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Federal Office of Public Health FOPH Health and Accident Insurance Directorate Section Health Technology Assessment

# Health Technology Assessment (HTA)

# **HTA Report**

Title	Ezetimibe-Containing Medicines for the Treatment of Hypercholesterolaemia and Mixed/Combined Hyperlipidaemia
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# **Conflicts of Interest**

The authors have no financial, academic, personal or any other conflicts of interest to declare in relation to this project.

### **Executive Summary**

This report evaluates the clinical effectiveness, safety, cost and cost-effectiveness associated with ezetimibe (monotherapy and combination therapies) in patients with hypercholesterolaemia without atherosclerotic cardiovascular disease (ASCVD), hypercholesterolaemia with ASCVD, mixed/combined hyperlipidaemia (herein referred to as hyperlipidaemia) without ASCVD, and hyperlipidaemia with ASCVD. Legal, social, ethical and organisational issues are also considered.

#### **Clinical Evaluation**

The safety and clinical effectiveness of ezetimibe (monotherapy and combination therapies) was informed by 30 randomised controlled trials (RCTs) in patients with hypercholesterolaemia without ASCVD, 42 RCTs in patients with hypercholesterolaemia and ASCVD, and 5 RCTs in patients with hyperlipidaemia without ASCVD. There were no studies evaluating ezetimibe in patients with hyperlipidaemia and ASCVD. The included RCTs were of moderate to high quality with key concerns relating to incomplete data, uncertain applicability to the Swiss context, and general reliance on surrogate markers to infer clinical effectiveness (i.e. low density lipoprotein-cholesterol [LDL-c], high density lipoprotein-cholesterol [HDL-c], etc.). This summary presents MACE results and the absolute change in surrogate markers at 3 months (short-term) and 12/15 months (long-term).

# Hypercholesterolaemia without ASCVD

There were no studies evaluating ezetimibe monotherapy beyond 3 months. The results for these comparisons were limited to surrogate markers. There were no studies using fenofibrate or ezetimibe plus fenofibrate.

#### Ezetimibe vs placebo

At 3 months, there were statistical differences in favour of ezetimibe with respect to the absolute change in LDL-c (mean difference [MD] -46.68mg/dL; 95% confidence interval [CI] -53.46, -39.90mg/dL; p<0.001), HDL-c (MD 1.72mg/dL; 95% CI 0.51, 2.94mg/dL; p=0.006) and total cholesterol (MD -56.25mg/dL; 95% CI -63.03, -49.46mg/dL; p<0.001). A greater proportion of patients achieved LDL-c goals on ezetimibe (<130mg/dL; risk ratio [RR] 6.93; 95% CI 3.66, 13.13; p<0.001); however, only one of three studies reported statistical differences in the absolute change in triglycerides. The LDL-c and total cholesterol results were subject to moderate-to-considerable heterogeneity. There were no statistical differences in mortality or adverse events.

# Ezetimibe vs statins

Compared to ezetimibe, statins significantly improved LDL-c (MD 10.77mg/dL; 95% CI 7.64, 13.90mg/dL; p<0.001) and total cholesterol (MD 4.61mg/dL; 95% CI -0.05, 9.27mg/dL; p=0.05), and increased the number of patients achieving LDL-c goals (<130mg/dL; RR 0.38; 95% CI 0.31, 0.47; p<0.001) at 3 months. The effects were subject to low heterogeneity. The results for the remaining outcomes were uncertain. No study reported statistical differences in the absolute change in triglycerides. There were no differences in mortality or adverse events.

# Ezetimibe plus statins vs statins

Compared to statins, ezetimibe plus statins significantly improved LDL-c (MD -16.72mg/dL; 95% CI -22.34, -11.11mg/dL; p<0.001), HDL-c (MD 3.82mg/dL; 95% CI 1.37, 6.28mg/dL; p<0.01) and total cholesterol (MD -18.02mg/dL, 95% CI -27.95, -8.09mg/dL; p<0.01) and increased the number of patients achieving LDL-c goals at 3 months (<130mg/dL; RR 1.14; 95% CI 1.09, 1.19; p<0.001). The statistical difference persisted at 15 months for LDL-c, but not for total cholesterol or HDL-c. However, the results were subject to considerable heterogeneity, and later timepoints were often informed by a single study. There were no differences in the absolute change in triglycerides. Treatment-related adverse events (not defined in the studies) were more common for ezetimibe plus statins compared to statins (RR 1.12; 95% CI 1.01, 1.25; p=0.04). Other adverse events were similar between groups.

# Hypercholesterolaemia with ASCVD

No studies evaluated ezetimibe monotherapy or ezetimibe plus fenofibrate. Furthermore, the results largely reflected patients with acute coronary syndrome (ACS) because the IMPROVE-IT trial was heavily weighted in the meta-analyses and was the only study sufficiently powered to detect group differences in 3-point major adverse cardiac events (3P-MACE, a composite measure of non-fatal myocardial infarction [MI], stroke and cardiovascular death).

#### Ezetimibe plus statins vs statins

In the IMPROVE-IT trial, ezetimibe plus simvastatin significantly reduced the incidence of 3P-MACE (hazard ratio [HR] 0.90; 95% CI 0.84, 0.96; p=0.003), non-fatal MI (HR 0.87; 95% CI 0.80, 0.95; p=0.002) and ischaemic stroke (HR 0.79; 95% CI 0.67, 0.94; p=0.008) compared to simvastatin at seven years. There were no differences in cardiovascular death, coronary revascularisation and unstable angina.

Compared to statins, ezetimibe plus statins significantly improved LDL-c (MD -17.22mg/dL; 95% CI -24.23, -10.22mg/dL; p<0.01) and total cholesterol (MD -21.18mg/dL; 95%

CI -28.93, -13.34mg/dL; p<0.01) and increased the number of patients achieving LDL-c goals (<100mg/dL; RR 1.73; 95% CI 1.32, 2.26; p<0.001) at 3 months. The results remained statistically different at 12 months for LDL-c (MD -16.82mg/dl; 95% CI -22.51, -11.12mg/dL; p<0.01) and total cholesterol (MD -17.84mg/dL; 95% CI -24.12, -11.56mg/dl; p<0.01). The results were subject to considerable heterogeneity. There were inconsistent differences between ezetimibe plus statins and statins with respect to the absolute change in triglycerides, HDL-c and markers of vascular damage. There were no statistical differences in mortality or adverse events (serious, treatment-related, any, or withdrawal due to).

# Hyperlipidaemia without ASCVD

No studies evaluated 3P-MACE outcomes or markers of vascular damage. The results were limited to lipid markers at 3 months for ezetimibe monotherapy and ezetimibe plus statins comparisons, and 12 months for ezetimibe plus fenofibrate comparisons.

# Ezetimibe vs placebo

Two studies provided evidence comparing ezetimibe to placebo. They were not meta-analysed owing to different methods of reporting outcomes (absolute and percentage change). There were statistical differences between ezetimibe and placebo groups with respect to the absolute change in LDL-c (p<0.001) and total cholesterol (p<0.001) but no differences in HDL-c (p=0.4) or triglycerides (p=0.1). Statistical significance was not reported for the percentage change, so it was unclear whether the groups differed.

# Ezetimibe vs statins

In one study, statins significantly improved LDL-c (p<0.001), total cholesterol (p<0.001) and triglycerides (p<0.001) and increased the number of patients achieving LDL-c goals (<NCEP-ATPIII, p<0.001) compared to ezetimibe. There was no difference in HDL-c (p>0.05).

# Ezetimibe plus statins vs statins

One study evaluated this comparison but did not report the statistical differences for the outcomes.

# Ezetimibe vs fenofibrate

At 3 months, there were no statistical differences between ezetimibe and fenofibrate for the percentage change in LDL-c (p=0.29) and total cholesterol (p=0.83). Fenofibrate significantly increased HDL-c (p=0.0005) and ezetimibe significantly increased the number of patients achieving LDL-c goals (NCEP-ATP III; p=0.003).

#### Ezetimibe plus fenofibrate vs fenofibrate

At 3 months, ezetimibe plus fenofibrate significantly improved LDL-c (p=0.001) and total cholesterol (p<0.001) and increased the number of patients achieving LDL-c goals (NCEP–ATP III; p<0.001). These effects persisted to 12 months in one extension study. At 3 and 12 months, there were limited statistical differences in triglycerides and no statistical differences in HDL-c. In general, there were no statistical differences between ezetimibe (monotherapies or combination therapies) and the respective comparators for adverse events (serious, treatment-related, any, or withdrawal).

# **Costs and Cost-Effectiveness**

A Markov model was created to evaluate the cost-effectiveness of ezetimibe plus statins compared to statins alone. There was sufficient MACE evidence to undertake an economic analysis in the hypercholesterolaemia with ASCVD population; the cost-effectiveness of ezetimibe (monotherapy/combination therapy) in the other populations is unknown.

Model inputs were informed by the IMPROVE-IT trial that compared ezetimibe plus simvastatin to simvastatin monotherapy in patients with ACS. The discounted incremental cost-effectiveness ratio (ICER) per quality-adjusted life year (QALY) gained was estimated at CHF62,242 over 7 years (trial duration). This decreased to CHF20,917 per QALY gained over a 20-year projection (extrapolated lifetime estimate).

Sensitivity analyses indicated that the ICERs were most impacted by the large range in annual medicine costs used in the model. Additional sensitivity analyses noted ezetimibe plus simvastatin was not cost-effective when compared to higher potency statins. This finding supports AGLA's current recommendation that ezetimibe should be limited to patients who are statin intolerant or have failed to reach treatment goals despite maximally tolerated statins. Therefore, budgetary impact analyses were performed to quantify the financial implication of limiting ezetimibe to these populations.

In the absence of Swiss-specific data, two hypothetical substitution scenarios (10% and 25% of patients substituting from ezetimibe monotherapy and ezetimibe in combination with rosuvastatin or simvastatin to high potency statin [atorvastatin 40mg]) were utilised. If 10% of patients substituted from ezetimibe monotherapy or ezetimibe combination therapy to a high potency statin, there is a net savings of CHF2.0 million in 2020, increasing to CHF2.3 million by 2023. If 25% of patients substituted from ezetimibe (monotherapy or combination therapy) to high potency statin, there is a net savings of CHF5.0 million in 2020, increasing to CHF5.7 million by 2023.

#### Legal, Social, Ethical and Organisational Issues

Non-adherence to statins is a common problem in clinical practice, increasing the risk of cardiovascular morbidity and mortality. Due to the presence of statins, this concern applies to ezetimibe combination treatments and may lead to inadequate treatment in patients with hypercholesterolaemia or ASCVD. Transitioning from statins to ezetimibe monotherapy may improve adherence because adverse events associated with statins (e.g. myopathy) are avoided.

Furthermore, research from Canada suggests limiting access to ezetimibe may reduce inappropriate prescribing practices; this has not been assessed in Switzerland.

#### Conclusion

In patients with hypercholesterolaemia without ASCVD, ezetimibe monotherapy was superior to placebo but inferior to statins regarding changes in LDL-c, HDL-c and total cholesterol at 3 months. Ezetimibe plus statins improved LDL-c in the long-term, but there was uncertainty whether it improved other outcomes.

The results for patients with hypercholesterolaemia and ASCVD were largely informed by the IMPROVE-IT trial. Ezetimibe plus statins significantly reduced the incidence of 3P-MACE, non-fatal MI and stroke at seven years. However, there were no differences in cardiovascular deaths, coronary revascularisations or unstable angina. Ezetimibe plus statins also improved LDL-c and total cholesterol, but not HDL-c or triglycerides at 12 months compared to statins.

Comparisons involving ezetimibe monotherapy and combination therapies for patients with hyperlipidaemia without ASCVD were limited to one or two trials with small numbers of patients. In the short term, ezetimibe monotherapy was superior to placebo, inferior to statins, and was generally no different to fenofibrate. Ezetimibe plus fenofibrate improved LDL-c and total cholesterol but was no different to fenofibrate for changes in HDL-c and triglycerides. Ezetimibe plus statins compared to statins could not be evaluated because statistical comparisons were not reported.

Ezetimibe monotherapy had a comparable safety profile to placebo and statins. Ezetimibe plus statins generally had a similar profile to statins, noting the incidence of treatment-related adverse events was higher in the combination therapy group.

Ezetimibe plus simvastatin was cost-effective compared to simvastatin monotherapy in patients with hypercholesterolaemia and ASCVD (using data from the IMPROVE-IT trial). Limiting access to ezetimibe (monotherapy or combination therapy) would result in a net cost saving to payers; savings were sensitive to the projected cost of the medicines and the concurrent use of free statin

combinations with ezetimibe monotherapy.

#### Zusammenfassung:

Dieser Bericht befasst sich mit der klinischen Wirksamkeit, Sicherheit, Kosten und Kosteneffektivität von Ezetimib (Monotherapie und Kombinationstherapien) bei Patienten mit Hypercholesterinämie ohne atherosklerotische kardiovaskuläre Erkrankung (ASCVD), Hypercholesterinämie mit ASCVD, gemischter/kombinierter Hyperlipidämie (hier als Hyperlipidämie bezeichnet) ohne ASCVD sowie Hyperlipidämie mit ASCVD. Rechtliche, soziale ethische und organisatorische Probleme werden ebenfalls berücksichtigt.

# **Klinische Beurteilung**

Die Sicherheit und klinische Wirksamkeit von Ezetimib (Monotherapie und Kombinationstherapien) wurde anhand von 30 randomisierten kontrollierten Studien (RCTs) bei Patienten mit Hypercholesterinämie ohne ASCVD, 42 RCTs bei Patienten mit Hypercholesterinämie und ASCVD und 5 RCTs bei Patienten mit Hyperlipidämie ohne ASCVD beurteilt. Studien zur Bewertung von Ezetimib bei Patienten mit Hyperlipidämie und ASCVD lagen nicht vor. Die eingeschlossenen RCTs wiesen eine mässige bis hohe Qualität auf, wobei die Hauptbedenken die Unvollständigkeit der Daten, die unsichere Übertragbarkeit auf den Schweizer Kontext und die allgemeine Abhängigkeit von Surrogatmarkern zur Ableitung der klinischen Wirksamkeit (d. h. LDL-Cholesterin [low density lipoprotein-cholesterol], HDL-Cholesterin [high density lipoprotein-cholesterol] usw.) betrafen. In dieser Zusammenfassung werden die MACE-Ergebnisse sowie die absolute Veränderung der Surrogatmarker nach 3 Monaten (kurzfristig) und nach 12/15 Monaten (langfristig) präsentiert.

# Hypercholesterinämie ohne ASCVD

Es lagen keine Studien vor, in denen eine Ezetimib-Monotherapie über 3 Monate hinaus untersucht wurde. Die Ergebnisse für diese Vergleiche beschränkten sich auf Surrogatmarker. Es gab keine Studien, in denen Fenofibrat allein oder Ezetimib zzgl. Fenofibrat untersucht wurden.

#### Ezetimib ggü. Placebo

Nach 3 Monaten lagen statistische Unterschiede zugunsten von Ezetimib hinsichtlich der absoluten Veränderung des LDL-Cholesterins vor (mittlere Differenz [MD] -46,68 mg/dl; 95%-Konfidenzintervall [KI] -53,46, -39,90 mg/dl; p<0,001), des HDL-Cholesterins (MD 1,72 mg/dl; 95%-KI 0,51, 2,94 mg/dl; p=0,006) sowie des Gesamtcholesterins (MD -56,25 mg/dl; 95%-KI -63,03, -49,46 mg/dl; p<0,001) vor. Unter Ezetimib erreichte ein grösserer Anteil der Patienten die LDL-Cholesterin-Ziele als unter Placebo (<130mg/dl; Risk Ratio [RR] 6,93; 95%-KI 3,66, 13,13; p<0,001). Allerdings befasste sich nur eine von drei Studien mit den statistischen Unterschieden in der

absoluten Veränderung der Triglyzeride. Die Ergebnisse für LDL-Cholesterin sowie Gesamtcholesterin unterlagen einer mässigen bis beträchtlichen Heterogenität. Statistische Unterschiede im Hinblick auf Sterblichkeit oder unerwünschte Ereignisse lagen nicht vor.

#### Ezetimib ggü. Statinen

Im Vergleich zu Ezetimib führten Statine zu einer signifikanten Verbesserung des LDL-Cholesterins (MD 10,77 mg/dl; 95%-KI 7,64, 13,90 mg/dl; p<0,001) sowie des Gesamtcholesterins (MD 4,61 mg/dl; 95%-KI -0,05, 9,27 mg/dl; p=0,05) und zu einer Erhöhung der Anzahl der Patienten, die die LDL-Cholesterin-Ziele (<130 mg/dl; RR 0,38; 95%-KI 0,31, 0,47; p<0,001) nach 3 Monaten erreicht hatten. Die Effekte wiesen eine geringe Heterogenität auf. Die Ergebnisse für die übrigen Endpunkte waren unsicher. Die statistischen Unterschiede in der absoluten Veränderung der Triglyzeride wurden in keiner Studie untersucht. Unterschiede im Hinblick auf Sterblichkeit oder unerwünschte Ereignisse lagen nicht vor.

#### Ezetimib zzgl. Statinen ggü. Statinen allein

Im Vergleich zu Statinen allein führte Ezetimib zzgl. Statinen zu einer signifikanten Verbesserung des LDL-Cholesterins (MD -16,72 mg/dl; 95-KI -22,34, -11,11 mg/dl; p<0,001), des HDL-Cholesterins (MD 3,82 mg/dl; 95%-KI 1,37, 6,28 mg/dl; p<0,01) sowie des Gesamtcholesterins (MD -18.02 mg/dl, 95%-KI -27,95, -8,09 mg/dl; p<0,01) und zu einer Erhöhung der Anzahl der Patienten, die die LDL-Cholesterin-Ziele nach 3 Monaten erreicht hatten (<130 mg/dl; RR 1,14; 95%-KI 1,09, 1,19; p<0,001). Nach 15 Monaten bestand eine statistische Differenz für das LDL-Cholesterin fort, jedoch nicht für das Gesamtcholesterin oder das HDL-Cholesterin. Die Ergebnisse unterlagen dabei einer erheblichen Heterogenität, und die Informationen für spätere Zeitpunkte stammten oft aus einer einzigen Studie. Es gab keine Unterschiede hinsichtlich der absoluten Veränderung der Triglyzeride. Behandlungsbedingte unerwünschte Ereignisse (in den Studien nicht definiert) traten bei Ezetimib zzgl. Statinen im Vergleich zu Statinen allein häufiger auf (RR 1,12; 95%-KI 1,01, 1,25; p=0,04). Andere unerwünschte Ereignisse waren zwischen den Gruppen ähnlich.

#### Hypercholesterinämie mit ASCVD

Die Ezetimib-Monotherapie oder Ezetimib zzgl. Fenofibrat wurden in keiner Studie untersucht. Zudem waren in den Ergebnissen überwiegend Patienten mit akutem Koronarsyndrom (ACS) repräsentiert, da die IMPROVE-IT-Studie in den Metaanalysen stark gewichtet wurde und die einzige Studie war, die über eine ausreichende Power verfügte, um Gruppenunterschiede in Bezug auf 3P-MACE (3-Punkt-MACE, Major Adverse Cardiac Events, eine zusammengesetzte Messgrösse für nicht-tödlichen Myokardinfarkt [MI], Schlaganfall und kardiovaskulären Tod) zu

# erkennen.

#### Ezetimib zzgl. Statinen ggü. Statinen allein

In der IMPROVE-IT-Studie reduzierte Ezetimib zzgl. Simvastatin im Vergleich zu Simvastatin allein nach sieben Jahren die Inzidenz von 3P-MACE (Hazard Ratio [HR] 0,90; 95%-KI 0,84, 0,96; p=0,003), nicht-tödlichem MI (HR 0,87; 95%-KI 0,80, 0,95; p=0,002) und ischämischem Schlaganfall (HR 0,79; 95%-KI 0,67, 0,94; p=0,008) signifikant. Hinsichtlich kardiovaskulären Todes, koronarer Revaskularisation und instabiler Angina pectoris wurden keine Unterschiede festgestellt.

