> <li>• LDL-c, HDL, triglycerides, total cholesterol</li> <li>• MACE, stroke, myocardial infarction, cardiovascular mortality</li> </ul>

Author; year; country; trial name	Inclusion criteria; Sample size	Design; Setting; Follow-up	Intervention; Comparator	Relevant efficacy outcomes
Masana 2005 <sup>123</sup>  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 <sup>124</sup>  Multicentre  48 weeks	Simvastatin (10, 20, 40, 80mg) + Ezetimibe (10mg)  Simvastatin (10, 20, 40, 80mg) + Placebo	<ul style="list-style-type: none"> <li>• LDL-c, HDL, triglycerides, total cholesterol</li> <li>• Non-cardiovascular mortality</li> </ul>
West 2011 <sup>125</sup>  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)	<ul style="list-style-type: none"> <li>• LDL-c, HDL, triglycerides, total cholesterol</li> <li>• MACE</li> <li>• Non-cardiovascular mortality</li> <li>• Vascular damage (MRI)</li> </ul>

#### **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 <sup>126</sup>  Spain  NR	Hypercholesterolaemia  LDL-c: $\geq 130$ mg/dL Triglycerides: $\leq 400$ mg/dL  n = 89	RCT, open-label  Multicentre  12 weeks	Fluvastatin (80mg)  Fluvastatin (80mg) + ezetimibe (10mg)	<ul style="list-style-type: none"> <li>• Withdrawal</li> <li>• Adverse events</li> <li>• ALT, AST, CK</li> </ul>
Ansquer 2009 <sup>127</sup>  Belgium, Germany, France  NCT00349284	Type IIb dyslipidaemia with metabolic syndrome (NCEP-ATP III definition)  LDL-c: $\geq 160$ mg/dL Triglycerides: 150 – 405mg/dL  n = 60	RCT, double-blind  International, multicentre  12 weeks	Ezetimibe (10mg)  Fenofibrate (145mg)  Fenofibrate (145mg) + ezetimibe (10mg)	<ul style="list-style-type: none"> <li>• Withdrawal</li> <li>• Adverse events</li> <li>• ALT, AST, CK</li> </ul>
Averna 2010 <sup>128</sup>  Italy  NCT00423579	Primary hypercholesterolaemia with CHD  LDL-c: 100 – 160mg/dL despite treatment Triglycerides: $\leq 350$ mg/dL  n = 120	RCT, double-blind  Multicentre  6 weeks	Simvastatin (40mg) + ezetimibe (10mg)  Simvastatin (40mg) + placebo	<ul style="list-style-type: none"> <li>• Withdrawal</li> <li>• Adverse events</li> <li>• ALT, AST, CK</li> <li>• Compliance</li> </ul>
Ballantyne 2003 <sup>119</sup>  USA  NR	Primary hypercholesterolaemia  LDL-c: 145 – 250mg/dL Triglycerides: $\leq 350$ mg/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	<ul style="list-style-type: none"> <li>• Withdrawal</li> <li>• Adverse events</li> <li>• ALT, AST, CK</li> <li>• Compliance</li> </ul>
Ballantyne 2004a <sup>118</sup>  USA  NCT00525824	Primary hypercholesterolaemia  LDL-c: 145 – 250mg/dL Triglycerides: $\leq 350$ mg/dL  n = 246	RCT, double-blind, extension study <sup>119</sup>  Multicentre  12 months	Ezetimibe (10mg) + Atorvastatin (10mg)  Atorvastatin (10mg) + Placebo	<ul style="list-style-type: none"> <li>• Withdrawal</li> <li>• Adverse events</li> <li>• ALT, AST, CK</li> </ul>
Ballantyne 2004b <sup>129</sup>  USA	Primary hypercholesterolaemia	RCT, double-blind  Multicentre	Atorvastatin (10mg) titered to 80mg)	<ul style="list-style-type: none"> <li>• Withdrawal</li> <li>• Adverse events</li> </ul>

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 titered to 80mg) + ezetimibe (10mg)	<ul style="list-style-type: none"> <li>• ALT, AST, CK</li> </ul>
Ballantyne 2007 <sup>130</sup>  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)	<ul style="list-style-type: none"> <li>• Withdrawal</li> <li>• Adverse events</li> <li>• ALT, AST, CK</li> <li>• Compliance</li> </ul>
Ballantyne 2019 <sup>131</sup>  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	<ul style="list-style-type: none"> <li>• Withdrawal</li> <li>• Adverse events</li> <li>• ALT, AST, CK</li> </ul>
Bardini 2010 <sup>132</sup>  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)	<ul style="list-style-type: none"> <li>• Withdrawal</li> <li>• Adverse events</li> <li>• ALT, AST, CK</li> <li>• Compliance</li> </ul>
Barrios 2005 <sup>133</sup>  Asia and Europe <sup>a</sup>  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)	<ul style="list-style-type: none"> <li>• Withdrawal</li> <li>• Adverse events</li> <li>• ALT, AST, CK</li> <li>• Compliance</li> </ul>
Bays 2004 <sup>134</sup>  USA + 22 countries <sup>b</sup>  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	<ul style="list-style-type: none"> <li>• Withdrawal</li> <li>• Adverse events</li> <li>• ALT, AST, CK</li> <li>• Compliance</li> </ul>