Im Vergleich zu Statinen allein führte Ezetimib zzgl. Statinen zu einer signifikanten Verbesserung des LDL-Cholesterins (MD -17.22 mg/dl; 95%-KI -24,23, -10,22 mg/dl; p<0,01) sowie des Gesamtcholesterins (MD -21,18 mg/dl; 95%-KI -28,93, -13,34mg/dl; p<0,01) und zu einer Erhöhung der Anzahl der Patienten, die die LDL-Cholesterin-Ziele (<100 mg/dl; RR 1,73; 95%-KI 1,32, 2,26; p<0,001) nach 3 Monaten erreicht hatten. Nach 12 Monaten wiesen die Ergebnisse vorwiegend weiterhin statistische Unterschiede hinsichtlich des LDL-Cholesterins (MD -16.82 mg/dl; 95%-KI -22,51, -11.12 mg/dl; p<0,01) sowie des Gesamtcholesterins (MD -17,84 mg/dl; 95%-KI -22,51, -11.12 mg/dl; p<0,01) auf. Die Ergebnisse unterlagen einer erheblichen Heterogenität. Es lagen inkonsistente Unterschiede zwischen Ezetimib zzgl. Statinen und Statinen allein im Hinblick auf die absolute Veränderung der Triglyzeride, des HDL-Cholesterins und der Marker für Gefässschädigung vor. Statistische Unterschiede im Hinblick auf Sterblichkeit oder unerwünschte Ereignisse (schwere, behandlungsbedingte, beliebige oder solche, die zum Abbruch der Behandlung führten) lagen nicht vor.

#### Hyperlipidämie ohne ASCVD

3P-MACE-Ergebnisse oder Marker für Gefässschädigung wurden in keiner der Studien untersucht. Die Ergebnisse beschränkten sich auf Lipidmarker nach 3 Monaten für die Vergleiche zwischen der Ezetimib-Monotherapie und Ezetimib zzgl. Statinen sowie nach 12 Monaten für die Vergleiche mit Ezetimib zzgl. Fenofibrat.

# Ezetimib ggü. Placebo

Zwei Studien lieferten die Evidenz durch den Vergleich von Ezetimib mit Placebo. Sie wurden nicht metaanalytisch ausgewertet, da die Ergebnisse mittels unterschiedlicher Methoden (absolute und prozentuale Veränderung) angegeben wurden. Zwischen den Ezetimib- und Placebo-Gruppen bestanden statistische Unterschiede hinsichtlich der absoluten Veränderung des LDL-Cholesterins (p<0,001) und des Gesamtcholesterins (p<0,001), jedoch keine Unterschiede hinsichtlich des HDL-Cholesterins (p=0,4) oder der Triglyzeride (p=0,1). Für die prozentuale Veränderung wurde keine

statistische Signifikanz angegeben, sodass es nicht klar war, ob sich die Gruppen unterschieden.

# Ezetimib ggü. Statinen

In einer Studie führten Statine im Vergleich zu Ezetimib zu einer signifikanten Verbesserung des LDL-Cholesterins (p<0,001), des Gesamtcholesterins (p<0,001) und der Triglyzeride (p<0,001) und erhöhten die Anzahl der Patienten, die LDL-Cholesterin-Ziele erreichten (<NCEP-ATPIII, p<0,001). Beim HDL-Cholesterin wurde kein Unterschied festgestellt (p>0,05).

# Ezetimib zzgl. Statinen ggü. Statinen allein

Dieser Vergleich wurde in einer Studie ausgewertet, wobei keine statistischen Unterschiede für die Ergebnisse angegeben wurden.

# Ezetimib ggü. Fenofibrat

Nach 3 Monaten wurden hinsichtlich der prozentualen Veränderung des LDL-Cholesterins (p=0,29) und des Gesamtcholesterin (p=0,83) keine statistischen Unterschiede zwischen Ezetimib und Fenofibrat festgestellt. Fenofibrat führte zu einem signifikanten Anstieg des HDL-Cholesterins (p=0,0005), während Ezetimib die Anzahl der Patienten, die LDL-Cholesterin-Ziele erreichten, signifikant erhöhte (NCEP–ATP III; p=0,003).

### Ezetimib zzgl. Fenofibrat ggü. Fenofibrat allein

Nach 3 Monaten führte Ezetimib zzgl. Fenofibrat zu einer signifikanten Verbesserung des LDL-Cholesterins (p=0,001) sowie des Gesamtcholesterins und erhöhte die Anzahl der Patienten, die LDL-Cholesterin-Ziele erreichten (NCEP–ATP III; p<0,001). Diese Effekte hielten in einer Verlängerungsstudie bis zu 12 Monate an. Nach 3 und 12 Monaten wurden begrenzte statistische Unterschiede bei den Triglyzeriden und keine statistischen Unterschiede bei dem HDL-Cholesterin festgestellt. Im Allgemeinen lagen keine statistischen Unterschiede zwischen Ezetimib (Monotherapien oder Kombinationstherapien) und den jeweiligen Vergleichstherapien hinsichtlich unerwünschter Ereignisse (schwere, behandlungsbedingte, beliebige oder solche, die zum Abbruch der Behandlung führten) vor.

# Kosten und Kosteneffektivität

Ein Markov-Modell wurde erstellt, um die Kosteneffektivität von Ezetimib zzgl. Statinen im Vergleich zu Statinen allein zu beurteilen. Dabei lag ausreichende MACE-Evidenz vor, um eine ökonomische Analyse in der Population mit Hypercholesterinämie und ASCVD durchzuführen. Die Kosteneffektivität von Ezetimib (Monotherapie/Kombinationstherapie) in den anderen Populationen ist unbekannt. Die Modelleingaben wurden der IMPROVE-IT-Studie entnommen, in der Ezetimib zzgl. Simvastatin mit einer Simvastatin-Monotherapie bei Patienten mit ACS verglichen wurde. Das diskontierte inkrementelle Kosten-Effektivitäts-Verhältnis (ICER) pro gewonnenes qualitätsadjustiertes Lebensjahr (QALY) wurde über 7 Jahre (Studiendauer) auf 62'242 CHF geschätzt. Diese Summe sank bei einer 20-Jahres-Projektion (extrapolierte Lebenszeitschätzung) auf CHF 20'917 pro gewonnenes QALY.

Sensitivitätsanalysen haben aufgezeigt, dass die ICERs durch die grosse Bandbreite der im Modell verwendeten jährlichen Arzneimittelkosten am meisten beeinflusst wurden. Zusätzliche Sensitivitätsanalysen zeigten zudem, dass Ezetimib zzgl. Simvastatin im Vergleich zu höher wirksamen Statinen nicht kosteneffektiv war. Dieses Ergebnis bekräftigt die aktuelle Empfehlung der AGLA, die besagt, dass Ezetimib auf Patienten beschränkt werden sollte, die statinintolerant sind oder trotz maximal verträglicher Statine die Behandlungsziele nicht erreicht haben. Daher wurden Budget-Impact-Analysen durchgeführt, mit dem Ziel, die finanziellen Auswirkungen einer Beschränkung von Ezetimib auf diese Populationen zu guantifizieren.

Angesichts fehlender für die Schweiz spezifischer Daten wurden zwei hypothetische Substitutionsszenarien (10 Prozent und 25 Prozent der Patienten, die von Ezetimib-Monotherapie und Ezetimib in Kombination mit Rosuvastatin oder Simvastatin auf ein hochwirksames Statin [Atorvastatin 40 mg] umgestellt wurden) verwendet. Die Umstellung von 10 Prozent der Patienten von einer Ezetimib-Monotherapie oder einer Ezetimib-Kombinationstherapie auf ein hochwirksames Statin würde zu einer Nettoeinsparung von 2,0 Mio. CHF im Jahr 2020 führen, die bis 2023 auf 2,3 Mio. CHF ansteigt. Die Umstellung von 25 Prozent der Patienten von einer Ezetimib (Monotherapie oder Kombinationstherapie) auf ein hochwirksames Statin würde zu einer Nettoeinsparung von 2,0 Mio. CHF ansteigt. Die Umstellung von 5,0 Mio. CHF im Jahr 2020 führen, die bis 2023 auf 5,7 Mio. CHF ansteigt.

#### Rechtliche, soziale ethische und organisatorische Probleme

Die mangelhafte Adhärenz gegenüber Statinen ist ein häufig auftretendes Problem in der klinischen Praxis, welche das Risiko für kardiovaskuläre Morbidität und Mortalität erhöht. Da Ezetimib-Kombinationstherapien Statine enthalten, besteht diese Problematik auch hier und kann dazu führen, dass Patienten mit Hypercholesterinämie oder ASCVD eine unzureichende Behandlung erhalten. Die Umstellung von Statinen auf eine Ezetimib-Monotherapie kann die Adhärenz verbessern, da unerwünschte Ereignisse, die mit Statinen im Zusammenhang stehen (z. B. Myopathie), vermieden werden.

Zudem deuten Forschungsarbeiten aus Kanada darauf hin, dass eine Beschränkung des Zugangs zu Ezetimib unangemessenen Verschreibungspraktiken entgegenwirken könnte. Dies wurde in der Schweiz jedoch nicht untersucht.

#### Fazit

Bei Patienten mit Hypercholesterinämie ohne ASCVD war die Ezetimib-Monotherapie nach 3 Monaten hinsichtlich der Veränderungen des LDL-Cholesterins, des HDL-Cholesterins und des Gesamtcholesterins dem Placebo überlegen, den Statinen jedoch unterlegen. Ezetimib zzgl. Statinen führte zu einer langfristigen Verbesserung des LDL-Cholesterins. Es war jedoch unklar, ob es auch Verbesserungen der anderen Endpunkte erreichte.

Die Ergebnisse bezüglich Patienten mit Hypercholesterinämie und ASCVD wurden weitgehend der IMPROVE-IT-Studie entnommen. Ezetimib zzgl. Statinen reduzierte signifikant die Inzidenz von 3P-MACE, nicht-tödlichem MI und Schlaganfall nach sieben Jahren. Hinsichtlich kardiovaskulärer Todesfälle, koronarer Revaskularisationen oder instabiler Angina pectoris wurden jedoch keine Unterschiede festgestellt. Ezetimib zzgl. Statinen führte im Vergleich zu Statinen allein nach 12 Monaten auch zu Verbesserungen beim LDL-Cholesterin sowie beim Gesamtcholesterin, jedoch nicht beim HDL-Cholesterin oder bei den Triglyzeriden.

Vergleiche zwischen der Ezetimib-Monotherapie und Kombinationstherapien bei Patienten mit Hyperlipidämie ohne ASCVD waren auf eine oder zwei Studien mit geringen Patientenzahlen beschränkt. Kurzfristig war die Ezetimib-Monotherapie dem Placebo überlegen, den Statinen unterlegen und unterschied sich generell nicht von Fenofibrat. Ezetimib zzgl. Fenofibrat verbesserte das LDL-Cholesterin sowie das Gesamtcholesterin, unterschied sich aber nicht von Fenofibrat allein hinsichtlich der Veränderungen des HDL-Cholesterins und der Triglyzeride. Ezetimib zzgl. Statinen konnte im Vergleich zu Statinen allein nicht beurteilt werden, da keine statistischen Vergleiche verfügbar waren.

Das Sicherheitsprofil der Ezetimib-Monotherapie war vergleichbar mit dem vom Placebo und von Statinen. Ezetimib zzgl. Statinen wies im Allgemeinen ein Profil auf, das dem der Statine allein ähnlich war, wobei die Inzidenz behandlungsbedingter unerwünschter Ereignisse in der Kombinationstherapie-Gruppe höher war.

Ezetimib zzgl. Simvastatin war im Vergleich zur Simvastatin-Monotherapie bei Patienten mit Hypercholesterinämie und ASCVD kosteneffektiv (unter Verwendung von Daten aus der IMPROVE-IT-Studie). Die Beschränkung des Zugangs zu Ezetimib (Monotherapie oder Kombinationstherapie) würde zu einer Netto-Kosteneinsparung für die Kostenträger nach sich ziehen. Die Einsparungen waren empfindlich gegenüber den projizierten Kosten der Arzneimittel sowie der gleichzeitigen Anwendung von freien Statin-Kombinationen mit der Ezetimib-Monotherapie.

#### Résumé

Le présent rapport évalue l'efficacité clinique, la sécurité, le coût et le rapport coût-efficacité de l'ézétimibe (en monothérapie et en association) chez des patients présentant une hypercholestérolémie sans maladie cardiovasculaire athéroscléreuse (*atherosclerotic cardiovascular disease*, ASCVD), une hypercholestérolémie avec ASCVD, une hyperlipidémie mixte (ci-après « hyperlipidémie ») sans ASCVD ou une hyperlipidémie avec ASCVD. Il examine également les aspects juridiques, sociaux, éthiques et organisationnels de ce traitement.

#### Évaluation clinique

La sécurité et l'efficacité clinique de l'ézétimibe (en monothérapie et en association) ont été évaluées dans 30 essais contrôlés randomisés (ECR) menés sur des patients présentant une hypercholestérolémie sans ASCVD, 42 ECR sur des patients présentant une hypercholestérolémie avec ASCVD, et 5 ECR sur des patients présentant une hyperlipidémie sans ASCVD. Nous n'avons pas trouvé d'études évaluant l'ézétimibe chez des patients présentant une hyperlipidémie et une ASCVD. Les ECR inclus étaient de qualité modérée à élevée, les principaux problèmes étant liés à des données incomplètes, des doutes sur leur pertinence dans le contexte suisse et l'utilisation généralisée de marqueurs de substitution pour déduire l'efficacité clinique (cholestérol à lipoprotéines de basse densité [LDL], cholestérol à lipoprotéines de haute densité [HDL], etc.). Le présent résumé expose les résultats en termes d'événements cardiovasculaires majeurs (MACE) et d'évolution en valeur absolue des marqueurs de substitution à 3 mois (court terme) et 12/15 mois (long terme).

#### Hypercholestérolémie sans ASCVD

Aucune étude n'a évalué l'ézétimibe en monothérapie au-delà de trois mois. Le résultat de ces comparaisons s'est limité à des marqueurs de substitution. Aucune étude n'a utilisé du fénofibrate ou de l'ézétimibe plus fénofibrate.

#### Comparaison entre ézétimibe et placebo

À trois mois, on a constaté des différences statistiquement significatives en faveur de l'ézétimibe pour l'évolution en valeur absolue du cholestérol LDL (différence moyenne [MD] -46,68 mg/dl, intervalle de confiance [IC] à 95 % de -53,46 à -39,90 mg/ dl ; p < 0,001), du cholestérol HDL (MD 1,72 mg/dl ; IC à 95 % de 0,51 à 2,94 mg/dl ; p = 0,006) et du cholestérol total (MD -56,25 mg/dl ; IC à 95 % de -63,03 à -49,46 mg/dl ; p < 0,001). La proportion de patients ayant atteint leurs objectifs de cholestérol LDL sous ézétimibe était plus élevée (< 130 mg/dl ; risque relatif [RR] 6,93 ; IC à 95 % de 3,66 à 13,13 ; p < 0,001), mais une seule des trois études a rapporté des différences statistiquement significatives dans l'évolution en valeur absolue des triglycérides. Les résultats de cholestérol LDL et de cholestérol total présentaient une hétérogénéité modérée à considérable. Il n'y a pas eu de différence statistiquement significative de mortalité ni d'effets indésirables.

#### Comparaison entre ézétimibe et statines

Par rapport à l'ézétimibe, les statines ont significativement amélioré le cholestérol LDL (MD 10,77 mg/dl; IC à 95 % de 7,64 à 13,90 mg/dl; p < 0,001) et le cholestérol total (MD 4,61 mg/dl; IC à 95 % de -0,05 à 9,27 mg/dl; p = 0,05) et augmenté le nombre de patients qui ont atteint leurs objectifs de cholestérol LDL (< 130 mg/dl; RR 0,38; IC à 95 % de 0,31 à 0,47; p < 0,001) à 3 mois. Les effets étaient affectés d'une légère hétérogénéité. Les résultats des autres paramètres d'évaluation étaient incertains. Aucune étude n'a rapporté de différence statistiquement significative dans l'évolution en valeur absolue des triglycérides. Il n'y a pas eu de différences de mortalité ni d'effets indésirables.

# Comparaison entre ézétimibe plus statines et statines seules

Par rapport aux statines seules, l'association d'ézétimibe plus statines a amélioré significativement le cholestérol LDL (MD -16,72 mg/dl ; IC à 95 % de -22,34 à -11,11 mg/dl ; p < 0,001), le cholestérol HDL (MD 3,82 mg/dl ; IC à 95 % de 1,37 à 6,28 mg/dl ; p < 0,01) et le cholestérol total (MD - 18,02 mg/dl ; IC à 95 % de -27,95 à -8,09 mg/dl ; p < 0,01) et augmenté le nombre de patients qui ont atteint leurs objectifs de cholestérol LDL (< 130 mg/dl ; RR 1,14 ; IC à 95 % de 1,09 à 1,19 ; p < 0,001) à 3 mois. La différence statistique persistait à 15 mois pour le cholestérol LDL, mais pas pour le cholestérol total ni le HDL. Toutefois, le résultat est affecté par une hétérogénéité considérable et les repères temporels ultérieurs ont souvent été renseignés par une seule étude. Il n'y a pas eu de différence dans l'évolution en valeur absolue des triglycérides. Les événements indésirables liés au traitement (non définis dans les études) étaient plus fréquents avec l'ézétimibe plus statines qu'avec les statines seules (RR 1,12 ; IC à 95 % de 1,01 à 1,25 ; p = 0,04). Les autres événements indésirables étaient similaires entre les groupes.

#### Hypercholestérolémie avec ASCVD

Aucune étude n'a évalué l'ézétimibe en monothérapie ni l'ézétimibe associé au fénofibrate. En outre, les résultats ont été, dans une large mesure, ceux de patients atteints d'un syndrome coronarien aigu (SCA), parce que l'étude IMPROVE-IT était fortement pondérée dans la métaanalyse et qu'elle était la seule qui soit suffisamment puissante pour détecter des différences entre les groupes pour les trois événements cardiaques indésirables majeurs (3P-MACE : mesure composite incluant infarctus du myocarde [IM] non fatal, AVC et décès d'origine cardiovasculaire).

#### Comparaison entre ézétimibe plus statines et statines seules

Dans l'étude IMPROVE-IT, l'ézétimibe plus simvastatine a significativement réduit l'incidence des 3P-MACE (rapport de risque [HR] 0,90 ; IC à 95 % de 0,84 à 0,96 ; p = 0,003), des IM non fatals (HR 0,87 ; IC à 95 % de 0,80 à 0,95 ; p = 0,002) et des accidents ischémiques (HR 0,79 ; IC à 95 % de 0,67 à 0,94 ; p = 0,008) par rapport à la simvastatine seule à sept ans. Il n'y a pas eu de différence en termes de décès d'origine cardiovasculaire, de revascularisation coronarienne ou d'angor instable.

Par rapport aux statines seules, l'ézétimibe plus statines a amélioré significativement le cholestérol LDL (MD -17,22 mg/dl , IC à 95 % de -24,23 à -10,22 mg/dl ; p < 0,01) et le cholestérol total (MD - 21,18 mg/dl ; IC à 95 % de -28,93 à -13,34 mg/dl ; p < 0,01) et augmenté le nombre de patients atteignant leurs objectifs de cholestérol LDL (< 100 mg/dl ; RR 1,73 ; IC à 95 % de 1,32 à 2,26 ; p < 0,01) à 3 mois. La différence est restée statistiquement significative à 12 mois pour le cholestérol LDL (MD -16,82 mg/dl ; IC à 95 % de -22,51 à -11,12 mg/dl ; p < 0,01) et le cholestérol total (MD - 17,84 mg/dl ; IC à 95 % de -24,12 à -11,56 mg/dl ; p < 0,01). Les résultats étaient cependant affectés par une hétérogénéité considérable. La différence entre l'ézétimibe plus statines et les statistiquement significative a une hétérol HDL et des marqueurs d'atteinte vasculaire. Il n'y a pas eu de différence statistiquement significative en termes de mortalité ou d'événements indésirables (graves, liés au traitement, quelconques ou ayant entraîné l'abandon).