Author; year; country; trial ID	Inclusion criteria; Sample size	Design; Setting; Follow-up	Intervention; Comparator	Safety outcomes
Bays 2008 <sup>135</sup> USA, 22 other countries <sup>b</sup> NR	Primary hypercholesterolaemia a  LDL-c: 145 – 250mg/dL Triglycerides: ≤350mg/dL  n = 768	RCT, double-blind, extension study <sup>136</sup>  International, multicentre  48 weeks	Simvastatin (10, 20, 40 or 80mg)  Simvastatin (10, 20, 40 or 80mg) + ezetimibe (10mg)	<ul style="list-style-type: none"> <li>• Withdrawal</li> <li>• Adverse events</li> <li>• ALT, AST, CK</li> </ul>
Bays 2011 <sup>137</sup> America, Europe <sup>c</sup> 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)	<ul style="list-style-type: none"> <li>• Withdrawal</li> <li>• Adverse events</li> <li>• ALT, AST, CK</li> <li>• Compliance</li> </ul>
Bays 2013 <sup>138</sup> America and Europe <sup>d</sup> NCT01154036	Primary hypercholesterolaemia with high risk of CVD  LDL-c: 166 – 190mg/dL Triglycerides: NR  n = 1547	RCT, double-blind  International, multicentre  12 weeks	Atorvastatin (20mg)  Atorvastatin (10mg) + ezetimibe (10mg)  Rosuvastatin (10mg)	<ul style="list-style-type: none"> <li>• Withdrawal</li> <li>• Adverse events</li> <li>• ALT, AST, CK</li> <li>• Compliance</li> </ul>
Bays 2015 <sup>139</sup> Australia, America and Europe <sup>e</sup> 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)	<ul style="list-style-type: none"> <li>• Withdrawal</li> <li>• Adverse events</li> <li>• ALT, AST, CK</li> <li>• Compliance</li> </ul>
Blagden 2007 <sup>140</sup> 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	<ul style="list-style-type: none"> <li>• Withdrawal</li> <li>• Adverse events</li> <li>• ALT, AST, CK</li> <li>• Compliance</li> </ul>
Brohet 2005 <sup>141</sup> Europe <sup>f</sup>	CHD	RCT, double-blind	Simvastatin (10 or 20mg)	<ul style="list-style-type: none"> <li>• Withdrawal</li> <li>• Adverse event</li> <li>• ALT, AST, CK</li> </ul>

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)	<ul style="list-style-type: none"> <li>Compliance</li> </ul>
Cannon 2015 <sup>45</sup> 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	<ul style="list-style-type: none"> <li>Withdrawal</li> <li>Adverse events</li> <li>ALT, AST, CK</li> </ul>
Catapano 2006 <sup>142</sup> 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)	<ul style="list-style-type: none"> <li>Withdrawal</li> <li>Adverse events</li> <li>ALT, AST, CK</li> </ul>
Chenot 2007 <sup>143</sup> 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)	<ul style="list-style-type: none"> <li>Adverse events</li> </ul>
Chirinos 2010 <sup>144</sup> 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)	<ul style="list-style-type: none"> <li>Withdrawal</li> <li>Adverse events</li> </ul>
Conard 2008 <sup>145</sup> 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)	<ul style="list-style-type: none"> <li>Withdrawal</li> <li>Adverse events</li> <li>ALT, AST, CK</li> </ul>
Cruz-Fernandez 2005 <sup>146</sup> Europe, North America <sup>9</sup> 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	<ul style="list-style-type: none"> <li>Withdrawal</li> <li>Adverse events</li> <li>ALT, AST, CK</li> <li>Compliance</li> </ul>