#### Hyperlipidémie sans ASCVD

Aucune étude n'a évalué les paramètres 3P-MACE ni les marqueurs d'atteinte vasculaire. Les résultats étaient limités aux marqueurs de lipémie à 3 mois pour les comparaisons de l'ézétimibe en monothérapie et de l'ézétimibe plus statines et à 12 mois pour la comparaison de l'ézétimibe plus fénofibrate.

### Comparaison entre ézétimibe et placebo

Deux études ont fourni des données de comparaison de l'ézétimibe avec un placebo. Elles n'ont pas été incluses dans la méta-analyse en raison des différences de méthode pour rapporter les résultats (changement absolu ou pourcentage). Des différences significatives ont été relevées entre les groupes ézétimibe et placebo en ce qui concerne le changement en valeur absolue du cholestérol LDL (p < 0,001) et du cholestérol total (p < 0,001), mais pas pour le cholestérol HDL (p = 0,04) ou les triglycérides (p = 0,1). La signification statistique n'a pas été rapportée pour l'évolution en pourcentage et il n'est donc pas possible de déterminer si les groupes étaient

# différents.

#### Comparaison entre ézétimibe et statines

Dans une étude, les statines ont amélioré significativement le cholestérol LDL (p < 0,001), le cholestérol total (p < 0,001) et les triglycérides (p < 0,001) et augmenté le nombre de patients atteignant leurs objectifs de cholestérol LDL (< NCEP-ATP III, p < 0,001) par rapport à l'ézétimibe. Il n'y a pas eu de différence pour le cholestérol HDL (p > 0,05).

#### Comparaison entre ézétimibe plus statines et statines seules

Une étude a évalué cette comparaison mais n'a pas rendu compte de différences statistiquement significatives pour les critères d'évaluation.

#### Comparaison entre ézétimibe et fénofibrate

À trois mois, il n'y avait pas de différence statistiquement significative entre l'ézétimibe et le fénofibrate pour l'évolution en pourcentage du cholestérol LDL (p = 0,29) et du cholestérol total (p = 0,83). Le fénofibrate ont significativement augmenté le cholestérol HDL (p = 0,0005) et l'ézétimibe a significativement augmenté le nombre de patients atteignant leurs objectifs de cholestérol LDL (NCEP-ATP III ; p = 0,003).

#### Comparaison entre ézétimibe plus fénofibrate et fénofibrate

À trois mois, l'ézétimibe plus fénofibrate a significativement amélioré le cholestérol LDL (p < 0,001) et le cholestérol total (p < 0,001) et augmenté le nombre de patients qui ont atteint leurs objectifs de cholestérol LDL (NCEP-ATP III ; p < 0,001). Dans une étude d'extension, ces effets ont persisté jusqu'à 12 mois. À 3 et 12 mois, il y a eu des différences statistiquement limitées pour les triglycérides et aucune différence statistique pour le cholestérol HDL. De manière générale, il n'y a pas eu de différence statistiquement significative entre l'ézétimibe (en monothérapie ou en association) et les molécules comparées en ce qui concerne les événements indésirables (graves, liés au traitement, quelconques ou abandon).

#### Coût et rapport coût-efficacité

Un modèle de Markov a été créé pour évaluer le rapport coût-efficacité de l'ézétimibe plus statines en comparaison avec les statines seules. Les données de MACE étaient suffisantes pour permettre une analyse économique de l'hypercholestérolémie dans la population ASCVD. Le rapport coûtefficacité de l'ézétimibe (en monothérapie ou en association) dans les autres populations est inconnu.

Les données d'entrée des modèles ont été fournies par l'essai IMPROVE-IT, qui comparait

l'ézétimibe plus simvastatine à la simvastatine en monothérapie chez des patients souffrant d'un SCA. Le rapport coût-efficacité incrémentiel (ICER) décompté par année de vie ajustée par la qualité (QALY) gagnée était estimé à 62 242 CHF sur sept ans (durée de l'essai). En projection sur 20 ans (estimation extrapolée de la durée de vie), il diminuait à 20 917 CHF par QALY gagnée.

Les analyses de sensibilité ont indiqué que l'ICER était surtout affecté par la grande diversité des coûts annuels du traitement médicamenteux utilisés dans le modèle. Les analyses de sensibilité supplémentaires notaient que l'ézétimibe plus simvastatine n'était pas économique par rapport aux statines plus puissantes. Cette observation concorde avec la recommandation actuelle de l'AGLA, qui réserve l'ézétimibe aux patients intolérants aux statines ou qui n'ont pas atteint leurs objectifs de traitement malgré un traitement par statines à la dose maximale tolérée. Des analyses d'impact budgétaire ont donc été réalisées afin de quantifier les implications financières d'une limitation de l'ézétimibe à ces populations.

En l'absence de données spécifiques pour la Suisse, deux hypothèses de substitution (10 % et 25 % de patients passant de l'ézétimibe, en monothérapie ou en association avec la rosuvastatine ou la simvastatine, à une statine plus puissante [atorvastatine à 40 mg]) ont été utilisées. Si 10 % des patients passaient de l'ézétimibe en monothérapie ou en association à une statine puissante, l'économie nette serait de 2,0 millions de francs en 2020 et de 2,3 millions d'ici 2023. Si 25 % des patients passaient de l'ézétimibe (en monothérapie ou en association) à une statine puissante, l'économie nette serait de 5,0 millions de francs en 2020 et de 5,7 millions d'ici 2023.

#### Questions juridiques, sociales, éthiques et organisationnelles

Le manque d'observance du traitement par statines est un problème fréquent dans la pratique clinique, qui entraîne un risque accru de morbidité et de mortalité cardiovasculaire. Du fait de la présence de statines, le traitement par l'ézétimibe en association avec des statines pose le même problème et risque donc d'être inadéquat chez les patients présentant une hypercholestérolémie ou une ASCVD. Le passage des statines à l'ézétimibe en monothérapie peut améliorer l'observance car il évite les effets indésirables associés aux statines (par ex. myopathie).

En outre, des données expérimentales canadiennes suggèrent que la limitation de l'accès à l'ézétimibe pourrait réduire les pratiques de prescription inappropriées. Ce point n'a cependant pas été évalué en Suisse.

#### Conclusion

Chez les patients présentant une hypercholestérolémie sans ASCVD, l'ézétimibe en monothérapie a été supérieur au placebo mais inférieur aux statines en ce qui concerne l'évolution du cholestérol LDL, du cholestérol HDL et du cholestérol total à 3 mois. Associé aux statines, il a amélioré le cholestérol LDL à long terme mais il n'est pas démontré qu'il ait amélioré d'autres paramètres d'évaluation.

Les résultats pour les patients présentant une hypercholestérolémie et une ASCVD ont été fournis, dans une large mesure, par l'étude IMPROVE-IT. L'ézétimibe associé aux statines a significativement réduit l'incidence des 3P-MACE, des IM non fatals et des AVC à sept ans. Il n'y a cependant pas eu de différence dans les décès d'origine cardiovasculaire, les revascularisations coronariennes ni l'angor instable. L'ézétimibe associé aux statines a amélioré le cholestérol LDL et le cholestérol total à 12 mois, mais pas le cholestérol HDL ni les triglycérides, en comparaison avec les statines.

Seuls un ou deux essais, portant sur un petit nombre de patients, ont comparé l'ézétimibe en monothérapie et en association chez les patients présentant une hyperlipidémie sans ASCVD. À court terme, l'ézétimibe en monothérapie était supérieur au placebo, inférieur aux statines et globalement comparable au fénofibrate. L'ézétimibe plus fénofibrate a amélioré le cholestérol LDL et le cholestérol total mais n'était pas différent du fénofibrate seuls en ce qui concerne l'évolution du cholestérol HDL et des triglycérides. L'ézétimibe associé aux statines n'a pas pu être évalué par rapport aux statines seules car aucune comparaison statistique n'a été rapportée.

L'ézétimibe en monothérapie a un profil de sécurité comparable à celui du placebo et des statines. L'ézétimibe plus statines a un profil globalement similaire à celui des statines, à ceci près que l'incidence des effets indésirables liés au traitement était plus élevée dans le groupe du traitement en association.

Le rapport coût-efficacité de l'ézétimibe plus simvastatine était meilleur que celui de la simvastatine en monothérapie chez les patients présentant une hypercholestérolémie et une ASCVD (selon les données de l'étude IMPROVE-IT). Limiter l'accès à l'ézétimibe (en monothérapie ou en association) entraînerait des économies nettes pour les caisses. Ces économies se sont avérées sensibles au coût projeté des médicaments et à l'utilisation d'associations libres de statines, en concurrence avec l'ézétimibe seul.

#### Sintesi

Questo rapporto valuta l'efficacia clinica, la sicurezza, il costo e il rapporto costo-efficacia dell'ezetimibe (monoterapia e terapie di associazione) in pazienti con ipercolesterolemia senza malattia cardiovascolare aterosclerotica (ASCVD), ipercolesterolemia e ASCVD, iperlipidemia mista/combinata (di seguito denominata «iperlipidemia») senza ASCVD e iperlipidemia e ASCVD. Vengono inoltre prese in considerazione questioni legali, sociali, etiche e organizzative.

#### Valutazione clinica

La sicurezza e l'efficacia clinica dell'ezetimibe (monoterapia e terapie di associazione) sono state valutate da 30 studi randomizzati controllati (RCT) in pazienti con ipercolesterolemia senza ASCVD, 42 RCT in pazienti con ipercolesterolemia e ASCVD e 5 RCT in pazienti con iperlipidemia senza ASCVD. Non sono stati condotti studi di valutazione dell'ezetimibe in pazienti con iperlipidemia e ASCVD. Gli RCT inclusi erano di qualità da moderata ad alta con questioni chiave relative a dati incompleti, applicabilità incerta al contesto svizzero e ricorso generale a marker surrogati per dedurre l'efficacia clinica (ossia lipoproteine a bassa densità [c-LDL], lipoproteine ad alta densità [c-HDL] ecc.). Questa sintesi presenta i risultati riguardanti i MACE (eventi cardiovascolari avversi maggiori) e la variazione assoluta dei marker surrogati a 3 mesi (breve termine) e a 12/15 mesi (lungo termine).

#### Ipercolesterolemia senza ASCVD

Non sono stati condotti studi per valutare la monoterapia con ezetimibe oltre i 3 mesi. I risultati di questi confronti erano limitati ai marker surrogati. Non sono stati effettuati studi con somministrazione di fenofibrato o ezetimibe più fenofibrato.

#### Ezetimibe vs placebo

A 3 mesi, sono state rilevate differenze statistiche a favore dell'ezetimibe per quanto riguarda la variazione assoluta dei livelli di c-LDL (differenza media [MD] -46,68 mg/dL; intervallo di confidenza [IC] al 95% -53,46, -39,90 mg/dL; p<0,001), c-HDL (MD 1,72 mg/dL; IC al 95% 0,51, 2,94 mg/dL; p=0,006) e colesterolo totale (MD -56,25 mg/dL; IC al 95% -63,03, -49,46 mg/dL; p<0,001). Una percentuale maggiore di pazienti ha raggiunto gli obiettivi di c-LDL usando l'ezetimibe (<130 mg/dL; rischio relativo [RR] 6,93; IC al 95% 3,66, 13,13; p<0,001); tuttavia, solo uno dei tre studi ha riportato differenze statistiche nella variazione assoluta dei trigliceridi. I risultati del c-LDL e del colesterolo totale erano soggetti a un'eterogeneità da moderata a considerevole. Non sono state rilevate differenze statistiche nella mortalità o negli eventi avversi.

# Ezetimibe vs statine

Rispetto all'ezetimibe, le statine hanno migliorato significativamente i livelli di c-LDL (MD 10,77 mg/dL; IC al 95% 7,64, 13,90 mg/dL; p<0,001) e colesterolo totale (MD 4,61 mg/dL; IC al 95% - 0,05, 9,27 mg/dL; p=0,05) e aumentato il numero di pazienti che hanno raggiunto gli obiettivi di c-LDL (<130 mg/dL; RR 0,38; IC al 95% 0,31, 0,47; p<0,001) a 3 mesi. Gli effetti erano soggetti a bassa eterogeneità. I risultati per i restanti esiti erano incerti. Nessuno studio ha riportato differenze statistiche nella variazione assoluta dei trigliceridi. Non sono state rilevate differenze nella mortalità o negli eventi avversi.

# Ezetimibe più statine vs statine

Rispetto alla monoterapia con statine, la somministrazione dell'ezetimibe in associazione con statine ha migliorato significativamente i livelli di c-LDL (MD -16,72 mg/dL; IC al 95% -22,34, -11,11 mg/dL; p<0,001), c-HDL (MD 3,82 mg/dL; IC al 95% 1,37, 6,28 mg/dL; p<0,01) e colesterolo totale (MD -18,02 mg/dL, IC al 95% -27,95, -8,09 mg/dL; p<0,01) e ha aumentato il numero di pazienti che hanno raggiunto gli obiettivi di c-LDL a 3 mesi (<130 mg/dL; RR 1,14; IC al 95% 1,09, 1,19; p<0,001). La differenza statistica persisteva a 15 mesi per il c-LDL, ma non per il colesterolo totale o il c-HDL. Tuttavia, i risultati erano soggetti a una notevole eterogeneità e i timepoint successivi sono stati spesso decisi in base a un singolo studio. Non sono state rilevate differenze nella variazione assoluta dei trigliceridi. Gli eventi avversi correlati al trattamento (non definiti negli studi) sono stati più frequenti nel caso dell'associazione ezetimibe-statine rispetto alla monoterapia con statine (RR 1,12; IC al 95% 1,01, 1,25; p=0,04). Altri eventi avversi erano simili tra i gruppi.

# Ipercolesterolemia con ASCVD

Nessuno studio ha valutato la monoterapia con ezetimibe o l'associazione ezetimibe-fenofibrato. Inoltre, i risultati si riferivano in gran parte a pazienti con sindrome coronarica acuta (SCA) perché lo studio IMPROVE-IT è stato preponderante nelle metanalisi ed è stato l'unico studio di potenza sufficiente a rilevare differenze di gruppo negli eventi cardiaci avversi maggiori a 3 punti (3P-MACE, una misura composita di infarto miocardico [IM] non fatale, ictus e morte cardiovascolare).

#### Ezetimibe più statine vs statine

Nello studio IMPROVE-IT l'associazione ezetimibe-simvastatina ha ridotto significativamente l'incidenza di 3P-MACE (rapporto di rischio [HR] 0,90; IC al 95% 0,84, 0,96; p=0,003), IM non fatale (HR 0,87; IC al 95% 0,80, 0,95; p=0,002) e ictus ischemico (HR 0,79; IC al 95% 0,67, 0,94; p=0,008) rispetto alla monoterapia con simvastatina a 7 anni. Non sono state rilevate differenze in termini di morte cardiovascolare, rivascolarizzazione coronarica e angina instabile.

Rispetto alla monoterapia con statine, l'associazione dell'ezetimibe con statine ha migliorato significativamente i livelli di c-LDL (MD -17,22 mg/dL; IC al 95% -24,23, -10,22 mg/dL; p<0,01) e colesterolo totale (MD -21,18 mg/dL; IC al 95% -28,93, -13,34 mg/dL; p<0,01) e ha aumentato il numero di pazienti che hanno raggiunto gli obiettivi di c-LDL (<100 mg/dL; RR 1,73; IC al 95% 1,32, 2,26; p<0,001) a 3 mesi. I risultati sono rimasti statisticamente diversi a 12 mesi per il c-LDL (MD - 16,82 mg/dl; IC al 95% -22,51, -11,12 mg/dL; p<0,01) e il colesterolo totale (MD -17,84 mg/dL; IC al 95% -24,12, -11,56 mg/dl; p<0,01). I risultati erano soggetti a una notevole eterogeneità. Tra le due terapie (associazione ezetimibe-statine e monoterapia con statine) sono state riscontrate differenze incoerenti per quanto riguarda la variazione assoluta di trigliceridi, c-HDL e marker di danno vascolare. Non sono state rilevate differenze statistiche nella mortalità o negli eventi avversi (gravi, correlati al trattamento o altri, o ritiro dallo studio dovuto a eventi avversi).

# Iperlipidemia senza ASCVD

Nessuno studio ha valutato gli esiti di 3P-MACE o di marker di danno vascolare. I risultati sono stati limitati ai marker lipidici a 3 mesi per il confronto tra monoterapia con ezetimibe e associazione ezetimibe-statine e a 12 mesi per il confronto con l'associazione ezetimibe-fenofibrato.

# Ezetimibe vs placebo

Due studi hanno fornito evidenze confrontando ezetimibe e placebo. Non sono stati sottoposti a metanalisi a causa dei diversi metodi di presentazione degli esiti (variazione assoluta e in percentuale). Tra i gruppi di pazienti trattati con ezetimibe e placebo sono state rilevate differenze statistiche nella variazione assoluta dei livelli di c-LDL (p<0,001) e colesterolo totale (p<0,001) ma non di c-HDL (p=0,4) o trigliceridi (p=0,1). La significatività statistica non è stata riportata per la variazione percentuale, quindi non era chiaro se i gruppi differissero.

#### Ezetimibe vs statine

In uno studio, le statine hanno migliorato significativamente i livelli di c-LDL (p<0,001), colesterolo totale (p<0,001) e trigliceridi (p<0,001) e aumentato il numero di pazienti che hanno raggiunto gli obiettivi di c-LDL (NCEP-ATP III, p<0,001) rispetto all'ezetimibe. Non sono state rilevate differenze nei livelli di c-HDL (p>0,05).

#### Ezetimibe più statine vs statine

Uno studio ha valutato questo confronto ma non ha riportato le differenze statistiche per gli esiti.

#### Ezetimibe vs fenofibrato

A 3 mesi, non sono state rilevate differenze statistiche tra l'ezetimibe e il fenofibrato nella variazione

percentuale del c-LDL (p=0,29) e del colesterolo totale (p=0,83). Il fenofibrato ha aumentato significativamente i livelli di c-HDL (p=0,0005) e l'ezetimibe ha aumentato significativamente il numero di pazienti che hanno raggiunto gli obiettivi di c-LDL (NCEP-ATPIII; p=0,003).

#### Ezetimibe più fenofibrato vs fenofibrato

A 3 mesi, l'associazione ezetimibe-fenofibrato ha migliorato significativamente i livelli di c-LDL (p=0,001) e colesterolo totale (p<0,001) e aumentato il numero di pazienti che hanno raggiunto gli obiettivi di c-LDL (NCEP-ATP III; p<0,001). Questi effetti persistevano fino a 12 mesi in uno studio di estensione. A 3 e 12 mesi sono state rilevate differenze statistiche limitate nei livelli di trigliceridi e nessuna differenza statistica nei livelli di c-HDL. In generale non sono state rilevate differenze statistiche tra la terapia con ezetimibe (monoterapie o terapie di associazione) e i rispettivi medicamenti di confronto in termini di eventi avversi (gravi, correlati al trattamento, o altri, o ritiro dallo studio dovuto a eventi avversi).

# Costi e rapporto costo-efficacia

È stato creato un modello di Markov per valutare il rapporto costo-efficacia dell'associazione ezetimibe-statine rispetto alla monoterapia con statine. C'erano evidenze sufficienti riguardo ai MACE per intraprendere un'analisi economica nella popolazione di pazienti con ipercolesterolemia con ASCVD; il rapporto costo-efficacia dell'ezetimibe (monoterapia/terapia di associazione) nelle altre popolazioni non è noto.

I dati immessi nel modello sono stati forniti dallo studio IMPROVE-IT, che ha confrontato l'associazione ezetimibe-simvastatina con la monoterapia con simvastatina in pazienti con SCA. Il rapporto costo-efficacia incrementale (ICER) scontato per anno di vita corretto per la qualità di vita (QALY) guadagnato è stato stimato a 62 242 franchi su 7 anni (durata dello studio) ed è sceso a 20 917 franchi per QALY guadagnato su una proiezione di 20 anni (stima della durata di vita estrapolata).