Author; year; country; trial ID	Inclusion criteria; Sample size	Design; Setting; Follow-up	Intervention; Comparator	Safety outcomes
Davidson 2002 <sup>147</sup> 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	<ul style="list-style-type: none"> <li>• Withdrawal</li> <li>• Adverse events</li> <li>• ALT, AST, CK</li> <li>• Compliance</li> </ul>
Davidson 2013 <sup>148</sup> 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	<ul style="list-style-type: none"> <li>• Withdrawal</li> <li>• Adverse events</li> </ul>
Deharo 2014 <sup>149</sup> 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)	<ul style="list-style-type: none"> <li>• Withdrawal</li> <li>• Adverse events</li> <li>• ALT, AST, CK</li> <li>• Compliance</li> </ul>
Dujovne 2002 <sup>150</sup> USA Protocol P00474	Primary hypercholesterolaemia  LDL-c: 130 – 200mg/dL Triglycerides: ≤350mg/dL  n = 892	RCT, double-blind  Multicentre  20 weeks	Ezetimibe (10mg)  Placebo	<ul style="list-style-type: none"> <li>• Withdrawal</li> <li>• Adverse events</li> <li>• ALT, AST, CK</li> <li>• Compliance</li> </ul>
Farnier 2005a <sup>151</sup> Asia, Europe <sup>h</sup> 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	<ul style="list-style-type: none"> <li>• Withdrawal</li> <li>• Adverse events</li> <li>• ALT, AST, CK</li> <li>• Compliance</li> </ul>
Farnier 2005b <sup>152</sup> 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	<ul style="list-style-type: none"> <li>• Withdrawal</li> <li>• Adverse events</li> <li>• ALT, AST, CK</li> <li>• Compliance</li> </ul>
Farnier 2007 <sup>153</sup> NR	Mixed hyperlipidaemia	RCT, double-blind	Fenofibrate (160mg)	<ul style="list-style-type: none"> <li>• Withdrawal</li> <li>• Adverse events</li> <li>• ALT, AST, CK</li> </ul>

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	<ul style="list-style-type: none"> <li>• Compliance</li> </ul>
Farnier 2009 <sup>154</sup>  Europe <sup>i</sup>  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)	<ul style="list-style-type: none"> <li>• Withdrawal</li> <li>• Adverse events</li> <li>• ALT, AST, CK</li> <li>• Compliance</li> </ul>
Feldman 2004 <sup>155</sup>  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)	<ul style="list-style-type: none"> <li>• Withdrawal</li> <li>• Adverse events</li> <li>• ALT, AST, CK</li> </ul>
Foody 2010 <sup>156</sup>  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)	<ul style="list-style-type: none"> <li>• Withdrawal</li> <li>• Adverse events</li> <li>• ALT, AST, CK</li> <li>• Compliance</li> </ul>
Gagne 2002 <sup>124</sup>  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 <sup>j</sup>	<ul style="list-style-type: none"> <li>• Withdrawal</li> <li>• Adverse events</li> <li>• ALT, AST, CK</li> </ul>



Author; year; country; trial ID	Inclusion criteria; Sample size	Design; Setting; Follow-up	Intervention; Comparator	Safety outcomes
Goldberg 2004 <sup>136</sup> USA + 22 countries <sup>b</sup> NR	Primary hypercholesterolaemia LDL-c: $\geq 145 - 250$ mg/dL Triglycerides $\leq 350$ mg/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	<ul style="list-style-type: none"> <li>Withdrawal</li> <li>Adverse events</li> <li>ALT, AST, CK</li> </ul>
Goldberg 2006 <sup>157</sup> USA NCT00110435	Primary hypercholesterolaemia with type 2 diabetes LDL-c: $\geq 100$ mg/dL Triglycerides: $\leq 400$ mg/dL n = 1229	RCT, double-blind Multicentre 6 weeks	Atorvastatin (10 or 20mg) Simvastatin (20mg) + ezetimibe (10mg)	<ul style="list-style-type: none"> <li>Withdrawal</li> <li>Adverse events</li> <li>ALT, AST, CK</li> </ul>
Hing Ling 2012 <sup>158</sup> Asia, Europe, South America <sup>k</sup> NCT00782184	Primary hypercholesterolaemia with high risk of CHD LDL-c: 100 – 160mg/dL Triglycerides: $\leq 400$ mg/dL n = 250	RCT, double-blind International, multicentre 6 weeks	Atorvastatin (40mg) Simvastatin (20mg) + ezetimibe (10mg)	<ul style="list-style-type: none"> <li>Withdrawal</li> <li>Adverse events</li> <li>ALT, AST, CK</li> </ul>
Hougaard 2017 <sup>120</sup> 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	<ul style="list-style-type: none"> <li>Withdrawal</li> <li>Adverse events</li> <li>ALT, AST, CK</li> </ul>
Japaridze 2017 <sup>159</sup> Georgia NR	Acute coronary syndrome LDL-c: $\geq 70$ mg/dL despite treatment Triglycerides: NR n = 292	RCT, open-label Single-centre 16 weeks	Atorvastatin (40mg) Atorvastatin (20mg) + ezetimibe (10mg)	<ul style="list-style-type: none"> <li>Withdrawal</li> <li>Adverse events</li> <li>ALT, AST, CK</li> </ul>
Jones 2010 <sup>160</sup> USA NCT00639158	Dyslipidaemia defined as fasting: LDL-c: $\geq 130$ mg/dL Triglyceride: 150 – 400 mg/dL HDL: $< 40$ mg/dL (male) and $< 50$ mg/dL (female) n = 543	RCT, double-blind Multicentre 12 weeks	Atorvastatin (40mg) + ezetimibe (10mg) Atorvastatin (40mg) + ezetimibe (10mg) + fenofibric acid (135mg)	<ul style="list-style-type: none"> <li>Withdrawal</li> <li>Adverse events</li> <li>ALT, AST, CK</li> </ul>
Kastelein 2008 <sup>121</sup>	Familial hypocholesterolaemia	RCT, double blind	Simvastatin (80mg) + ezetimibe (10mg)	<ul style="list-style-type: none"> <li>Withdrawal</li> <li>Adverse events</li> </ul>

Author; year; country; trial ID	Inclusion criteria; Sample size	Design; Setting; Follow-up	Intervention; Comparator	Safety outcomes
America, Africa and Europe <sup>1</sup> NCT00552097	LDL-c: >210mg/dL; or <210mg/dL + existing lipid lowering therapy Triglycerides: NR  n = 720	International, multicentre  24 months	Simvastatin (80mg) + placebo	<ul style="list-style-type: none"> <li>ALT, AST, CK</li> <li>Compliance</li> </ul>
Knopp 2003 <sup>161</sup> USA NR	Primary hypercholesterolaemia  LDL-c: ≥130mg/dL Triglycerides: ≤250mg/dL  n = 827	RCT, double-blind  Multicentre  12 weeks	Ezetimibe (10mg)  Placebo	<ul style="list-style-type: none"> <li>Withdrawal</li> <li>Adverse events</li> <li>ALT, AST, CK</li> </ul>
Kosoglou 2004a <sup>162</sup> 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	<ul style="list-style-type: none"> <li>Withdrawal</li> <li>Adverse events</li> </ul>
Kosoglou 2004b <sup>163</sup> 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	<ul style="list-style-type: none"> <li>Withdrawal</li> <li>Adverse events</li> <li>ALT, AST, CK</li> </ul>
Kouvelos 2013 <sup>122</sup> 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)	<ul style="list-style-type: none"> <li>Withdrawal</li> <li>Adverse events</li> <li>ALT, AST, CK</li> </ul>
Krysiak 2012a <sup>165</sup> 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	<ul style="list-style-type: none"> <li>Withdrawal</li> <li>Adverse events</li> <li>Compliance</li> </ul>
Krysiak 2012b <sup>166</sup> Poland NR	Hypercholesterolaemia	RCT, double-blind  Multicentre  12 weeks	Ezetimibe (10mg)  Simvastatin (40mg)	<ul style="list-style-type: none"> <li>Withdrawal</li> <li>Adverse events</li> <li>Compliance</li> </ul>

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 <sup>167</sup>  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)	<ul style="list-style-type: none"> <li>• Withdrawal</li> <li>• Adverse events</li> <li>• ALT, AST, CK</li> </ul>
Kusters 2015 <sup>94</sup>  Europe, North America <sup>m</sup>  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	<ul style="list-style-type: none"> <li>• Withdrawal</li> <li>• Adverse events</li> <li>• ALT, AST, CK</li> <li>• Compliance</li> </ul>
Lakoski 2010 <sup>168</sup>  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	<ul style="list-style-type: none"> <li>• Withdrawal</li> <li>• Adverse events</li> <li>• Compliance</li> </ul>
Leiter 2008 <sup>169</sup>  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)	<ul style="list-style-type: none"> <li>• Withdrawal</li> <li>• Adverse events</li> <li>• ALT, AST, CK</li> </ul>
Masana 2005 <sup>123</sup>  NR  NR	Primary hypcholesterolaemia  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 <sup>124</sup>  Multicentre  48 weeks	Simvastatin (10, 20, 40, 80mg) + ezetimibe (10mg)  Simvastatin (10, 20, 40, 80mg) + placebo	<ul style="list-style-type: none"> <li>• Withdrawal</li> <li>• Adverse events</li> <li>• ALT, AST, CK</li> <li>• Compliance</li> </ul>
McCormack 2010 <sup>170</sup>	CVD or high-risk CVD	RCT, double-blind	Atorvastatin (40mg)	<ul style="list-style-type: none"> <li>• Withdrawal</li> <li>• Adverse events</li> </ul>