Le analisi di sensibilità hanno indicato che gli ICER sono stati maggiormente influenzati dall'ampia gamma di costi annuali dei medicamenti utilizzati nel modello. Ulteriori analisi di sensibilità hanno rilevato che l'associazione ezetimibe-simvastatina non era efficace in termini di costi rispetto alla monoterapia con statine di maggiore potenza. Questa scoperta supporta l'attuale raccomandazione del GSLA secondo cui l'ezetimibe dovrebbe essere limitato ai pazienti che sono intolleranti alle statine o che non sono riusciti a raggiungere gli obiettivi del trattamento nonostante la somministrazione di dosi massimamente tollerate di statine. Pertanto, sono state eseguite analisi dell'impatto sul budget per quantificare le implicazioni finanziarie della limitazione dell'ezetimibe a

queste popolazioni.

In assenza di dati specifici per la Svizzera, sono stati utilizzati due ipotetici scenari di sostituzione (10% e 25% dei pazienti che hanno sostituito la monoterapia con ezetimibe e l'associazione ezetimibe-rosuvastatina o ezetimibe-simvastatina con statine ad alta potenza [atorvastatina 40 mg]). Se il 10% dei pazienti sostituisse la terapia con ezetimibe (monoterapia o terapia di associazione) con statine ad alta potenza, si otterrebbe un risparmio netto di 2 milioni di franchi nel 2020, valore che aumenterebbe a 2,3 milioni di franchi entro il 2023. Se il 25% dei pazienti sostituisse la terapia o terapia di associazione) con statine ad alta potenza o terapia o terapia di sostituisse la terapia con ezetimibe (monoterapia o terapia di associazione) con statine ad alta potenza, si otterrebbe un risparmio netto di 2 milioni di franchi entro il 2023. Se il 25% dei pazienti sostituisse la terapia con ezetimibe (monoterapia o terapia di associazione) con statine ad alta potenza, si otterrebbe un risparmio netto di 5 milioni di franchi nel 2020, valore che aumenterebbe a 5,7 milioni di franchi entro il 2023.

#### Questioni legali, sociali, etiche e organizzative

La non aderenza alle statine è un problema comune nella pratica clinica, che aumenta il rischio di morbilità e mortalità cardiovascolare. A causa della presenza di statine, questa preoccupazione si applica alle terapie di associazione con ezetimibe e può portare a un trattamento inadeguato nei pazienti con ipercolesterolemia o ASCVD. Il passaggio dalle statine alla monoterapia con ezetimibe può migliorare l'aderenza perché si evitano gli eventi avversi associati alle statine (ad es. miopatia).

Inoltre, una ricerca canadese suggerisce che limitare l'accesso alla terapia con ezetimibe può ridurre la pratica di prescrizioni inappropriate; questo aspetto non è stato valutato in Svizzera.

#### Conclusioni

Nei pazienti con ipercolesterolemia senza ASCVD, la monoterapia con ezetimibe si è dimostrata superiore rispetto al placebo ma inferiore alla terapia con statine per quanto riguarda le variazioni dei livelli di c-LDL, c-HDL e colesterolo totale a 3 mesi. L'associazione ezetimibe-statine ha migliorato i livelli di c-LDL a lungo termine, ma non si sa con esattezza se abbia migliorato altri esiti.

I risultati per i pazienti con ipercolesterolemia e ASCVD sono stati in gran parte forniti dallo studio IMPROVE-IT. L'associazione ezetimibe-statine ha ridotto significativamente l'incidenza di 3P-MACE, IM non fatale e ictus a 7 anni. Tuttavia, non sono state rilevate differenze in termini di morte cardiovascolare, rivascolarizzazione coronarica e angina instabile. L'associazione ezetimibe-statine ha anche migliorato i livelli di c-LDL e colesterolo totale, ma non i livelli di c-HDL o trigliceridi a 12 mesi, rispetto alla monoterapia con statine.

I confronti tra la monoterapia con ezetimibe e le terapie di associazione in pazienti con iperlipidemia senza ASCVD sono stati limitati a uno o due studi con un piccolo numero di pazienti. A breve termine, la monoterapia con ezetimibe era superiore al placebo, inferiore alla terapia con statine e generalmente non era diversa dalla terapia con fenofibrato. L'associazione ezetimibe-fenofibrato ha migliorato i livelli di c-LDL e colesterolo totale, ma non sono state riscontrate differenze rispetto alla terapia con fenofibrato in termini di cambiamenti dei livelli di c-HDL e trigliceridi. Non è stato possibile valutare l'associazione ezetimibe-statine rispetto alla monoterapia con statine perché non sono stati riportati confronti statistici.

La monoterapia con ezetimibe ha mostrato un profilo di sicurezza comparabile a quello del placebo e delle statine. Generalmente, l'associazione ezetimibe-statine ha mostrato un profilo simile a quello della terapia con statine, notando che l'incidenza di eventi avversi correlati al trattamento è stata più alta nel gruppo che ha ricevuto la terapia di associazione.

L'associazione ezetimibe-simvastatina è risultata efficace in termini di costi rispetto alla monoterapia con simvastatina in pazienti con ipercolesterolemia e ASCVD (utilizzando i dati dello studio IMPROVE-IT). Limitare l'accesso alla terapia con ezetimibe (monoterapia o terapia di associazione) comporterebbe un risparmio netto sui costi per i paganti; i risparmi erano sensibili al costo previsto dei medicamenti e all'uso concomitante di terapie di associazione libera di statine con ezetimibe in monoterapia.

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# Abbreviations and acronyms

5x ULN	5 times the upper limit of normal
ACS	Acute coronary syndrome
AE	Adverse event
AGLA	Arbeitsgruppe Lipide und Atherosklerose (Swiss Atherosclerosis Association)
APOB	Gene coding for the apolipoprotein B protein
Аро-В	Apolipoprotein B
ASCVD	Atherosclerotic cardiovascular disease
cIMT	Carotid intima-media thickness
CHD	Coronary heart disease
CI	Confidence intervals
СК	Creatinine kinase
CKD	Chronic kidney disease
DARE	Database of Abstracts of Reviews of Effects
EAS	European Atherosclerosis Society
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
ESC	European Society of Cardiology
EUnetHTA	European Network for Health Technology Assessment
EQ-5D	EuroQol 5 dimensions questionnaire
FH	Familial hypercholesterolaemia
FOPH	Federal Office of Public Health
GRADE	Grading of Recommendations, Assessment, Development and Evaluations
HDL-c	High density lipoprotein-cholesterol
HeFH	Heterozygous familial hypercholesterolaemia
HMG-CoA	3-Hydroxy 3-methylglutaryl-coenzyme A
HR	Hazard ratio
HTA	Health technology assessment
IHD	Ischaemic heart disease
IVUS	Intravascular ultrasound
LDL-c	Low density lipoprotein-cholesterol
LDLR	Gene coding for low-density lipoprotein receptors
MACE	Major adverse cardiovascular events
MD	Mean difference

mg/dL	Milligram per decilitre
MI	Myocardial infarction
mmol/L	Millimole per litre
n	Number of patients with event
Ν	Total number of patients
NA	Not applicable
NCEP-ATP	National Cholesterol Education Program–Adult Treatment Panel III
NHS EED	National Health Service Economic Evaluation Database
NICE	National Institute of Clinical Excellence
NPC1L1	Protein Nieman Pick C1
NR	Not reported
NS	Not significant
PCSK9	Proprotein convertase subtilisin/kexin type 9
PICO	Population, intervention, comparator, outcome
PPAR	Peroxisome proliferator-activated receptors
PROCAM	Prospective cardiovascular münster
RCT	Randomised controlled trial
RR	Risk ratios
SAE	Serious adverse event
SCORE	Systematic coronary risk estimation
SD	Standard deviation
SE	Standard error
SF-12	12-Item Short Form Survey
STAE	Serious treatment-related adverse event
TAE	Treatment-related adverse event
TIMI TRS 2 ⁰P	Thrombolysis in Myocardial Infarction Risk Score for Secondary Prevention

# **Objective of the HTA report**

The objective of a health technology assessment (HTA) is to generate a focused assessment of various aspects of a health technology. The analytic methods applied to assess the value of using a health technology are described. The analytical process is comparative, systematic and transparent, and involves multiple stakeholders. The domains covered in an HTA report include clinical effectiveness and safety, costs, cost-effectiveness and budget impact, legal, social, ethical and organisational issues. The purpose is to inform health policy and decision-making to promote an efficient, sustainable, equitable and high-quality health system.

# **1** Policy Question and Context

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

However, there is ongoing debate regarding the clinical effectiveness of ezetimibe medications (monotherapy or combination therapies). Therefore, the applicant (santésuisse) suggests limiting the use of all ezetimibe therapies to patients who i) do not reach proposed low density lipoprotein-cholesterol (LDL-c) targets under statin monotherapies, or ii) cannot tolerate high statin monotherapy doses, or iii) were hospitalised due to acute coronary syndrome (ACS).

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

# 2 Research Questions

This HTA aims to address the following research questions:

- What is the safety, clinical effectiveness, cost-effectiveness and budgetary impact of ezetimibe (alone or in combination with statins or fenofibrate) compared to placebo, statins or fenofibrate monotherapy in patients who have (i) hypercholesterolaemia without pre-existing ASCVD, (ii) hypercholesterolaemia with ASCVD, or (iii) 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

Atherosclerotic cardiovascular disease (ASCVD) is a broad term encompassing a range of diseases affecting the heart and blood vessels, including coronary heart disease (CHD), cerebrovascular disease and peripheral artery disease.<sup>1</sup> These diseases can lead to events such as ACS, which includes unstable angina and myocardial infarction (MI), or stroke resulting in significant morbidity or mortality.<sup>12</sup> A major risk factor for cardiovascular disease is atherosclerosis, the accumulation of plaque—a build-up of substances including lipids, calcium, and connective tissue—in blood vessels.<sup>3</sup> Over time, this plaque build-up causes vessels to narrow and harden, increasing the risk of thromboembolic events such as stroke, transient ischaemic attack, pulmonary embolism and MI.<sup>3 4</sup> The exact cause of atherosclerosis and plaque build-up is currently unknown. However, there are several modifiable and non-modifiable life risk factors associated with its progression, including age and obesity.<sup>3</sup> Of relevance to this report is **dyslipidaemia**, which encompasses a broad class of disease characterised by abnormal lipoprotein, lipid, cholesterol or triglyceride levels in the blood.<sup>56</sup> Specific dyslipidaemias include:

Hypercholesterolaemia - characterised by higher-than-normal levels of circulating LDL-c, a lipoprotein involved in the transport of cholesterol.<sup>6</sup> Defined thresholds for abnormal levels are complex, taking into account age, sex, ethnicity and patient history.<sup>7</sup> The disorder is characterised into primary and secondary hypercholesterolaemia. The origin of primary hypercholesterolaemia can be predominately genetic (familial hypercholesterolaemia) or a combination of genetic and lifestyle factors (non-familial hypercholesterolaemia). Lifestyle factors contributing to non-familial hypercholesterolaemia include high saturated-fat diet, smoking and a lack of physical activity.<sup>68</sup> Familial hypercholesterolaemia (FH) is a group of inherited disorders resulting from defects in genes (e.g. LDLR, APOB, PCSK9) associated with the synthesis, metabolism or transport of lipoproteins or cholesterol.<sup>9</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>10</sup> Secondary hypercholesterolaemia is generally caused by pre-existing conditions (e.g. diabetes) or certain medications (e.g. diuretics).<sup>6 8</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>7</sup> Correspondingly, hypercholesterolemia increases the risk of developing ASCVD. This risk is more pronounced in individuals with FH compared to non-FH.11 12

**Mixed/combined hyperlipidaemia** – characterised by increased LDL-c coupled with increased triglycerides and/or decreased high density lipoprotein cholesterol (HDL-c). 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>13 14</sup>

Individuals with hypercholesterolaemia or mixed/combined hyperlipidaemia are at an increased risk of ASCVD, ACS, and death.<sup>7</sup> For these individuals, medications that aim to lower blood concentration of LDL-c are often prescribed.<sup>15</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>7</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>7</sup> In individuals who have experienced an adverse cardiac event (e.g. MI or stroke), LDL-c-lowering medications are intended to reduce the risk of further adverse events (i.e. secondary prevention).<sup>16</sup>

In summary, individuals with hypercholesterolaemia or mixed/combined hyperlipidaemia utilising lipidlowering interventions who have not experienced an adverse cardiac event are denoted as the primary prevention population. Individuals utilising lipid-lowering therapies who have experienced an adverse cardiac event are denoted as the secondary prevention population.

### 3.2 Symptoms and Diagnostic Pathway

Most patients with hypercholesterolaemia present with elevated LDL-c levels (>100mg/dL) and often do not exhibit clinical symptoms indicative of CVD. (Specific LDL-c values are dependent on age and other risk factors.)<sup>17</sup> In severe cases, hypercholesterolaemia can cause skin or tendon lesions (xanthomas) and cholesterol deposits in the eye (corneal arcus).<sup>18</sup> Age, genetic testing, family history and LDL-c levels are considered to ascertain whether hypercholesterolaemia is non-familial, familial or mixed/combined origin.<sup>10</sup> <sup>19</sup> Patients who have first-degree relatives with a history of elevated LDL-c levels, tendon xanthomas or corneal arcus , premature CVD or who have died from a cardiovascular event are candidates for genetic testing for FH.<sup>17</sup> Genetic testing screens for mutations in the *LDLR*, *APOB* and *PCSK9* genes, however, approximately 10–40% of patients with phenotypical characteristics of FH do not exhibit genetic defects in these genes.<sup>17</sup> Lastly, LDL-c measures are generally higher in familial than non-familial hypercholesterolaemia.

Once diagnosed, the individual's cardiovascular risk score is calculated. In Switzerland, the Swiss Atherosclerosis Association (AGLA) recommends the use of prospective cardiovascular münster (PROCAM) and systematic coronary risk estimation (SCORE) (except for FH and individuals aged older than 75) to calculate patient risk.<sup>20</sup> The cardiovascular risk score determines the absolute risk of a fatal

coronary event or non-fatal MI within 10 years.<sup>21</sup> This, in turn, determines appropriate treatment strategy and goals. A summary of the risk categories and their corresponding criteria is shown in *Table 1*. The table represents a simplified risk score, as additional considerations such as age, blood pressure, sex, smoking habits and diabetes influence an individual's overall risk categorisation.<sup>21</sup>

Individuals classified as very high and high risk require immediate intervention to greatly reduce their lipid and triglyceride levels. Individuals at moderate and low risk are able to tolerate higher levels of LDL-c owing to the lack of additional risk factors. Lifestyle interventions or low intensity statins are typically required to achieve treatment goals. If treatment goals are not reached, individuals are at greater risk of developing an ASCVD and experiencing adverse cardiovascular events such as ACS and stroke.

Cardiovascular risk category	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 such as 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 highly recommended for risk assessment. Low HDL-c is associated with increased cardiovascular risk. When viewing HDL-c as an isolated measure, <39mg/dL (1mmol/L) is recommended level.	No treatment target, but highly recommended for risk assessment.No treatment t highly recomm for risk assessLow HDL-c is associated with increasedUse LDL-c val determine app levels.	No treatment target, but highly recommended for risk assessment. Use LDL-c values to determine appropriate levels.	target, but mended sment. alues to propriate <b>Moderate hypertriglyceridaemia</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 >190mg/dL (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)		ardiovascular risk. Vhen viewing HDL-c s an isolated measure, 39mg/dL (1mmol/L) is ecommended level. Correct lifestyle factors nd evaluate other risk actors to address HDL- concerns.	Severe hypertriglyceridaemia TG >886mg/dL (>10mmol/L) Primary goal is to prevent acute pancreatitis, lower triglycerides,	
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)	Correct lifestyle factors and evaluate other risk factors to address HDL- c concerns.		eliminate chylomicronemia. Secondary goal is to treat underlying disease and reduce LDL-c and non-HDL-c to target levels.	
Low risk	10-year risk <10% <sup>b</sup>	No target value: optimise lifestyle interventions	No target value			Mixed hyperlipidaemia TC >233mg/dl (6mmol/L), TG >177mg/dL (2mmol/L) Primary goal is to lower LDL-c and non-HDL-c to target levels. Secondary	
General therapy recommendations: Before starting pharmacological interventions, the lifestyle of the patient (activity, diet and body weight) should be accounted for and optimised. In secondary							

Table 1	Summary of risk categories as	reported by the Swiss	Atherosclerosis As	ssociation (AGLA) <sup>21</sup>
		······································		

General therapy recommendations: Before starting pharmacological interventions, the lifestyle of the patient (activity, diet and body weight) should be accounted for and optimised. In secondary prevention, both pharmacological and lifestyle interventions should start at the same time.

### Abbreviations

eGFR = estimated glomerular filtration rate, HDL-c = high density lipoprotein-cholesterol, 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.

<u>Notes</u>

**a** = Previous MI, ACS, coronary revascularisation and other arterial revascularisation procedures, stroke/transient ischemic attack, aortic aneurysm, peripheral arterial occlusive disease.

**b** = Absolute risk (%) of fatal coronary event or a non-fatal event within 10 years.

c = Total of atherogenic lipoproteins.

### 3.3 Prevalence and Burden of Disease

### Cardiovascular disease

CVD is the leading cause of mortality globally. In 2017, an estimated 17.8 million deaths were attributed to CVD, of which 2.6 million deaths were attributable to raised cholesterol.<sup>1</sup> <sup>22</sup> Specifically, high cholesterol accounts for approximately one third of all ischaemic heart disease (IHD) cases worldwide.<sup>22</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>22</sup>

In Switzerland, CVD is the second most common cause of death and the third most common reason for hospitalisation.<sup>23</sup> In 2017, CVD was responsible for 31% of deaths in Switzerland, representing the major cause of death for males and females over age 85 and the second most common cause of death for those aged 65–84 years.<sup>24-26</sup>

### High cholesterol

Approximately 20% of participants in the 2007 Swiss Health survey self-reported high cholesterol levels,<sup>27</sup> with significant differences found between regions.<sup>28</sup> Ticino and the western part of Switzerland (Leman) reported the highest prevalences at 22.9% and 21.9% of surveyed individuals, respectively, with the eastern part of Switzerland reporting the lowest rate (16.2%). Of participants reporting high cholesterol, 40% reported receiving appropriate treatment. Again, treatment rates where highest in Ticino and the western part of Switzerland (Leman) and lowest in the eastern part of Switzerland.<sup>28</sup>

In 2012, the prevalence of high cholesterol was similar, at approximately 17% 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>29</sup>

In 2017, 14.3% of females and 10.8% of males aged 15 years and older reported having high cholesterol. The highest prevalence was observed in males and females aged 75 years and older (*Figure 1*).<sup>30</sup>

#### Personnes avec un taux de cholestérol trop élevé

Population de 15 ans et plus vivant en ménage privé



Personnes déclarant avoir un taux de cholestérol trop élevé ou avoir pris des médicaments contre le cholestérol

#### Figure 1 Prevalence of high cholesterol among Swiss males and females in 2002 and 2017

#### Notes

Title: People with high cholesterol or are taking cholesterol medication, population aged 15 and over living in private households. Ans = age, hommes = males, femmes = females.

## Source

Federal Statistical Office<sup>30</sup>

#### Dyslipidaemias

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

- An evaluation of a nationwide primary care database (FIRE) and hospital discharge statistics (MEDSTAT) estimated approximately 3.7% of Swiss women and 6.3–6.7% of Swiss men have dyslipidaemia.<sup>31</sup> The authors noted that the prevalence of the condition changes depending on the subpopulation studied (e.g. age and gender) and other factors such as lifestyle and other pre-existing conditions (e.g. smoking and diabetes).<sup>31 32</sup>
- An evaluation of Swiss patients hospitalised with ACS determined that 1.6% and 17.8% had probable/definite and possible FH, respectively.<sup>33</sup>
- A sample of the Swiss population determined that 7 of the 2,221 subjects had FH as inferred by mutations in the *LDLR* gene, corresponding to a prevalence rate of 1/317 (0.3%).<sup>34</sup> Prevalence of FH due to all different genetic variants (*LDLR*, *PCSK9* and *APOB*) was 1/132 (0.7%).<sup>34</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>35</sup>
- Between 2009 and 2012, 4% of patients with dyslipidaemia were classified as very high risk, 10% were high risk, 62% were low risk and 14% were very low risk (as inferred by the PROCAM risk calculator) in Lausanne, Switzerland. A further 10% of patients with dyslipidaemia had experienced an adverse cardiac event.<sup>36</sup>

More broadly, the prevalence of mixed/combined hyperlipidaemia, heterozygous and homozygous FH in Europe varies from 1:100, 1:200–1:500 and 1:500,000, respectively.<sup>17</sup>

### 3.4 Treatment Pathway

### 3.4.1 Dyslipidaemia

The Swiss AGLA guidelines (*Figure 2*) and those from the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS) are fairly consistent with respect to management of dyslipidaemias.<sup>7 17</sup> Both guidelines emphasise the role of risk calculators that utilise patient history and blood lipid levels to calculate 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). The European guidelines also emphasise the variability in patient response to lifestyle and pharmaceutical interventions and highlight that total risk reduction and treatment goals should be individualised in order to achieve desired outcomes.<sup>7</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 that the cardiovascular risk and respective treatment goals differ according to risk category. Similarly, treatment goals may vary between certain types of FH.<sup>7 17</sup> The guidelines do not apply to adolescents and children, who require separate treatment management strategies – a discussion of which is beyond the scope of this report.

The following recommendations represent the Swiss guidelines (*Figure 2*) with additional information supplemented from the European guidelines. (The Swiss guidelines were updated during the drafting of the HTA, for a summary of the key changes refer to *Section 11*.)

Lifestyle interventions are the first-line treatment for management of dyslipidaemias (including both familial and non-familial dyslipidaemias) irrespective of risk level.<sup>7 17</sup> These interventions consist of lipid-lowering diets, increased physical activity and cessation of smoking. If patients fail to achieve their goals or are classified as very-high-, high- or moderate-risk, statins are recommended.<sup>17</sup> The response to statin treatment is often variable, therefore statin dosage is often titrated to the maximum tolerated dose before higher potency statins or further treatments (e.g. ezetimibe or fenofibrate) are considered.<sup>7</sup> The

statin initially selected should largely reflect patients' overall cardiovascular risk and their respective treatment goals.<sup>7</sup> For patients with FH, LDL apheresis may additionally be considered at this stage.<sup>7 17</sup>

If patients do not reach their treatment goals or are intolerant to statins, ezetimibe or ezetimibe-statin combination therapy is recommended.<sup>7 17</sup> ESC guidelines further suggest a bile acid sequestrant may be considered for patients unable to reach their treatment goal, noting that the level of evidence and the class of recommendation is lower than that for ezetimibe. Proprotein convertase subtilisin/kexin type 9 protein (PCSK9) inhibitors are recommended for patients (with or without ASCVD) at very high risk of not achieving their goals on a maximally tolerated dose of statin and ezetimibe.<sup>17</sup> In Switzerland, PCSK9 inhibitors are restricted to adults with hypercholesterolaemia, and adults and adolescents with homozygous FH who have a high or very high cardiovascular risk despite the use of maximally tolerated lipid-lowering medication.<sup>37</sup> In addition, individuals must be intolerant to statins or have used the maximally tolerated dose of lipid-lowering therapy for at least 3 months.

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### Figure 2 Clinical management pathway for dyslipidaemia (focus on hypercholesterolaemia)

### (AGLA)<sup>21</sup>

#### Abbreviations

**ASCVD** = atherosclerotic cardiovascular disease, **ESC** = European Society for Cardiology, **FOPH** = Federal Office of Public Health, **LDL-c** = low density lipoprotein-cholesterol, **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 ASCVD: coronary heart disease (CHD), symptomatic peripheral atherosclerosis or ischemic stroke.

**2** = See p. 33/34 of the Prävention der Atherosklerose (2018) for FOPH limitations for use of PCSK9 inhibitors.

3 = Additional risk indicators according to 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) and first-degree relatives with ASCVD; imaging indicators (high-risk markers in coronary computed tomography) for severe/extensive atherosclerosis; rapid progression of ASCVD.

**4** = Risk factors according to FOPH: diabetes mellitus; lipoprotein A >50 mg/dl; pronounced arterial hypertension; premature (men <55 years, women <60 years) clinically manifest familial ASCVD.

**5** = Progression according to FOPH limitation: progressive clinical ASCVD (repeated acute coronary syndrome, MI, stroke, or unplanned repeated coronary revascularisation within 5 years of first cardiovascular event).

### 3.4.2 Statin Intolerance

Statins are the principle treatment for the management of dyslipidaemia. However, approximately 1–5% of patients are intolerant to statins at any dose, leading to discontinuation of the drug.<sup>38</sup> Statin non-adherence, that is, poor compliance due to patient-, physician- or medication-related factors, increases the risk of adverse cardiovascular events, specifically MI or CHD, because the baseline risk remains untreated.<sup>39-41</sup> While there is no consensus regarding the definition of statin intolerance,<sup>41</sup> AGLA defines it as the inability to take statins due to statin-associated myopathy, liver damage or other adverse events.<sup>17</sup> Diagnosis of statin intolerance typically relies on the presentation of myopathy and/or an increase in the muscle injury marker creatinine kinase (CK). Symptoms generally begin within the first 4 weeks of treatment (rarely occurs after >12 weeks) and resolve after ceasing the statin. Resumption of the statin results in recurrence of symptoms within 4 weeks.<sup>17</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>17</sup> For further information regarding clinical management of statin intolerance refer to *Figure* **3**.



### Figure 3 Clinical management pathway for statin intolerance (AGLA)<sup>17</sup>

#### Abbreviations

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

a = Symptoms: clinical and/or CK increase.

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

c = Statins are generally taken daily. If symptoms recur, 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 that acts on the brush boarder cells of the intestine, selectively inhibiting the cholesterol transport protein Nieman Pick C1 (NPC1L1).<sup>42</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>42</sup> In support of this, individuals with genetic mutations inactivating NPC1L1 report lower LDL-c and overall ASCVD risk.<sup>43</sup>

It is unclear whether ezetimibe exhibits effects beyond reductions in LDL-c. Some evidence suggests ezetimibe modifies HDL-c, triglycerides and endothelial function, however, it is unclear whether the effects are clinically relevant.<sup>44</sup> Ezetimibe may improve glycaemic control as inferred by improvements in HbA1C levels.<sup>45</sup>

In Switzerland, ezetimibe exists as an individual medicine<sup>37 46</sup> or in fixed combination with statins, including simvastatin,<sup>47</sup> atorvastatin<sup>48</sup> and rosuvastatin.<sup>49</sup> Ezetimibe is additionally licensed for free combinations with fenofibrate or other licensed statins (each drug administered as a separate pill).<sup>37 46</sup> Generic ezetimibe medications are available (see *Table 2* for further information).

Ezetimibe-containing medicines are indicated for primary FH (heterozygous and homozygous), 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 treatment goal despite using the maximum tolerated dose of statins or those who are statin intolerant.<sup>17</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 4.2*.

Name (manufacturer)	Active ingredient (dose) Administration	Indications	Contraindications	Limitations for reimbursement
Ezetimibe				
Ezetrol®, Ezetimibe MSD® (Merck Sharp & Dohme) Ezetimib Zentiva® (Helvepharm AG)	Ezetimibe (10mg) Available as tablet taken once daily at any time regardless of food intake.	Primary heterozygous and homozygous FH Primary non-familial hyper- cholesterolaemia	Contraindicated in patients with hypersensitivity to ezetimibe or active liver disease.	No limitations

Table 2	Ke	v formulations	of	ezetimibe	available	in	Switzerland
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Name (manufacturer)	Active ingredient (dose) Administration	Indications	Contraindications	Limitations for reimbursement
Ezetimib Spirig HC® (Spirig HealthCare AG) Ezetimib Sandoz® (Sandoz Pharmaceuticals AG) Ezetimib-Mepha Teva (Mepha Pharma AG) Ezetimib Axapharm (Axapharm AG)	Patients should follow a lipid-lowering diet while taking the medication. Can be taken with a statin or fenofibrate, however, in combination with both statin and fenofibrate is not permitted.	Mixed/combined hyperlipidaemia Homozygous sitosterolemia (phytosterolemia) <sup>a</sup>	Not recommended in children under 10 years.	
Ezetimibe plus simva	statin		1	1
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) plus simvastatin (10, 20, 40 or 80mg) Available as tablet taken once daily in the evening regardless of food intake. Patients should follow a lipid-lowering diet while taking the medication. Dosage based on individual baseline LDL-c levels, treatment goals and response to therapy.	Primary heterozygous and homozygous FH Primary non-familial hypercholesterolaemi a Mixed/combined hyperlipidaemia	Contraindicated in patients with hypersensitivity to ezetimibe or simvastatin; active liver disease (moderate to severe); who are pregnant or breast feeding; or using CYP3A4 inhibitors and gemfibrozil, cyclosporine or danazol. Not recommended for children or adolescents under 18 years. Should be used with caution in elderly patients (>65 years).	No limitations
Ezetimibe plus atorva	statin		I	I
Atozet® (MSD Merck Sharp & Dohme)	Ezetimibe (10mg) plus atorvastatin (10, 20, 40 or 80mg) Available as tablet taken once daily regardless of time of day and food intake. Patients should follow a lipid-lowering diet while taking the medication. Dosage based on individual baseline LDL-c levels, treatment goals and response to therapy.	Primary heterozygous and homozygous FH Primary non-familial hyper- cholesterolaemia Mixed/combined hyperlipidaemia	Contraindicated in patients with hypersensitivity to ezetimibe or atorvastatin; active liver disease (moderate to severe); or who are pregnant or breast feeding. Not recommended for children or adolescents under 18 years. Should be used with caution in elderly patients (>65 years).	Patients who have high or very high cardiovascular risk (as per AGLA) and are above target LDL-c values despite using maximum tolerated statin therapy.

Name (manufacturer)	Active ingredient (dose) Administration	Indications	Contraindications	Limitations for reimbursement
Ezetimibe plus rosuva	astatin			
Ezetimib- Rosuvastatin Mepha (Mepha Pharma AG)	Ezetimibe (10mg) plus rosuvastatin (10 or 20mg) Available as tablet taken once daily at same time of day regardless of food intake. Patients should follow a lipid-lowering diet while taking the medication. Dosage based on individual baseline LDL-c levels, treatment goals and response to therapy.	Indicated as a replacement therapy in adults receiving ezetimibe and rosuvastatin as separate tablets.	Contraindicated in patients with hypersensitivity to ezetimibe or rosuvastatin; are taking cyclosporin; have myopathy, active liver disease, renal impairment; or who are pregnant or breast feeding. Not recommended for children or adolescents under 18 years. In the elderly (>65 years), fixed dose combination is not suitable as initial therapy.	Ezetimibe- Rosuvastatin-Mepha indicated as a replacement therapy in adult patients already receiving ezetimibe and rosuvastatin as separate tablets at same dose level.

### **Abbreviations**

**FH** = familial hypercholesterolaemia, **LDL-c** = low density lipoprotein-cholesterol, **mg** = milligram. **Notes** 

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

### 4.1.2 Route of Administration, Dosage and Treatment Duration

Ezetimibe is prescribed by general practitioners, cardiologists, endocrinologists and nephrologists and is administered as a fixed dose (10mg) irrespective of whether it is in a combination or by itself.<sup>37 47-49</sup> For combination treatments the statin dose varies from 10mg to 80mg for simvastatin and atorvastatin<sup>47</sup> <sup>48</sup> and 10mg to 20mg for rosuvastatin.<sup>49</sup> Ezetimibe tablets are taken once daily regardless of 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>50</sup>

Once consumed, ezetimibe is rapidly absorbed and metabolised to its active form, ezetimibeglucuronide, which has a half-life of approximately 22 hours.<sup>42 51</sup> There are no significant effects of sex or race on the pharmacokinetics of ezetimibe,<sup>51</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>47 49</sup> 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>48 49</sup>

Duration of ezetimibe use is unclear because contemporary guidelines do not mention prescription limitations and there are few studies evaluating long-term risks associated with ezetimibe.<sup>52</sup>

### 4.1.3 Adverse Effects and Contraindications

Adverse effects associated with ezetimibe are generally mild and self-limiting and include abdominal pain, diarrhoea, flatulence, headache and myalgia.<sup>37</sup> Uncommon adverse effects include but are not limited to: dyspepsia, cough, body aches, back pain, chest pain, joint pain, fatigue and weakness.<sup>37 47</sup> Early reports observed an increased incidence of cancer associated with ezetimibe use,<sup>53</sup> however, pooled data from three clinical trials noted that the incidence of cancer was similar between ezetimibe and placebo.<sup>54</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>37</sup> Ezetimibe-statin combinations are associated with more numerous 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; or are pregnant or breast feeding. Combination treatments are not recommended in children but it is unclear whether this is a contraindication.<sup>47-49</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>15 55</sup> Other possible treatments comprise 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>56</sup> however there is limited evidence supporting the remaining supplements.<sup>7 57</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.

### 4.2.2 Statins

In addition to lifestyle changes, statins are often considered first-line treatment for primary dyslipidaemia and secondary prevention.<sup>7</sup> <sup>17</sup> Statins inhibit 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>7</sup> <sup>58</sup> By lowering LDL-c concentrations, the rate of plaque formation is reduced and overall CVD risk decreases. Despite being the most commonly prescribed treatment for dyslipidaemia, statin intolerance and resistance can occur. Statin medications can sometimes contain a statin combined with another active ingredient such as ezetimibe (*Table 2*) or fibrates. Three of the six statins covered by Swiss mandatory health insurance, are also found in fixed combination with ezetimibe, being 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).

Name/ manufacturer(s)	Active ingredient (dose administration	Indications/applications	Contraindications
Atorvastatin <sup>59</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 cardiovascular disease or have a high 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 or lactating.

Table 3 Formulations of statins available in Switzerland

Name/ manufacturer(s)	Active ingredient (dose administration	Indications/applications	Contraindications
<i>Fluvastatin</i> <sup>60</sup> Mepha Pharma AG and Novartis Pharma Schweiz AG, Sandoz Pharmaceuticals AG	Fluvastatinum (20, 40 or 80mg/day) Oral	Adults with CHD, mixed dyslipidaemia or primary hypercholesterolaemia who have failed dietary interventions. Males (9–16 years), and post-menarche females (10–16 years) with familial hypercholesterolaemia.	Patients who are hypersensitive to the active ingredient or any of the excipients; have active liver disease or unexplained persistent elevations of serum transaminases; or are pregnant or lactating.
<i>Pitavastatin</i> <sup>61</sup> Recordati AG	Pitavastatinum (1, 2 or 4mg/day) Oral	Adults with mixed dyslipidaemia and primary hypercholesterolaemia who have failed dietary and other non-pharmacological interventions.	Patients who are hypersensitive to the active ingredient or any of the excipients; have active liver disease or unexplained persistent elevations of serum transaminases, myopathy; using cyclosporine; or are pregnant or lactating. Not recommended for individuals under 18 years.
Pravastatin <sup>62</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	Pravastatinum natricum (10, 20 or 40mg/day) Oral	Individuals with primary hypercholesterolaemia, combined hyperlipidaemia, CHD, angina pectoris or post-myocardial infarction.	Patients who are hypersensitive to the active ingredient or any of the excipients; have active liver disease or unexplained persistent elevations of serum transaminases; or are pregnant and lactating. Not recommended for children under 8 years
<i>Rosuvastatin</i> <sup>63</sup> AstraZeneca AG Axapharm AG, Drossapharm AG Helvepharm, Sandoz Pharmaceuticals AG, Spirig HealthCare AG, and Mepha Pharma AG	Rosuvastatinum (5, 10 or 20mg/day) Oral	Adults with mixed dyslipidaemia, primary hypercholesterolaemia or at high cardiovascular risk	Patients of Asian descent or who are 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 or lactating. Not recommended for children under 10 years

Name/ manufacturer(s)	Active ingredient (dose administration	Indications/applications	Contraindications
Simvastatin <sup>64</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 CHD.	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

CHD = coronary heart disease.

### 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>65 66</sup> Fibrates are agonists of PPARs and regulate steps involved with lipid and lipoprotein metabolism. Consequently, fibrates lower lipoprotein levels, triglycerides and triglyceride-rich lipoprotein remnant particles.<sup>65 66</sup>

Fibrates are generally well tolerated by most patients, with less than 2–5% of users reporting skin rashes and gastrointestinal incidents.<sup>67</sup> However, fibrates are also associated with several serious adverse effects, the most common being myopathy, liver-enzyme elevations and cholelithiasis (gallstone formation).<sup>67</sup>

Several fibrate medications are available in Switzerland. Of relevance to this HTA is Lipanthyl<sup>®</sup> 200M/267M (Mylan Pharma GmbH), a fibrate medication containing fenofibratum. The typical starting dose for this medication is 200mg daily (one tablet). Lipanthyl<sup>®</sup> is contraindicated in cases of hepatic issues, pancreatitis, kidney failure and gallbladder issues.<sup>59</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>7 17</sup> These medications are either not widely used in Switzerland, have limited efficacy or are considered third-line treatments.<sup>7 17 68</sup> Consequently, these drugs will not be included as comparators and will not be discussed further in this report.

### 4.3 Regulatory Status / Provider

See Sections 4.1.1 to 4.1.3.

### 5 PICO

### 5.1 Population

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

The population includes patients with 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 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 FH. In contrast, combination regimes including ezetimibe plus atorvastatin, simvastatin or rosuvastatin are not recommended for individuals under the age of 10.<sup>46</sup> <sup>49</sup> <sup>69</sup> Further, the pharmacokinetics of these drugs differ in the elderly (>65 years) compared to younger patients.<sup>37</sup> Given the uncertainty and potentially different response in these age groups, sub-group analysis evaluating the elderly, children and adolescents will be performed if there are suitable numbers of studies.

Statin intolerance increases the risk of cardiovascular events such as MI and CHD compared to individuals who are successfully treated with statins.<sup>39 40</sup> These populations have different cardiovascular risk profiles and require different treatment management strategies and respond differently to lipid-lowering medication.<sup>41</sup> Therefore, these populations will be investigated in sub-group analyses to determine whether their response to ezetimibe differs.

ASCVD encompasses a broad range of range of disease and symptoms. For this HTA, ASCVD includes ACS, a history of MI, angina, coronary or other arterial revascularisation, stroke, transient ischemic attack, peripheral arterial disease, coronary artery or CHD.<sup>70</sup>

The AGLA guideline stratifies patients based on overall cardiovascular risk as determined by age, blood pressure, smoking status, presence of diabetes, ASCVD and familial cardiac events (e.g. MI), as well as LDL-c, HDL-c and triglyceride levels.<sup>21</sup> Patients stratified into very high, high, moderate and low risk categories have different cardiovascular risks and consequently treatment management strategies and goals also differ. Since it is unlikely there will be specific studies stratifying patients based on risk scores

(specifically AGLA), the applicability of the trial population to the AGLA risk groups will be discussed in **Sections 7.3.4** and **12**.

#### 5.2 Intervention

The technology under investigation is ezetimibe alone (monotherapy) or in combination (fixed or free) with a statin or fenofibrate. In Switzerland, four ezetimibe containing medicines are registered: ezetimibe, ezetimibe with simvastatin, ezetimibe with atorvastatin and ezetimibe with rosuvastatin (*Table 2* and *Table 3*). Ezetimibe is available in 10mg tablets taken once daily.<sup>17 37</sup> Statins are administered in fixed or free combination with 10mg of ezetimibe. The dose of concomitant statins varies and can be increased according to individual response. For example, when added to ezetimibe, simvastatin and atorvastatin have doses ranging from 10mg to 80mg. Rosuvastatin is dosed from 10mg to 20mg.<sup>46 49 69</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>71</sup> Sub-group analysis will be used to determine relative effectiveness between classes of statins (as inferred by their active ingredient) used in conjunction with ezetimibe. In addition to these combinations, therapeutic regimes combining ezetimibe with 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>7</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>7 17</sup> PCSK9 inhibitors are the last-line treatment for primary and secondary prevention and are strictly limited for reimbursement.<sup>17 68</sup> Consequently, they are excluded from this 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. Thus, the comparators for this HTA include placebo, fenofibrate and statins.