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)	<ul style="list-style-type: none"> <li>Compliance</li> </ul>
McKenney 2007 <sup>171</sup> 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)	<ul style="list-style-type: none"> <li>Withdrawal</li> <li>Adverse events</li> <li>ALT, AST, CK</li> </ul>
McKenney 2006 <sup>172</sup> NR NCT00092573	Mixed hyperlipidaemia LDL-c: 130 – 220mg/dL Triglycerides: 200 - 500mg/dL n = 576	RCT, double-blind, extension study <sup>152</sup> International, multicentre 48 weeks	Fenofibrate (160mg) Fenofibrate (106mg) + ezetimibe (10mg)	<ul style="list-style-type: none"> <li>Withdrawal</li> <li>Adverse events</li> <li>ALT, AST, CK</li> </ul>
Melani 2003 <sup>173</sup> 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)	<ul style="list-style-type: none"> <li>Withdrawal</li> <li>Adverse events</li> <li>ALT, AST, CK</li> <li>Compliance</li> </ul>
Moutzouri 2011 <sup>174</sup> 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)	<ul style="list-style-type: none"> <li>Withdrawal</li> <li>ALT, AST, CK</li> <li>Compliance</li> </ul>
Nicholls 2017 <sup>175</sup> 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)	<ul style="list-style-type: none"> <li>Withdrawal</li> <li>Adverse events</li> <li>ALT, AST, CK</li> </ul>

Author; year; country; trial ID	Inclusion criteria; Sample size	Design; Setting; Follow-up	Intervention; Comparator	Safety outcomes
Ose 2007 <sup>176</sup> USA + 24 countries <sup>b</sup> Protocol 038-10	Primary hypercholesterolaemia LDL-c: 145 – 250mg/dL Triglycerides: ≤350mg/dL n = 1104	RCT, double-blind, extension study <sup>134</sup> International, multicentre 14 weeks	Simvastatin (10, 20, 40 or 80mg) + ezetimibe (10mg) Simvastatin (10, 20, 40 or 80mg)	<ul style="list-style-type: none"> <li>Withdrawal</li> <li>Adverse events</li> <li>ALT, AST, CK</li> </ul>
Ostad 2009 <sup>177</sup> Germany ISRCTN34110682	CAD LDL-c: ≥100mg/dL Triglycerides: NR n = 58	RCT, double-blind Single-centre 8 weeks	Atorvastatin (80mg) Atorvastatin (10mg) + ezetimibe (10mg)	<ul style="list-style-type: none"> <li>Withdrawal</li> <li>Adverse events</li> <li>ALT, AST, CK</li> </ul>
Pandey 2011 <sup>178</sup> 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	<ul style="list-style-type: none"> <li>Withdrawal</li> <li>Adverse events</li> </ul>
Patel 2006 <sup>179</sup> 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	<ul style="list-style-type: none"> <li>Withdrawal</li> <li>Adverse events</li> <li>ALT, AST, CK</li> <li>Compliance</li> </ul>
Pearson 2006 <sup>180</sup> 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	<ul style="list-style-type: none"> <li>Withdrawal</li> <li>Adverse events</li> <li>ALT, AST, CK</li> </ul>
Reckless 2008 <sup>181</sup> Asia, Europe <sup>n</sup> 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)	<ul style="list-style-type: none"> <li>Withdrawal</li> <li>Adverse events</li> <li>ALT, AST, CK</li> <li>Compliance</li> </ul>
Robinson 2009 <sup>182</sup> 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)	<ul style="list-style-type: none"> <li>Withdrawal</li> <li>Adverse events</li> <li>ALT, AST, CK</li> </ul>