#### 5.4 Outcomes

#### 5.4.1 Effectiveness Outcomes

#### 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/effectiveness outcome by the European Medicines Agency (EMA) for trials investigating treatments of lipid disorders.<sup>72</sup> There is no standardised definition of MACE and different definitions can lead to different conclusions.<sup>73</sup> In this instance, the EMA recommendation for MACE will be prioritised, this encompasses

cardiovascular mortality, non-fatal stroke and non-fatal MI.<sup>72</sup> The individual events forming MACE will be included and reported/analysed separately as well. Decreasing the risk and incidence of MACE will 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 an individual's physical and mental health. The SF-12 or -36 and the EuroQoL-5D (EQ-5D) are commonly used measures evaluating quality of life. These tools require patients to self-asses their current status across multiple dimensions including mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Any health-related quality of life measure will be considered.<sup>74-76</sup>

#### Important

**Total cholesterol, triglycerides, HDL-c and LDL-c** are lipids or lipoproteins and are surrogate markers used to infer cardiovascular risk. Swiss,<sup>17</sup> European<sup>7</sup> and American guidelines<sup>77 78</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>7</sup> a lipoprotein involved in lipid deposition and the progression of atherosclerotic plaques.<sup>3</sup> Multiple studies have demonstrated a relationship between changes in LDL-c and cardiovascular risk and mortality.<sup>79 80</sup> Consequently, most clinical guidelines use LDL-c levels as a measure to determine overall cardiovascular risk and set treatment goals.<sup>7 81</sup> For example, AGLA-recommended target goals for very high, high and moderate risk groups are 70, 100 and 115mg/dL, respectively.<sup>17 82</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>83-85</sup> Consequently, EMA recommends LDL-c as a suitable primary efficacy outcome for hypercholesterolaemia provided the medication's claims are limited to its lipid-lowering effect.<sup>72</sup>

**HDL-c** is a measure of a variety of lipoproteins (most notably ApoA) and cholesterol.<sup>7</sup> It is involved in reverse cholesterol transport and is therefore thought to play an important role in prevention of atherosclerosis.<sup>86</sup> HDL-c is inversely associated with cardiovascular risk, although a causal relationship between HDL-c and atherosclerosis has not been established.<sup>7</sup> Contemporary guidelines, including AGLA, do not have treatment goals associated with HDL-c and EMA suggests HDL-c should only be viewed in conjunction with other non-HDL-c markers to determine the efficacy of lipid-lowering drugs.<sup>72</sup>

**Triglycerides** are a measure of circulating fat that is typically carried throughout the body in lipoproteins.<sup>87</sup> Elevated triglyceride levels are associated with an increased risk of CVD and are routinely used in clinical risk calculators,<sup>81</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>87-90</sup> This reflects the hypothesis that the cholesterol component of triglyceride-rich lipoproteins is responsible for atherosclerosis and CVD, rather than the triglycerides themselves.<sup>87</sup> Like for HDL-c, EMA recommends triglycerides should be viewed in conjunction with other cholesterol markers to determine the efficacy of lipid-lowering drugs.<sup>72</sup>

**Total cholesterol** is a composite measure of LDL-c, HDL-c and other lipid components. Total cholesterol levels are associated with risk of developing CVD in adults and are therefore included in risk calculators.<sup>81 91 92</sup> However, guidelines recommend that total cholesterol should only be viewed in the context of other lipoprotein markers or levels applied in risk calculators when those markers are unavailable.

**Vascular damage**, as inferred by narrowed blood vessels or increased atherosclerotic plaque size, is a marker of atherosclerosis progression. These pathological changes are typically measured using imagining techniques such as intravascular ultrasound (IVUS) and magnetic resonance imaging (MRI).<sup>72</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>93</sup> however, it is unclear whether imaging of vascular damage is limited to research settings or if it is utilised in clinical practice.

**For all effectiveness-related outcomes**, randomised controlled trials (RCTs), 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 RCTs, lower levels of evidence will be considered. The minimum length of follow-up is 3 months for LDL-c, HDL-c, total cholesterol and triglycerides and 12 months for health-related quality of life, markers of vascular damage, MACE, non-cardiovascular mortality, hospitalisation for unstable angina and coronary revascularisation.

#### 5.4.2 Safety Outcomes

#### Critical

All-cause mortality, withdrawal or discontinuation due to adverse events, serious adverse events and treatment-related 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, requires intervention, causes death, or is any other event deemed serious by the study investigators.<sup>94</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 Pharmaceuticals for Human Use (ICH) guidelines<sup>95</sup> to

studies because adverse events are often under-reported and lack detail. Therefore, only adverse events noted as serious by the study investigators will be included.

#### Important

Any adverse events and any treatment-related adverse events are important safety outcomes. Like serious adverse events, they reflect the principle that patients should not be harmed. Any adverse events represent the total number of events that occur in the treated population irrespective of severity.

**For all 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.

### Table 4 PICO Table

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

## Critical outcomes

- 3 point-major adverse cardiovascular events (3P-MACE, defined as non-fatal stroke, non-fatal MI and cardiovascular mortality)<sup>b</sup>
- 4P-MACE (defined as cardiovascular mortality, non-fatal MI, non-fatal ischaemic stroke and unstable angina)<sup>b</sup>
- 5P-MACE (defined as cardiovascular mortality, non-fatal MI, non-fatal ischaemic stroke and unstable angina and coronary revascularisation) <sup>b</sup>
- Non-fatal MI
- Non-fatal ischaemic stroke
- Cardiovascular mortality
- Non-cardiovascular mortality
- Coronary revascularisation
- Hospitalisation for unstable angina
- Health-related quality of life

## Important outcomes

- Change in LDL-c concentration
- Change in HDL-c concentration
- Change in triglyceride concentration
- Change in total cholesterol concentration
- Number of patients achieving LDL-c goals
- Vascular damage <sup>c</sup>

# Safety <sup>d</sup>:

## Critical outcomes

- Serious adverse event
- Serious treatment-related adverse events
- Withdrawal (i.e. treatment cessation) due to adverse events
- All-cause mortality

## Important outcomes

- Any adverse event
- Treatment-related adverse event

## E: Economic outcomes

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

## **Abbreviations**

**ASCVD** = atherosclerotic cardiovascular disease, **HDL-c** = high density lipoprotein cholesterol, **LDL-c** = low-density lipoprotein cholesterol, **MACE** = major adverse cardiac event, **MI** = myocardial infarction, **PCSK9** = proprotein convertase subtilisin/kexin type 9, **RCTs** = randomised controlled trials.

### **Notes**

**a** = Clinical 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 = Non-invasive imaging techniques detecting plaque burden, artery calcification or narrowing.

d = Safety outcomes have no minimum follow-up period.

# 5.5 Amendments to PICO

- The number of patients achieving LDL-c goals was included as an important outcome. 4P-MACE (non-fatal MI, non-fatal stroke, unstable angina and death from cardiovascular causes) and 5P-MACE (non-fatal MI, non-fatal stroke, unstable angina requiring hospitalisation, coronary revascularisation and death from cardiovascular disease) were included as additional critical outcomes.
- Compliance and biochemical markers of injury were removed as outcomes because they do not aid in addressing the policy question and are unlikely to influence an investment/disinvestment or limitation decision. Adverse events were delineated into any adverse event, treatment-related adverse event, serious adverse event and serious treatment-related adverse event.
- Primary hypercholesterolaemia with or without ASCVD has been changed to hypercholesterolaemia with or without ASCVD because approximately 30% of included studies did not explicitly state primary hypercholesterolaemia and studies enrolling patients with primary hypercholesterolaemia often did not disclose how the disorder was confirmed (whether genetic testing was used).
- Comparisons which did not have effectiveness outcomes were excluded from the report.
- Primary and secondary prevention populations were removed from sub-groups because the population stratified patients based on the presence or absence of an ASCVD.

# 6 HTA Key Questions

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

- 1. Is ezetimibe (monotherapy and combination therapies) effective compared to placebo, statins or fenofibrate?
- 2. Is ezetimibe (monotherapy and combination therapies) safe compared to placebo, statins or fenofibrate?
- 3. What are the costs of ezetimibe (monotherapy and combination therapies)?
- 4. What is the budget impact of ezetimibe (monotherapy and combination therapies)?
- 5. Is ezetimibe (monotherapy and combination therapies) cost effective compared to statins or fenofibrate?
- 6. Are there legal, social or ethical issues related to ezetimibe (monotherapy and combination therapies)?
- 7. Are there organisational issues related to ezetimibe (monotherapy and combination therapies)?

## 6.1 Additional Question(s)

Key sub-questions of relevance to the HTA have been informed by the EUnetHTA HTA Core Model<sup>®</sup> (Version 3.0). The sub-questions were used to frame the responses to the key questions for each assessment domain (i.e. effectiveness, safety, cost-effectiveness, ethical, patient/social, legal, organisational).

- 1. *Safety*: Are the harms related to dosage or frequency of ezetimibe monotherapy, ezetimibestatin 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)
- Resource utilisation: How do ezetimibe monotherapy, ezetimibe-statin and ezetimibefenofibrate 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)
- 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 Clinical Effectiveness and Safety

## 7.1 Summary Statement Clinical Effectiveness and Safety

#### Hypercholesterolaemia without ASCVD

The evidence base evaluating patients with hypercholesterolaemia without ASCVD consisted of 30 moderate-to-high quality RCTs. The main methodological concerns were the losses to follow-up, which may lead to an over- or under-estimation of effectiveness outcomes, uncertain applicability of the evidence base to the Swiss context and reliance on surrogate markers to infer clinical effectiveness.

Follow-up times of 3 months and 12 or 15 months (reflecting the outcome) were selected to reflect shortand long-term timepoints, respectively. There were no studies evaluating ezetimibe to fenofibrate and ezetimibe plus fenofibrate to fenofibrate. There were also no studies evaluating ezetimibe monotherapy beyond 3 months. Therefore, analyses involving ezetimibe monotherapy were limited to surrogate markers.

#### Ezetimibe vs placebo

By 3 months, there were statistical differences in favour of ezetimibe for absolute and percentage changes in LDL-c, HDL-c and total cholesterol and number of patients achieving LDL-c goals. LDL-c and total cholesterol results were subject to moderate-to-considerable heterogeneity. There were limited statistical differences in absolute and percentage change in triglycerides and no differences in mortality or adverse events (serious, treatment-related, any, or withdrawal due to). Withdrawal and treatment-related adverse events were adequately powered. *Table 50* shows the grading of recommendations, assessment, development and evaluations (GRADE) summary of findings table for ezetimibe vs placebo.

#### Ezetimibe vs statins

By 3 months, there were statistical differences in favour of statins for absolute and percentage changes in LDL-c, HDL-c and total cholesterol and number of patients achieving LDL-c goals. LDL-c and total cholesterol results were subject to low-to-considerable heterogeneity. No study reported statistical differences in the absolute change in triglycerides and the statistical significance was not reported for the percentage change in triglycerides, so it is unclear whether the groups differed. There were no statistical differences in mortality or adverse events (serious, treatment-related, any, or withdrawal due to). Serious- and treatment-related adverse events were adequately powered. *Table 51* shows the GRADE summary of findings table for ezetimibe vs statins.

#### Ezetimibe plus statins vs statins

By 3 months, there were statistical differences in favour of ezetimibe plus statins for absolute and percentage changes in LDL-c, HDL-c and total cholesterol and number of patients achieving LDL-c goals. The statistical difference for LDL-c and total cholesterol persisted at longer timepoints. There were no statistical differences in markers of vascular damage or incidence of 3P-MACE or coronary revascularisation in one study. There was a significantly higher incidence of treatment-related adverse events in the ezetimibe plus statin group compared to the statin group. There were no statistical differences for the remaining safety outcomes. Safety outcomes were adequately powered. *Table 52* shows the GRADE summary of findings table for ezetimibe plus statins vs statins.

#### Hypercholesterolaemia with ASCVD

The evidence base evaluating patients with hypercholesterolaemia and ASCVD consisted of 42 moderate-to-high quality RCTs and 3 secondary analyses. The main methodological concerns were the losses to follow-up and uncertain applicability. Additionally, the results were largely driven by the IMPROVE-IT trial<sup>52</sup> and consequently, were more reflective of patients with ACS. Follow-up times of 3 and 12 months were selected to reflect short- and long-term timepoints, respectively. There were no studies comparing ezetimibe monotherapy to placebo, statins or fenofibrate and ezetimibe plus fenofibrate to fenofibrate.

#### Ezetimibe plus statins vs statins

By 3 months, there were statistical differences in favour of ezetimibe plus statins with respect to the absolute and percentage changes in LDL-c and total cholesterol and number of patients achieving LDL-c goals. There was no difference between ezetimibe plus statins and statins in HDL-c. At 12 months, the statistical effect persisted for the absolute change in LDL-c and total cholesterol but not for the percentage change . There was no difference between ezetimibe plus statistical differences in HDL-c. There were few statistical differences in triglycerides and no statistical differences in markers of vascular damage at any timepoint.

Two studies reported that the incidence of 3P-MACE was similar between the ezetimibe plus statin and statin groups at 12 and 24 months, noting these studies were not adequately powered to detect group differences in 3P-MACE. In contrast, the IMPROVE-IT trial<sup>52</sup> showed that ezetimibe plus simvastatin significantly reduced the incidence of 3P-MACE, non-fatal MI and ischaemic stroke compared to simvastatin at seven years. However, there were no statistical differences in cardiovascular death, coronary revascularisation and unstable angina. There were also no statistical differences in mortality or adverse events (serious, treatment-related, any, or withdrawal due to). Safety outcomes were

adequately powered. *Table 53* shows the GRADE summary of findings table for ezetimibe plus statins vs statins.

### Hyperlipidaemia without ASCVD

The evidence base evaluating patients with hyperlipidaemia without ASCVD consisted of five moderateto-high quality RCTs. The main methodological concerns were the losses to follow-up, uncertain applicability and reliance on surrogate markers. Comparisons involving ezetimibe monotherapy or in combination therapies were limited to one or two studies, increasing the uncertainty of the results. There were also no studies evaluating outcomes beyond 3 months for comparisons involving ezetimibe monotherapy and ezetimibe plus statins, and no studies evaluating MACE or markers of vascular damage.

#### Ezetimibe vs placebo

Two studies provided evidence comparing ezetimibe to placebo. In one study, there were statistical differences in favour of ezetimibe with respect to the absolute change in LDL-c and total cholesterol but not in HDL-c or triglycerides. The statistical difference was not reported in the other study, so it was unclear whether the groups differed. **Table 54** shows the GRADE summary of findings table for ezetimibe vs placebo.

#### Ezetimibe vs statins

In one study, there were statistical differences in favour of statins with respect to the percentage change in LDL-c, total cholesterol and triglycerides and number of patients achieving LDL-c goals. There was no difference in HDL-c. *Table 55* shows the GRADE summary of findings table for ezetimibe vs statins.

## Ezetimibe plus statins vs statins

In one study, the percentage change in LDL-c, HDL-c, total cholesterol and triglycerides was slightly greater in the ezetimibe plus statin group compared to the statin group. However, the statistical difference was not reported, so it was unclear whether the groups differed. *Table 56* shows the GRADE summary of findings table for ezetimibe plus statins vs statins.

#### Ezetimibe vs fenofibrate

In two studies, there were no statistical differences between ezetimibe and fenofibrate with respect to the percentage change in LDL-c and total cholesterol. There were statistical differences in HDL-c in favour of fenofibrate and statistical differences in the number of patients achieving LDL-c goals in favour of ezetimibe. *Table 57* shows the GRADE summary of findings table for ezetimibe vs fenofibrate.

#### Ezetimibe plus fenofibrate vs fenofibrate

By 3 months, there were statistical differences in favour of ezetimibe plus fenofibrate with respect to the percentage change in LDL-c and total cholesterol and number of patients achieving LDL-c goals. There were no differences in HDL-c, and the statistical difference for triglycerides was inconsistent. In 1 study the statistical effect persisted at 12 months for percentage change in LDL-c, total cholesterol and triglycerides. *Table 58* shows the GRADE summary of findings table for ezetimibe plus fenofibrate vs fenofibrate.

In general, there were no statistical differences between ezetimibe (monotherapy or combination therapies) and the respective comparators for adverse events (serious, treatment-related, any, or withdrawal due to). Most safety outcomes were adequately powered.

## 7.2 Methodology

## 7.2.1 Literature Search

## Databases and search strategy

A systematic literature search for the 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. Websites for HTA agencies were searched to identify relevant HTA reports that included cost-effectiveness analyses (CEA). An updated search was performed (31 December 2019–4 May 2020) to identify additional studies published between completion of the scoping report and commencement of the HTA.

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 *Table 83*. Search filters were applied during the initial search to limit the results to humans and to exclude conference abstracts. All languages were screened by title and abstract, although the study selection was limited to English, French, German or Italian languages. Relevant studies in additional languages were identified to estimate the likelihood of language bias in the search results.

## Other sources

Ongoing or unpublished clinical trials were searched in five clinical trial databases (ClinicalTrals.gov, Cochrane Central Register of Controlled Trials, EU Clinical Trials Registry, World Health Organization International Clinical Trials Registry Platform, Current Controlled Trials MetaRegister and Australian New Zealand Clinical Trials Registry). For the list of ongoing clinical trials refer to **Table 92**.

### Study Selection

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).<sup>96</sup> Differences in study selections were settled via consensus at each stage of the selection process. During the full-text screen, studies with predominantly Asian, African Central and South American trial populations were excluded since they do not reflect the Swiss context and they have different cardiovascular risk profiles compared to Western populations.<sup>97-99</sup> Studies were considered eligible if they met the PICO criteria, were RCTs, and had a minimum follow-up period of at least 3 months for effectiveness studies. 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 also included.

## 7.2.2 Data Analyses

#### Assessment of quality of evidence

Owing to the large volume of RCTs, one researcher conducted the quality appraisal, with a second independent researcher checking a random sample (40 studies). Any differences were settled via consensus. RCTs were appraised for risk of bias using the Cochrane risk-of-bias tool for randomised trials version 2.0. The quality of the evidence per outcome was assessed using the GRADE approach (Grading of Recommendations, Assessment, Development and Evaluations). One researcher appraised the outcomes using GRADE, which was checked by an independent researcher.

#### Meta-Analysis of Dichotomous Outcomes

For dichotomous outcomes with at least two RCTs, a meta-analysis was performed using Review Manager Version 5.3.<sup>100</sup> Dichotomous outcomes were analysed using the Mantel-Haenszel statistical method with random-effects models. The results of the analyses were reported as risk ratios (RR) with 95% confidence intervals (CI). Random-effects models were used to account for variations in different doses and classes of statins and other population-based factors, and differences in the conduct of the interventions across the included studies. The interpretation of RRs is in accordance with the Cochrane Handbook (version 6.0).<sup>100</sup> A RR of one indicated that the estimated effects were the same for the intervention (ezetimibe monotherapy or combination therapy) and comparator (statin or fenofibrate). A RR greater than one indicated an increased probability of the event occurring in the intervention group relative to the comparator group. A RR less than one indicated a reduced probability of the event occurring in the intervention group relative to the comparator group.

For outcomes with fewer than two RCTs, or where it was inappropriate to pool trials, the results were described narratively.

#### Meta-Analysis of Continuous Outcomes

The meta-analyses performed in this report were mixed-effect meta-regression models, which incorporated time of follow-up as a covariate factor, or moderator in technical terminology. This type of model considers not only the effectiveness differences between the intervention (e.g. ezetimibe plus statin) and the comparator (e.g. statin monotherapy) via random-effect models but also compares the differences across timepoints via a fixed-effect model. As the result of using the mixed-effect models, the heterogeneity estimated in those models was assumed to be at the same level across different follow-up timepoints (hence a single heterogeneity value for each analysis). This is considered appropriate as the data from the trial were produced by the same patients longitudinally; hence this model was better than running individual meta-analyses across different timepoints and pooling them together afterwards.<sup>101</sup> On the other hand, the limited number of studies available at each timepoint prevented performing a more complex longitudinal meta-analyses model to account for the time trend. Therefore, different timepoints were treated as nominal factors where the different gaps between timepoints were not accounted for.

Moreover, baseline values (i.e. timepoint zero) were also incorporated into these meta-analyses. The baseline results were embedded within the outcomes for the percentage change in surrogate markers; hence the values were not explicitly shown in the forest plots. However, the scores that are measured at baseline were included in the meta-analyses as a separate sub-group as well as presented in their forest plots. This approach had the benefit of incorporating heterogeneities at baseline measurements, as well as demonstrating the consistency at baseline in forest plots.

The results of the meta-analyses with moderators were presented using forest plots where the data at different timepoints were grouped and ranked by ascending order. The estimates of mean differences at each timepoint were illustrated by grey diamonds together with a p value for significance levels. The omnibus heterogeneity estimates for the overall analysis were computed by the  $\tau^2$  value, the l<sup>2</sup> value in percentages and a p value for the testing of significant heterogeneity. The impact of the moderator was also computed using a Chi<sup>2</sup> test with a p value. Raw data at study level together with their weights in the meta-analyses were also plotted in forest plots.

The triglyceride results were not meta-analysed because the distribution of data differed between the studies, as inferred by the use of either parametric or non-parametric tests. These results were described narratively.

## Sub-Group Analysis

Outcomes with two or more studies underwent further analysis based on the following sub-groups: statin type, patient age (children, adolescents and older adults) and risk group (low, moderate, high and patients with diabetes). The sub-groups were analysed using the meta-analyses as previously described. At least two studies per sub-group were required to perform meta-analyses.

For sub-groups with only one study, the mean and standard deviation (SD) were converted to mean difference and 95% CI for consistency. To determine whether the intervention and comparator group statistically differed in this sub-group, the statistics provided in the respective study were used. Sub-groups analysed using this method are not comparable to sub-groups analysed using the meta-analysis.

The mean difference could not be calculated for triglycerides because it was unclear whether the scores were normally distributed.

Only studies that used the same type of statin in the intervention and comparator arm (e.g. both arms used simvastatin or atorvastatin) were analysed. Studies that compared different types of statins (e.g. simvastatin in the intervention group and rosuvastatin in the comparator group) were excluded from this sub-group analysis to minimise confounding effects.

### Heterogeneity

Results of the meta-analysis were presented using forest plots for a visual representation of variability in reported effect sizes across studies. Heterogeneity and inconsistency were assessed statistically using the Chi<sup>2</sup> test (p<0.10 representing significant heterogeneity) and the l<sup>2</sup> statistic for the meta-analysis of dichotomous outcomes, and Tau<sup>2</sup> and l<sup>2</sup> for continuous outcomes. The thresholds for low, moderate, substantial and considerable heterogeneity followed those proposed in the Cochrane handbook (l<sup>2</sup> 0–40% might not be important; 30–60% moderate; 50–90% substantial; 75–100% considerable heterogeneity).<sup>102</sup> The importance of the l<sup>2</sup> result was dependent on the size and direction of the measured effect, and the strength of evidence for heterogeneity (i.e. Chi<sup>2</sup> and Tau<sup>2</sup>).

## Assessment of Publication Bias

The risk of publication bias was assessed for analyses including at least 10 studies by visual inspection of the funnel plot.<sup>103</sup> In addition, clinical trial registries (e.g. clinicaltrials.gov) were searched to identify unpublished studies as a means of narratively describing the risk of publication bias.

## **Missing Values**

Missing standard deviations were obtained from available standard errors (SE) and CI using the following formula:

SD =  $\sqrt{N}$  \* (upper limit – lower limit) / 3.92\* (\*95% CI)

For studies only reporting outcomes graphically, Webplot digitizer was used to generate numerical values.

Trials reporting both absolute and percentage change from baseline often failed to report the standard deviation for one of the measures (i.e. SD reported for absolute but not percentage change). For an outcome with missing standard deviation, the studies were omitted from the analyses but cited in the text to ensure transparency in reporting.

#### Efficacy and Effectiveness

The delineation between efficacy and effectiveness trials was not considered for this HTA.

Statistical interpretation of studies using an active comparator differs from that of placebo trials. A lack of statistically significant difference between treatment groups could indicate that two interventions are equally effective, equally ineffective, or that there is no difference between the two groups.

For treatment goals, patients achieving LDL-c <130mg/dL, <70mg/dL and NCEP-ATP II or III goals (National Cholesterol Education Program-adult treatment panel II or III [NCEP-ATP]) are reported. Other goals such as a reduction in LDL-c by 15% are not reported as the precise value cannot be determined and hence it is unclear whether treatment goals have been achieved.

## Safety

For safety-related outcomes, the number of patients experiencing an event was reported, unless otherwise stated.

When defining severe adverse events, the definition within the study was used. (Retrospectively applying ICH guidelines, for example, is likely inappropriate given the general under-reporting of adverse events and frequent lack of detail.<sup>94</sup>) The lack of standardisation of adverse events may limit the conclusions of the safety sections as the true effect may be under- or over-estimated. Post-hoc power calculation was used to determine what level of power each outcome had.

Both placebo groups were pooled when reporting adverse events from Koren (2012).<sup>104</sup>

## Study reporting

Multiple studies used different doses (e.g. 10mg, 20mg, 40mg or 80mg) or types of statins in the intervention (ezetimibe plus statin) and comparator arms (statin monotherapy). To minimise confounding effects the following framework was used when selecting which arm to use for the analysis.

- The lowest statin dose used by both intervention and comparator arms was preferentially included (e.g. 10mg simvastatin plus ezetimibe vs 10mg simvastatin was reported over 40mg simvastatin plus ezetimibe vs 40mg simvastatin).
- For comparator arms that used different statin doses to the intervention arm (e.g. 10mg atorvastatin plus ezetimibe vs 20mg or 40mg atorvastatin), the closest doses were selected.
- In studies that compared different doses and types of statins, statins of similar intensity, as inferred by the percentage reduction in LDL-c in NICE (2014), were reported.<sup>105</sup> However, studies that used statins of differing intensity were omitted from sub-group analyses to minimise the effects of confounding.

There was an overlap of reporting in Bays (2008)<sup>106</sup> and Goldberg (2004).<sup>107</sup> In this instance, Goldberg (2004)<sup>107</sup> was used because it had larger patient numbers and had not re-randomised patients.

## 7.3 Results Clinical Effectiveness and Safety

## 7.3.1 PRISMA Flow Diagram

Results from the systematic literature searches are presented in *Figure 4*. Database searches and pearling of relevant studies yielded a total of 15,553 results. (Results from each database are listed in *Section 15.1, Appendix A*.) After removal of duplicates 10,660 citations were reviewed by title and abstract and, of these, 269 were reviewed by full text. A total of 80 publications evaluating ezetimibe were identified, comprising patients with hypercholesterolaemia without ASCVD (k=30), hypercholesterolaemia with ASCVD (k=45), hyperlipidaemia without ASCVD (k=5) and hyperlipidaemia with ASCVD (k=0). Of these publications, 77 were RCTs and 3 were secondary analyses of the IMPROVE-IT trial.<sup>52</sup>

A comprehensive list of all excluded trials is not provided, however notable excluded trials are listed in *Section 15.2, Appendix B.* 

English, French, German and Italian articles were eligible for inclusion in this report. Articles written in other languages were not included in the HTA but were screened by title and abstract.

PRISMA diagrams were not provided for ethical, legal, social and organisational issues as the searches were conducted in both a systematic and non-systematic manner.



## Figure 4 PRISMA flow chart for study inclusion

### <u>Notes</u>

When discussing the number of trials for each intervention, only the number of unique trials were discussed not the total number of publications.

Most studies report both safety and effectiveness results.

## 7.3.2 Study Characteristics

Overall, 77 RCTs were included, of which 71 were original studies and 6 were extensions trials. Three secondary analyses were also included. Given that the extension studies and the secondary analyses were conducted in the same location and contained all, or part, of the populations of the original trials, their characteristics (except for outcomes) will not be discussed below to prevent double-counting of the evidence base. For further information regarding the characteristics of all identified studies, including the extension studies, refer to **Section 15.3**, **Appendix C**.

#### Hypercholesterolaemia without ASCVD

Overall, 30 studies were included in the assessment of safety and clinical effectiveness (*Table 97*). Of the included studies, 25 were original and 5 were extension studies. Of the original trials, 22 were parallel design and 3 were cross-over trials. The cross-over trials were only included in the assessment of safety.

The included RCTs consisted of single- (k=7) and multi-centre trials (k=17) conducted in Europe (k =15), North America (k=14) and Australia (k=3). (One trial did not report number of centres or location.<sup>108</sup>) In addition, several larger multicentre trials included patients from South America (k=2) and South Africa (k=3), however it was unclear how many patients were included from those locations (noting for the applicability of trials, see *Section 7.3.4*). No study was fully conducted in Switzerland, although one international multicentre trial had centres in Switzerland with research sites in Bellinzona, Geneva, Lausanne, Münsterlingen, St. Gallen and Zurich.<sup>109</sup> Eleven studies were fully or partially conducted in central/western European countries including Austria, Belgium, Croatia, France, Germany, Poland and The Netherlands.

To be eligible for the trials, patients required a diagnosis of hypercholesterolaemia, resting LDL-c concentrations of 130–250mg/dL and resting triglyceride concentrations below 350mg/dL. Three studies recruited children (6–10 years), adolescents (10–17 years) or adults (30–75 years) with FH. The remaining studies did not specify the type of hypercholesterolaemia. The LDL-c concentration required for entry into the study were generally higher for patients with FH. Common exclusion criteria included the presence of cancer, cardiovascular diseases (e.g. heart failure, peripheral artery disease), endocrine and metabolic diseases (e.g. diabetes), renal or hepatobiliary dysfunction, or coagulation disorders; use of corticosteroids and/or immunosuppressants and those pregnant or breastfeeding. Nine studies excluded patients who had used lipid-lowering therapies in the previous 1 to 2 months.

The median sample size was 153 patients (range 18–1,528). Patients were aged 50–60 years, overweight (BMI 25–30kg/m<sup>2</sup>), Caucasian (50–93%) and had few comorbidities such as diabetes or hypertension. Patients with FH generally had higher LDL-c, total cholesterol and triglyceride concentrations than patients with non-specified hypercholesterolaemia. The population contained a mix

of individuals who had used or were naive to statins or other lipid-lowering therapies. Only seven studies quantified the number of patients who had used statins, ranging from 28% to 80% of enrolled patients.

Patients generally underwent a washout period (cessation of previous lipid-lowering medication) of 4 to 12 weeks followed by a dietary and single-blind placebo/statin lead-in period during which lipid levels were stabilised. Ezetimibe was administered as a monotherapy in 18 studies or in combination with a statin in 17 studies. Eight studies evaluated both monotherapy and combination therapies. The dose of ezetimibe was fixed (10mg) across all studies, whereas the statin dose varied from 10mg to 80mg. Ezetimibe plus simvastatin (k=12) was the most frequently studied combination. Other ezetimibe-statin combinations included atorvastatin, fluvastatin and pravastatin.

The comparator was either placebo or statin monotherapy. The dose of statin in the intervention and comparator groups was generally the same. In several studies, statin dose was increased on an asneeds or a predetermined basis (i.e. every 2 weeks) throughout the course of the trial. However, it was not reported how many patients increased their statin dose, and studies often pooled a range of statin doses when evaluating the effectiveness and safety of the intervention.

The median follow-up time was 3 months for safety outcomes and 12 months for clinical effectiveness outcomes. Total cholesterol, LDL-c and HDL-c levels (important outcomes) were the most frequently studied clinical effectiveness outcomes (k=25) with few studies evaluating MACE and markers of vascular damage (k=1). No studies evaluated quality of life. Adverse events (k=23) and withdrawals due to adverse events (k=27) were the most frequently reported safety outcomes. For further information, refer to **Table 97**.

#### Hypercholesterolaemia with ASCVD

Overall, 45 studies were included in the assessment of safety and clinical effectiveness (*Table 98*). Of the included studies, 42 were original trials and 3 were secondary analyses of the IMPROVE-IT trial. Of the original trials, all 42 were parallel design trials.

The included RCTs consisted of single- (k=8) and multi-centre trials (k=32) conducted in Europe (k=35), North America (k=17) and Australia (k=3). (Two studies did not report the number of centres). In addition, several larger multicentre trials included patients from South America (k=8), Asia (k=3) and South Africa (k=2), however it was unclear how many patients were included from those locations (noting for the applicability of trials, see *Section 7.3.4*). No study was fully conducted in Switzerland, although three international multicentre trials had centres in Switzerland.<sup>52 110 111</sup> The exact location in two trials was not reported. One trial had participating centres in Geneva, Lugano, Kreuzlingen, Bellinzona, La Chaux-de-Fonds, Bern, Biel, Mendrisio, Bruderholz, St. Gallen, Baar, Winterthur, Sion and Zurich. Seventeen

studies were fully or partially conducted in central/western European countries including Austria, Belgium, Croatia, France, Germany, Poland and The Netherlands.

The inclusion criteria varied, reflecting the diversity of ASCVD. Commonly studied indications were hypercholesterolaemia with established or high risk of developing CHD (k=20), coronary artery disease (k=3), ASCVD (k=3), ACS (k=2) and MI (k=2). Several studies did not specify whether patients had hypercholesterolaemia, but their inclusion criteria of minimum LDL-c and maximum triglyceride levels were similar to definitions of hypercholesterolaemia in other studies, suggesting these patients likely had hypercholesterolaemia. Common exclusion criteria included the presence of cancer, cardiovascular diseases (e.g. heart failure, peripheral artery disease), endocrine and metabolic diseases (e.g. diabetes), renal or hepatobiliary dysfunction, or coagulation disorders; use of corticosteroids or immunosuppressants and those pregnant or breastfeeding. Nine studies also excluded patients if they had used a lipid-lowering agent 6 weeks to 12 months prior to randomisation.

Median sample size was 315 patients (range 30–18,144). Patients were aged 60–70 years, overweight (BMI 25–30kg/m<sup>2</sup>) and Caucasian (50–93%). There were slightly more male patients and 30–60% of patients had comorbidities (diabetes or hypertension). CHD was the most commonly reported ASCVD. Baseline LDL-c and total cholesterol varied across the included populations, likely reflecting the type of ASCVD. The population contained a mix of individuals who had used or were naive to statins or lipid-lowering therapies. In 12 studies, 31–100% of patients had previously used lipid-lowering agents (typically statins). The remaining studies did not report previous lipid-lowering agent use.

Before initiating treatment, patients underwent a 4- to 6-week washout period, followed by a dietary and single-blind placebo/statin lead-in period during which lipid levels were stabilised. Ezetimibe was administered in combination with statins in all studies. The dose of ezetimibe was fixed (10mg) across all studies, whereas statin dose varied (10–80mg). Ezetimibe plus simvastatin (k=22) was the most frequently studied combination. Other ezetimibe-statin combinations included atorvastatin, fluvastatin and rosuvastatin (k=1–13 studies).

The comparator was statin monotherapy, which included atorvastatin, fluvastatin, simvastatin and rosuvastatin. Statin dose varied from 10mg to 80mg and was generally fixed throughout the course of the trial. (Of those studies that allowed up-titration, it was not reported how many patients increased their dose and studies would often pool statin doses when evaluating effectiveness and safety outcomes.) Ten studies evaluated different statins in the comparator and intervention arms. Two studies did not specify the type of statin, rather the patients doubled their existing doses of statin.

The median follow-up time was 2 months for safety outcomes and 6 months for clinical effectiveness outcomes. Total cholesterol, LDL-c and HDL-c levels (important outcomes) were the most frequently

studied clinical effectiveness outcomes (k=17) with few studies evaluating MACE (k=3) and markers of vascular damage (k=2). No study evaluated quality of life (k=0). Adverse events (k=31) and withdrawals due to adverse events (k=38) were the most frequently reported safety outcomes. For further information refer to **Table 98**.

#### Hyperlipidaemia without ASCVD

Overall, five studies were included in the assessment of safety and clinical effectiveness (*Table 99*). Of the included studies, four were original and one was an extension study. Of the original trials, there were three parallel-design studies and one cross-over RCT. The RCT consisted of single- (k=1) and multi-centre trials (k=3) conducted in Europe (k=2) and North America (k=1). One study did not specify the location. No study was fully or partially conducted in Switzerland. Two studies were fully or partially conducted in central/western European countries including Belgium, France and Germany.

To be eligible, patients generally required a diagnosis of hyperlipidaemia and resting LDL-c concentrations above 130–160mg/dL and triglyceride concentrations above 150–200mg/dL. One study included only patients who experienced muscle-related side effects following statin treatment (statin intolerance). Patients were excluded if they had cancer, cardiovascular diseases (e.g. heart failure, peripheral artery disease), endocrine and metabolic diseases (e.g. diabetes), renal or hepatobiliary dysfunction or coagulation disorders.

Median sample size was 199 patients (range 25–625). Patients were aged 40–60 years, were overweight (BMI 25–30kg/m<sup>2</sup>), Caucasian and had few comorbidities. Both sexes were equally represented. Specific hyperlipidaemias included type IIb hyperlipidaemia (elevated LDL-c and very-low-density lipoprotein levels) and mixed hyperlipidaemia (elevated triglycerides and cholesterol levels). Two studies did not specify hyperlipidaemia type, however, patient baseline triglycerides and total cholesterol were consistent with the AGLA definition of mixed hyperlipidaemia (triglycerides >177mg/dL [2mmol/L] and total cholesterol >232mg/dL [6mmol]). Patients had high LDL-c, total cholesterol and triglyceride levels and low HDL-c levels. One study reported that 66% of patients had previously used lipid-lowering agents and another study reported that 100% of patients had used statins. The remaining studies did not report use of lipid-lowering agents.

Patients underwent a 4-week washout and a dietary lead-in period before initiating treatment. Ezetimibe was administered as a monotherapy (four studies) or in combination with a statin or fenofibrate (three studies). Three studies administered both monotherapy and combination therapies. The dose of ezetimibe was fixed (10mg) across all studies, as was the dose of statin (80mg). Fenofibrate doses ranged from 145mg to 160mg. The comparator was either placebo, statin monotherapy or fenofibrate monotherapy, with the doses of statins and fenofibrate matching those in combination therapy.

Four studies followed patients for 3 months and one study followed for 12 months. LDL-c, HDL-c, total cholesterol and triglyceride levels were the only effectiveness outcomes studied (k=5). No study evaluated MACE, markers of vascular damage or quality of life outcomes. Adverse events (k=4) and withdrawals due to adverse events (k=4) were the most frequently reported safety outcomes. For further information, refer to **Table 99**.

## 7.3.3 Risk of Bias

The risk-of-bias graphs and the risk-of-bias summaries (per study) for safety and clinical effectiveness outcomes are reported in *Figure 5* to *Figure 16*. Risk of bias was assessed on a per outcome basis (clinical effectiveness and safety).

There were several bias issues common to all populations. To minimise repetition, the following discussion is reflective of all populations, with subsequent sections dedicated to population-specific biases. For an additional summary of population-specific biases refer to the GRADE summary of findings tables (*Table 50* to *Table 58*).

## All populations

Overall, the included studies were largely subject to inadequate reporting, rather than poor methodology per se. For example, most studies did not provide adequate descriptions of randomisation, concealment and blinding procedures. When reported, descriptions of randomisation techniques were limited to 'computer-generated randomisation schedules' or 'permuted block designs'. Several studies also reported stratifying randomisation based on patient demographics such as LDL-c concentration, age or sex. Few studies reported concealment strategies, rather they stated that patients and study personnel were unaware of treatment allocation. Similarly, the description of blinding was limited, and it was unclear whether medications differed in their appearance.

Most trials were double-blind with relatively few single-blind and open-label trials. The lack of blinding in single-blind and open-label trials was not a concern for effectiveness outcomes, owing to their objective nature. However, for outcomes involving judgement, such as the severity of adverse events and/or their relationship to treatment, if these were not defined a priori, awareness of the intervention may have introduced bias.