Author; year; country; trial ID	Inclusion criteria; Sample size	Design; Setting; Follow-up	Intervention; Comparator	Safety outcomes
	<p>≥100mg/dL without ASCVD Triglycerides: NR</p> <p>n = 1143</p>		<p>Simvastatin (20mg) + ezetimibe (10mg)</p> <p>Simvastatin (40mg) + ezetimibe (10mg)</p>	
<p>Roeters 2008<sup>183</sup></p> <p>The Netherlands</p> <p>EASEGO</p>	<p>CHD with/without Type 2 diabetes</p> <p>LDL-c: 96 – 193mg/dL despite treatment Triglycerides: &lt;350mg/dL</p> <p>n = 367</p>	<p>RCT, open-label</p> <p>Multicentre</p> <p>14 weeks</p>	<p>Double Statin dose</p> <p>Simvastatin (20mg) + ezetimibe (10mg)</p>	<ul style="list-style-type: none"> <li>• Withdrawal</li> <li>• Adverse events</li> <li>• ALT, AST, CK</li> </ul>
<p>Rosen 2013<sup>184</sup></p> <p>Europe, North and South America<sup>o</sup></p> <p>NR</p>	<p>CVD with Type 1 or 2 diabetes</p> <p>LDL-c: 70 – 160mg/dL despite treatment Triglycerides: ≤ 400mg/dL</p> <p>n = 808</p>	<p>RCT, double-blind</p> <p>International, multicentre</p> <p>6 weeks</p>	<p>Double Statin dose</p> <p>Rosuvastatin (10mg)</p> <p>Simvastatin (20mg) + ezetimibe (10mg)</p>	<ul style="list-style-type: none"> <li>• Withdrawal</li> <li>• Adverse events</li> <li>• ALT, AST, CK</li> </ul>
<p>Ruggenenti 2010<sup>185</sup></p> <p>Italy</p> <p>NCT00157482</p>	<p>Elevated LDL-c with type 2 diabetes</p> <p>LDL-c ≥135mg/dL despite lipid-lowering therapy</p> <p>n = 108</p>	<p>RCT, double-blind</p> <p>Multicentre</p> <p>8 weeks</p>	<p>Simvastatin (40mg) + ezetimibe (10mg)</p> <p>Simvastatin (40mg) + Placebo</p>	<ul style="list-style-type: none"> <li>• Withdrawal</li> <li>• Adverse events</li> <li>• ALT, AST, CK</li> </ul>
<p>Stein 2004<sup>186</sup></p> <p>21 countries<sup>b</sup></p> <p>NR</p>	<p>Primary hypercholesterolaemia with CHD and 2 cardiovascular risk factors or HeFH with LDL-c ≥130mg/dL despite treatment</p> <p>n = 621</p>	<p>RCT, double-blind</p> <p>International, multicentre</p> <p>14 weeks</p>	<p>Atorvastatin (20mg)</p> <p>Atorvastatin (10mg) + ezetimibe (10mg)</p>	<ul style="list-style-type: none"> <li>• Withdrawal</li> <li>• Adverse events</li> <li>• ALT, AST, CK</li> </ul>
<p>Stojakovic 2010<sup>187</sup></p> <p>Germany</p> <p>NCT00814723</p>	<p>With or at high-risk of CHD</p> <p>LDL-c: 100 – 160mg/dL Triglycerides: NR</p> <p>n = 84</p>	<p>RCT, single-blind</p> <p>Single-centre</p> <p>12 weeks</p>	<p>Fluvastatin (80mg)</p> <p>Fluvastatin (80mg) + ezetimibe (10mg)</p>	<ul style="list-style-type: none"> <li>• ALT, AST, CK</li> </ul>
<p>Strony 2008<sup>188</sup></p> <p>USA</p> <p>NR</p>	<p>Primary hypercholesterolaemia<sup>a</sup></p>	<p>RCT, double-blind, extension study<sup>147</sup></p> <p>Multicentre</p>	<p>Simvastatin (10, 20, 40 or 80mg) + ezetimibe (10mg)</p>	<ul style="list-style-type: none"> <li>• Withdrawal</li> <li>• Adverse events</li> <li>• ALT, AST, CK</li> <li>• Compliance</li> </ul>

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 <sup>189</sup>  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	<ul style="list-style-type: none"> <li>• Adverse events</li> <li>• ALT, AST, CK</li> </ul>
Sudhop 2009 <sup>190</sup>  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	<ul style="list-style-type: none"> <li>• Withdrawal</li> <li>• Adverse events</li> <li>• ALT, AST, CK</li> </ul>
van der Graff 2008 <sup>95</sup>  The Netherlands  NCT00129402	Familial hypercholesterolaemia  LDL-c value based on genotype  Triglyceride: ≤ 350mg/dL  Adolescents  n = 248	RCT, double-blind/open label <sup>p</sup>  Multicentre  52 weeks	Simvastatin (10, 20 or 40mg) + ezetimibe (10mg)  Simvastatin (10, 20 or 40mg) + placebo	<ul style="list-style-type: none"> <li>• Withdrawal</li> <li>• Adverse events</li> <li>• ALT, AST, CK</li> </ul>
West 2011 <sup>125</sup>  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)	<ul style="list-style-type: none"> <li>• Withdrawal</li> <li>• Adverse events</li> <li>• ALT, AST, CK</li> <li>• Compliance</li> </ul>
Zieve 2010 <sup>96</sup>  America and Europe <sup>q</sup>  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)	<ul style="list-style-type: none"> <li>• Withdrawal</li> <li>• Adverse events</li> <li>• ALT, AST, CK</li> </ul>

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 <sup>108</sup>	Spain	<b>Intervention</b> <ul style="list-style-type: none"> <li>• A40 + E10</li> <li>• A80 + E10</li> </ul> <b>Comparators</b> <ul style="list-style-type: none"> <li>• A (10, 20, 30, 40, 50, 60, 80)</li> <li>• C (0.2, 0.4, 0.6, 0.8)</li> <li>• F (20, 40)</li> <li>• L (10, 20, 40, 60, 80, 120)</li> <li>• P (10, 20, 40, 60, 80)</li> <li>• S (10, 20, 30, 40, 50, 60, 80, 120)</li> </ul>	2005	Lifetime	Government	<ul style="list-style-type: none"> <li>• 18 to 82 years old</li> <li>• Genetic FH patients, 44% Men</li> </ul>	Variation in age and gender cohorts	Life-table	<ul style="list-style-type: none"> <li>• 6 based on CVD events;</li> <li>• MI</li> <li>• Other ischemic heart disease</li> <li>• Heart failure</li> <li>• Ictus</li> <li>• CVD death</li> <li>• Non-CVD death</li> </ul>	<ul style="list-style-type: none"> <li>• Scenario analysis</li> <li>• best case scenario: upper limit of SMR and management costs &lt;10%</li> <li>• worst case scenario: lower limit of SMR and management</li> <li>• Costs &gt; 10%</li> <li>• Revision of discount rate to 6%</li> </ul>	3% of Effects 6% of cost	Spanish FH Registry (1999-2002)	NR	Cost per LYG from PYLL
Ara 2008a <sup>107</sup>	UK	<b>Intervention</b> <ul style="list-style-type: none"> <li>• Simvastatin (NOS) + Ezetimibe (NOS)</li> <li>• Atorvastatin (NOS) + Ezetimibe (NOS)</li> </ul> <b>Comparators</b> <ul style="list-style-type: none"> <li>• Simvastatin (NOS)</li> <li>• Atorvastatin (NOS)</li> </ul>	2006	<ul style="list-style-type: none"> <li>• 5 years</li> <li>• 10 years</li> <li>• 20 years</li> <li>• Lifetime</li> </ul>	Government	<ul style="list-style-type: none"> <li>• Men</li> <li>• 55-year old</li> <li>• History of CVD</li> <li>• LDL-c (116mg/dL [3.0 mmol/l])</li> </ul>	NR	Markov model	<ul style="list-style-type: none"> <li>• 6 based on CHD History;</li> <li>• No CHD</li> <li>• Non-fatal CVD</li> <li>• Recurrent CVD</li> <li>• Healthy secondary prevention</li> <li>• Fatal CVD from stroke and CHD</li> <li>• Non-CVD death</li> </ul>	<ul style="list-style-type: none"> <li>• Variations in baseline parameters</li> <li>• Health state utility variation ±20%</li> <li>• Health state cost ±50%</li> <li>• PSA</li> </ul>	3.5%	<ul style="list-style-type: none"> <li>• British National Formulary</li> <li>• Nottingham Heart Attack Register.</li> <li>• South London Stroke Register</li> <li>• 12 weeks of treatment</li> </ul>	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 <sup>97</sup>	UK	<b>Intervention</b> <ul style="list-style-type: none"> <li>Ezetimibe (10)</li> <li>A (10, 20, 40) + E10</li> <li>S (10, 20, 40, 80) + E10</li> <li>P (10, 20, 40) + E10</li> </ul> <b>Comparators</b> <ul style="list-style-type: none"> <li>A (10, 20, 40, 80)</li> <li>S (10, 20, 40)</li> <li>R (10, 20, 40)</li> <li>No treatment</li> </ul>	2006	<ul style="list-style-type: none"> <li>20 years</li> <li>Lifetime</li> </ul>	Healthcare payer	<ul style="list-style-type: none"> <li>≥ 18 years</li> <li>LDL-c 129.93 – 251.35 mg/dL (3.36–6.50 mmol/l)</li> <li>FH patients</li> <li>Statin intolerant</li> </ul>	<ul style="list-style-type: none"> <li>CHD or non-CHD diabetic patients</li> <li>Different ethnic groups</li> <li>HeFH and non-HeFH patients</li> <li>Different LDL-c levels; 96.67, 116 and 135.34mg/dL (2.5, 3.0 and 3.5 mmol/l)</li> </ul>	Markov model	9 based on CHD History <ul style="list-style-type: none"> <li>Stable angina</li> <li>unstable angina</li> <li>Non-fatal MI</li> <li>Non-fatal stroke</li> <li>TIA</li> <li>CHD-death</li> <li>Fatal stroke</li> <li>Fatal TIA</li> <li>Non-CHD death</li> </ul>	<ul style="list-style-type: none"> <li>Variations in baseline parameters</li> </ul>	3.5%	<ul style="list-style-type: none"> <li>Review of existing studies</li> <li>Expert opinion</li> <li>SchHARR economic analysis of statin therapy</li> </ul>	EQ-5D	<ul style="list-style-type: none"> <li>Cost per QALY gained</li> <li>Cost per LYG</li> </ul>
Ara 2008c <sup>106</sup>	UK	<b>Intervention</b> <ul style="list-style-type: none"> <li>Ezetimibe (NOS)</li> </ul> <b>Comparators</b> <ul style="list-style-type: none"> <li>No treatment</li> </ul>	2006	<ul style="list-style-type: none"> <li>2 years</li> <li>5 years</li> <li>20 years</li> <li>45 years (Lifetime)</li> </ul>	Government	<ul style="list-style-type: none"> <li>Male CVD patients</li> <li>Statin intolerant or contraindications</li> <li>55 years</li> <li>LDL-c 154.68mg/dL (4.0 mmol/l)</li> </ul>	Variation in gender and age cohort (75)	Markov Model	6 based on CHD History; <ul style="list-style-type: none"> <li>No CHD</li> <li>Non-fatal CVD</li> <li>Recurrent CVD</li> <li>Healthy secondary prevention</li> <li>Fatal CVD from stroke and CHD</li> <li>Non-CVD death</li> </ul>	<ul style="list-style-type: none"> <li>Variation in drug cost</li> <li>Variation in LDL-c.</li> <li>Variation in effectiveness rate of Ezetimibe</li> <li>Variation in relative risk of CVD events</li> <li>PSA</li> </ul>	3.5%	<ul style="list-style-type: none"> <li>Published studies</li> <li>British Heart Foundation</li> <li>Nottingham Heart Attack Register.</li> <li>South London Stroke Register</li> </ul>	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 <sup>98</sup>	Germany Norway Spain	<b>Intervention</b> • S (10, 20, 40, 80) + E10 • A (10, 20, 40, 80) + E10 <b>Comparators</b> • 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 $\geq 100\text{mg/dL}$ • Norway: -LDL-c 193.55mg/dL ( $\geq 5.0\text{ mmol/l}$ )	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 <sup>99</sup>	US	<b>Intervention</b> • A (10, 20, 40, 80) + E10 • S (10, 20, 40, 80) + E10 • R (5,10, 20, 40, 80) + E10 <b>Comparator</b> • 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 $\geq 70\text{mg/dL}$	LDL-c levels $\geq 100\text{mg/dL}$ Diabetic patients with LDL-c levels $\geq 70\text{mg/dL}$	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 <sup>100</sup>	Canada	<b>Intervention</b> • A (10, 20, 40) + E10 <b>Comparators</b> • 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 <sup>101</sup>	Portugal	<b>Intervention</b> • A10+E10 • A20+E10 <b>Comparators</b> • 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 <sup>102</sup>	UK	<b>Intervention</b> • S40+E10 • S80+E10 <b>Comparators</b> • 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 <sup>103</sup>	Spain	<b>Intervention</b> Each comparator + E10 <b>Comparators</b> • 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 <sup>104</sup>	UK	<b>Intervention</b> S40 + E10 <b>Comparators</b> • 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 <sup>105</sup>	Netherlands	<b>Intervention</b> <ul style="list-style-type: none"> <li>• S20 + E10</li> <li>• S40 + E10</li> </ul> <b>Comparators</b> <ul style="list-style-type: none"> <li>• A20</li> <li>• A40</li> <li>• S40</li> </ul>	2008	100 years	Healthcare payer	<ul style="list-style-type: none"> <li>• CHD patients on a stable (≥4 weeks) statin dose (S20 or A10)</li> <li>• LDL-c &gt;96.67mg/dL (2.5 mmol/l)</li> <li>• Female 24.3%</li> </ul>	NR	Markov model	6 based on CHD History; <ul style="list-style-type: none"> <li>• No CHD</li> <li>• Non-fatal CVD</li> <li>• Recurrent CVD</li> <li>• Healthy secondary prevention</li> <li>• Fatal CVD.</li> <li>• Non-CVD death</li> </ul>	PSA output as CEAC with variation in WTP threshold	1.5% of Effects 4% of cost	<ul style="list-style-type: none"> <li>• Dutch EASEGO</li> <li>• 2006 Dutch Guideline on Cardiovascular Risk Management</li> <li>• 2008 Dutch Healthcare Performance Report</li> </ul>	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, **EVPIPI** = 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
<i>EU Clinical Trials Register</i>						
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
<i>Clinicaltrials.gov</i>						
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 <sup>a</sup> 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).

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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.

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