Co-interventions were used throughout the studies and included open-label statin, diets and exercise programs. Co-interventions were generally available to all treatment groups, however, patient adherence to the diet and exercise programs was not reported and their impact on lipid and triglyceride levels was not assessed. This may confound treatment effects because diet and exercise programs influence lipid and triglyceride levels.<sup>112-114</sup>

Losses to follow-up were a key bias concern. Losses to follow-up ranged from 10-60% of randomised patients and were related to adverse events, withdrawn consent, lack of efficacy or missing data. Common methods to correct for losses to follow-up included multiple imputation or last-observation carried forward. No studies performed sensitivity analyses to evaluate the impact of missing data, and it was unclear how data was collected and analysed from individuals who violated the protocol. Losses may have enriched the patient population, confounding the treatment effect.

For clinical effectiveness outcomes, the reporting and analysis of outcomes was generally appropriate, with limited evidence to suggest publication bias. Most effectiveness outcomes used intent-to-treat, with few studies using per protocol or not defining the analysis method. For safety-related outcomes, adverse events were infrequently defined and were not listed on trial protocols. Safety analyses were generally per protocol and were at greater risk of bias owing to the large loss to follow-up and general under-reporting of adverse events.

Lastly, most trials received sponsorship from Merck/Schering-Plough Pharmaceuticals. Eleven studies stated the sponsor's role in the study, which ranged from no input to participating in the design, management, analysis and interpretation of the data. The remaining studies did not report sponsor involvement in the study.

#### Hypercholesterolaemia without ASCVD

There was incomplete reporting of results in extension studies and in trials testing multiple statin doses. For example, the measure of variance was reported for either the absolute change or percentage change in lipids, but rarely both measures. Further, statin doses were pooled during the analysis. The number of patients receiving each dose was not reported and it was unclear whether the pooled effect was more representative of specific doses. Thus, the effect of ezetimibe may have been over- or underestimated.

The extension study partially re-randomised patients. Individuals assigned to the ezetimibe and placebo arms in the base study were randomly reassigned to statin monotherapy or combination therapy in the extension study. Patients in the statin monotherapy and combination therapy groups in the base study continued the same treatment. As there was no washout between the base and the extension study, it was unclear whether there were carry-over effects from previous treatments. Only a proportion of patients from the base study participated in the extension study. Reasons for discontinuing in the extension trial were infrequently reported so it was unclear if the extension study had an enriched patient population.

#### Hypercholesterolaemia with ASCVD

The type and dose of statin used in the intervention group often differed to the statin used in the comparator group. This may confound treatment effects because higher potency statins (e.g. atorvastatin and rosuvastatin) reduce LDL-c more than do moderate or low intensity statins (simvastatin, fluvastatin or pravastatin).<sup>105</sup>

The investigators of the IMPROVE-IT trial were unblinded to the treatment allocation during the study period to investigate the incidence of cancer.<sup>115</sup> The impact of the unblinding on other outcomes could not be determined.

Risk-of-bias assessment was not performed for secondary analyses of the IMPROVE-IT trial as most bias concerns reflected those in the original study. The main bias concern of the secondary analyses related to baseline imbalances. The analyses stratified the patients based on diabetes status, risk category and age post hoc. This invalidated the randomisation process because it resulted in baseline imbalances between treatment groups. For example, there were differences in age, sex, BMI, comorbidities, previous medication, and LDL-c and triglyceride concentrations in Giugliano (2018).<sup>116</sup> The baseline imbalances potentially confound the treatment effects.

#### Hyperlipidaemia without ASCVD

The RCTs evaluating hyperlipidaemia without ASCVD provided slightly more methodological information than did trials from other populations. For example, the randomisation strategy was usually reported, the analysis approach was appropriate and adverse events were pre-defined in several studies. However, these studies reported substantial losses to follow-up, an effect particularly evident in the extension study. Again, it was unreported how losses to follow-up and missing data were addressed.

The extension trial had additional bias concerns. For example, patients assigned to the ezetimibe and placebo groups in the base study were assigned to the ezetimibe plus fenofibrate and fenofibrate groups, respectively. Patients in the fenofibrate plus ezetimibe and fenofibrate groups continued on their base study treatment. It was unclear whether the lack of re-randomisation introduced additional biases because the statistical difference for patient characteristics was not reported. There was also an imbalance in the number of patients withdrawing due to lack of efficacy (50.8% in the fenofibrate group and 24.1% in the fenofibrate plus ezetimibe group). The difference between groups likely enriched the patient population and confounded treatment effects.

Lastly, there was one cross-over trial. This had no washout period and therefore it was unclear whether there were carry-over effects.



# Figure 5 Hypercholesterolaemia without ASCVD: risk-of-bias graph for RCTs assessing clinical effectiveness outcomes (25 studies)



# Figure 6 Hypercholesterolaemia without ASCVD: risk-of-bias graph for RCTs assessing safety outcomes (29 studies)



Figure 7 Hypercholesterolaemia without

ASCVD: risk-of-bias summary for clinical effectiveness outcomes in the RCTs

Notes

+ = low risk, - = high risk, ? = unclear risk.



Figure 8 Hypercholesterolaemia without

## ASCVD: risk-of-bias summary for

## safety outcomes in the RCTs

## Notes

+ = low risk, - = high risk, ? = unclear risk.



# Figure 9 Hypercholesterolaemia with ASCVD: risk-of-bias graph for RCTs assessing clinical effectiveness outcomes (17 studies)



# Figure 10 Hypercholesterolaemia with ASCD: risk-of bias-graph for RCTs assessing safety outcomes (40 studies)



Figure 11 Hypercholesterolaemia with

ASCVD: risk-of-bias summary for clinical effectiveness outcomes in the RCTs

Notes

+ = low risk, - = high risk, ? = unclear risk.



Figure 12 Hypercholesterolaemia with ASCVD: risk-of-bias summary for safety outcomes in the

RCTs

## Notes

+ = low risk, - = high risk, ? = unclear risk.



Figure 13 Hyperlipidaemia without ASCVD: risk-of-bias graph for RCTs assessing clinical effectiveness outcomes (5 studies)



Figure 14 Hyperlipidaemia without ASCVD: risk-of-bias graph for RCTs assessing safety outcomes (5 studies)



Figure 15 Hyperlipidaemia with ASCVD: risk-of-bias summary for clinical effectiveness

outcomes in the RCTs

### **Notes**

+ = low risk, - = high risk, ? = unclear risk.



Figure 16 Hyperlipidaemia without ASCVD: risk-of-bias summary for safety outcomes in the

## RCTs

<u>Notes</u> + = low risk, - = high risk, ? = unclear risk.

# 7.3.4 Applicability of Evidence Base to Switzerland

Applicability refers to the generalisability of the clinical trials to the Swiss context. It involves comparing patient demographics and clinical characteristics in the RCTs to what generally occurs in Swiss practice. An overview of the demographic and procedural characteristics associated with ezetimibe in Switzerland is provided in *Table 5* to *Table 7*.

## Hypercholesterolaemia without ASCVD

There was limited literature regarding the demographics of Swiss patients with hypercholesterolaemia. In the absence of literature addressing patients with hypercholesterolaemia, literature pertaining to Swiss patients with dyslipidaemia and patients with high cholesterol were presented. The generalisability of these patient populations to hypercholesterolaemia was uncertain owing to differences in disease severity.

# Table 5 Swiss demographic information and procedural characteristics associated with hypercholesterolaemia without ASCVD

Parameter	Characteristics
Demographics	Hypercholesterolaemia, mixed/combined hyperlipidaemia or homozygous sitosterolemia (phytosterolemia) <sup>47 49</sup>
	Mostly Caucasian <sup>117 118</sup>
	Older adults (aged 65 and above) <sup>30-32 34</sup>
	Comorbidities (dyslipidaemia 30–75%) <sup>119</sup>
	Normal to overweight (dyslipidaemia) <sup>32 119</sup>
	Similar proportion of males (familial hypercholesterolaemia <sup>34</sup> ) to slightly higher proportion of males (high cholesterol <sup>30</sup> )
	Most dyslipidaemia patients were low to moderate risk (PROCAM), and 40% had not achieved LDL-c goals <sup>36</sup>
Intervention	Ezetimibe monotherapy and ezetimibe in fixed or free combination with statins or fenofibrate (see <i>Table 2</i> )
Comparator	Any statin or fenofibrate licenced in Switzerland (see Table 3)
Clinical	AGLA recommendations
characteristics	High- or very-high-risk patients who are unable to achieve LDL-c goals despite maximum tolerated statin and patients who are intolerant to statins <sup>17 21</sup>
	Medication restrictions
	Ezetimibe monotherapy not restricted.
	Ezetimibe plus atorvastatin restricted to patients at very high cardiovascular risk (as per AGLA guidelines) (LDL-c >70mg/dL) on maximally tolerated statin therapy <sup>68</sup>
	Ezetimibe plus simvastatin not restricted.
	Ezetimibe plus rosuvastatin not restricted.
Settings	General practitioner, cardiologist, endocrinologist, nephrologists
	Primary care setting or hospital

## **Abbreviations**

**ASCVD** = atherosclerotic cardiovascular disease, **LDL-c** = low density lipoprotein-cholesterol, **mg/dL** = milligrams per decilitre, **PROCAM** = prospective cardiovascular münster risk calculator.

Of the RCTs, 19 had centres in Europe, 6 had centres in the USA and 2 had centres in Africa, Asia or South America. One study had centres in Switzerland, with research sites located in Bellinzona, Geneva, Lausanne, Münsterlingen, St. Gallen and Zurich.<sup>109</sup> The number of patients enrolled at each site was not reported. France, Germany, Greece, Italy and the Netherlands were common study locations for the trials conducted in Europe (number of patients enrolled at each centre not reported). These countries are likely more applicable to the Swiss context owing to similarities in population, clinical practice (i.e. following ESC/EAS guidelines) and healthcare systems.

Of the included studies, three were in patients with FH.<sup>120-122</sup> The trial populations were similar to Swiss FH patients with respect to sex, ethnicity and baseline lipid and triglyceride levels (for children and adolescents).<sup>34</sup> However, baseline lipid and triglyceride levels were higher among Swiss adults.<sup>34</sup>

The remaining studies had similar characteristics to Swiss dyslipidaemia patients and those with high cholesterol. For example, patients were mostly Caucasian, between 50 to 60 years old, with equal numbers of males and females. However, trial patients had fewer comorbidities and lower LDL-c than Swiss dyslipidaemia patients and likely represent a comparatively healthier population.<sup>36</sup>

The included studies were partially consistent with Swiss practice. For example, trial patients underwent a washout period when initiating a new lipid-lowering therapy and were generally monitored every 4 weeks for the first 12 weeks in longer trials. The dose of ezetimibe and statins used in the trials were the same as those listed on SwissMedic and the Spezialitätenliste. However, because trial patients were not stratified according to AGLA risk categories, it is unclear whether the dose and type of statin used were appropriate. Typically, it was unreported whether trial patients had used statins or other lipid-lowering therapies and whether they had up-titrated to the maximum tolerated statin dose before enrolling in the studies. This is likely inconsistent with AGLA guidelines and suggests patients may have used ezetimibe at an earlier treatment stage than is recommended in Swiss practice, noting it may be appropriate to start treatment at higher statins doses depending on an individual's cardiovascular risk. Studies that up-titrated over the course of the trial increased the doses on an 'as needed' or a predetermined basis (i.e. every 2 weeks). Forced up-titration is also inconsistent with AGLA guidelines if patients are achieving treatment goals with lower doses.

Lastly, patients were generally assessed at university/academic hospitals. It was not reported whether patients were observed by a cardiologist, endocrinologist, nephrologist or general practitioner.

## Hypercholesterolaemia with ASCVD

There was limited literature regarding the demographics of Swiss patients with hypercholesterolaemia and ASCVD. In the absence of this, literature was used pertaining to Swiss patients with familial or non-familial hypercholesterolaemia and ACS and Swiss patients who had recently experienced MI. The extent to which these populations reflect Swiss patients with hypercholesterolaemia with other ASCVDs is uncertain.

Table 6	Swiss	demographic	information	and	procedural	characteristics	associated	with	
hypercholesterolaemia with ASCVD									
Paramet	er	Characterist	tics						

Parameter	Characteristics				
Demographics	Hypercholesterolaemia, mixed/combined hyperlipidaemia or homozygous sitosterolemia (phytosterolemia) <sup>47 49</sup>				
	Mostly Caucasian <sup>117 118</sup>				
	Higher portion of males (ASCVD, <sup>30</sup> ACS <sup>33</sup> and MI <sup>123</sup> )				
	Older adults (50–75 years) <sup>30 33</sup>				
	Comorbidities (30–60%) <sup>33 123 a</sup>				
	Smoker (30%) <sup>33</sup>				
	Previous statin use (20–40%) <sup>33</sup>				
Intervention	Ezetimibe monotherapy and ezetimibe in fixed or free combination with statins or fenofibrate (see <i>Table 2</i> )				
Comparator	Any statin or fenofibrate licenced in Switzerland (see <b>Table 3</b> )				
Clinical	AGLA recommendations				
characteristics	High- or very-high-risk patients who are unable to achieve LDL-c goals despite maximum tolerated statin and patients who are intolerant to statins <sup>17 21</sup>				
	Medication restrictions				
	Ezetimibe monotherapy not restricted.				
	Ezetimibe plus atorvastatin restricted to patients at very high cardiovascular risk (as per AGLA guidelines) (LDL-c >70mg/dL) on maximally tolerated statin therapy <sup>68</sup>				
	Ezetimibe plus simvastatin not restricted.				
	Ezetimibe plus rosuvastatin not restricted.				
Settings	General practitioner, cardiologist, endocrinologist, nephrologists				
	Primary care setting or hospital				

## **Abbreviations**

ACS = acute coronary syndrome, ASCVD = atherosclerotic cardiovascular disease, LDL-c = low density lipoproteincholesterol, mg/dL = milligrams per decilitre, MI = myocardial infarction.

# Notes

**a** = depends on indication (acute coronary syndrome or MI).

Thirty-five RCTs were conducted in Europe with Belgium, France, Germany, Italy, the Netherlands and Poland as common study locations. Three studies had centres in Switzerland, however, the number of patients enrolled at each site was not reported.<sup>52 111 124</sup> Nine studies were performed in North America and several larger multicentre trials included patients from South America, Asia or South Africa. The number of patients enrolled from each country in multicentre trials was not reported. Studies conducted within Europe were more comparable to the Swiss setting than those conducted outside this region owing to differences in population demographics and healthcare systems.

The trial patients shared some similarities to Swiss patients who had ACS or a recent MI. For example, trial patients were mostly Caucasian males aged 60 and above. When reported, the prevalence of comorbidities such as diabetes and hypertension, smoking status, baseline lipid levels and use of medications including statins, lipid-lowering agents and aspirin was also similar between Swiss and trial patients.

The included studies were partially consistent with Swiss practice. For example, trial patients underwent a washout period when initiating a new lipid-lowering therapy and were generally monitored every 4 weeks for the first 12 weeks in longer trials. The doses of ezetimibe and statins used in the trials were the same as those listed on SwissMedic and the Spezialitätenliste. However, because trial patients were not stratified according to AGLA risk categories, it is unclear whether the dose and type of statin used were appropriate. Typically, it was not reported whether trial patients had used statins or other lipid-lowering therapies and whether they had up-titrated to the maximum tolerated statin dose before enrolling in the studies. This is likely inconsistent with AGLA guidelines and reimbursement practices for ezetimibe plus atorvastatin and suggests patients may have used ezetimibe at an earlier treatment stage than is recommended in Swiss practice, noting, it may be appropriate to start treatment at higher statins doses depending on an individual's cardiovascular risk. Most trials used a fixed statin dose whether combined with ezetimibe or administered as a monotherapy. Studies infrequently up-titrated patients who were not achieving treatment goals. While this approach is necessary to discern the clinical effectiveness and safety of an intervention, it does not align with Swiss practice.

Lastly, patients were generally assessed at university/academic hospitals. It was not reported whether patients were observed by a cardiologist, endocrinologist, nephrologist or general practitioner.

## Hyperlipidaemia without ASCVD

There was limited literature regarding the demographics of Swiss patients with hyperlipidaemia. In the absence of literature addressing these patients, literature pertaining to Swiss patients with dyslipidaemia will be used. The generalisability of dyslipidaemia to hyperlipidaemia (a sub-class of dyslipidaemia) is uncertain.

Table 7	Swiss	demographic	information	and	procedural	characteristics	associated	with
	hyperli	ipidaemia witho	out ASCVD					

Parameter	Characteristics				
Demographics	Hypercholesterolaemia, mixed/combined hyperlipidaemia or homozygous sitosterolemia (phytosterolemia) <sup>47 49</sup>				
	Mostly Caucasian <sup>117 118</sup>				
	Similar proportion of males and females <sup>31 32 119</sup>				
	Mostly older adults (>50 years) <sup>31 32</sup>				
	Comorbidities (30–75%) <sup>119</sup>				
	Normal to overweight <sup>32 119</sup>				
	Dyslipidaemia is adequately controlled (40%)				
	Most dyslipidaemia patients were low to moderate risk (PROCAM), and 40% had not achieving LDL-c goals <sup>36</sup>				
Intervention	Ezetimibe monotherapy and ezetimibe in fixed or free combination with statins or fenofibrate (see <i>Table 2</i> )				
Comparator	Any statin or fenofibrate licenced in Switzerland (see Table 3)				
Clinical	AGLA recommendations				
characteristics	High- or very-high-risk patients who are unable to achieve LDL-c goals despite maximum tolerated statin and patients who are intolerant to statins <sup>17 21</sup>				
	Medication restrictions				
	Ezetimibe monotherapy not restricted.				
	Ezetimibe plus atorvastatin restricted to patients at high or very high cardiovascular risk (as per AGLA guidelines) (LDL-c >70mg/dL) on maximally tolerated statin therapy <sup>68</sup>				
	Ezetimibe plus simvastatin not restricted.				
	Ezetimibe plus rosuvastatin not restricted.				
Settings	General practitioner, cardiologist, endocrinologist, nephrologists				
	Primary care setting or hospital				

## **Abbreviations**

LDL-c = low density lipoprotein-cholesterol, mg/dL = milligrams per decilitre, PROCAM = prospective cardiovascular münster risk calculator.

Of the RCTs, two were conducted in Europe with centres in Belgium, France and Germany; one was performed in Canada and one did not specify trial location. No study was conducted in Switzerland. Studies conducted within Europe were more comparable to the Swiss setting than those conducted outside this region owing to differences in population demographics and healthcare systems.

The trial patients shared some similarities to Swiss patients with dyslipidaemia. For example, trial patients were mostly Caucasian with one or more comorbidities (mainly diabetes and hypertension). There were similar proportions of males to females in the trials. However, trial patients were slightly younger (50–60 years) and reported higher LDL-c, HDL-c, total cholesterol and triglyceride levels compared to Swiss patients with dyslipidaemia. The lower lipid levels among Swiss patients likely reflects that 40% of patients in Sudano (2011) were adequately treated with lipid-lowering agents.<sup>119</sup> Patients entering clinical trials likely reflect an inadequately controlled population.

The included studies were partially consistent with Swiss practice. For example, trial patients underwent a washout period when initiating a new lipid-lowering therapy and were generally monitored every 4 weeks for the first 12 weeks in longer trials. The doses of ezetimibe and statins used in the trials were the same as those listed on SwissMedic and the Spezialitätenliste. However, the doses of fenofibrate used in the trials were lower than is listed on SwissMedic. Because trial patients were not stratified according to AGLA risk categories, it is unclear whether the dose and type of statin or fenofibrate used were appropriate.

One study enrolled patients with statin-induced muscle-related adverse events (i.e. patients were intolerant to statins).<sup>125</sup> In the remaining trials, it was not reported whether trial patients had used statins or other lipid-lowering therapies and whether they had up-titrated to the maximum tolerated statin dose before enrolling in the studies. This is likely inconsistent with AGLA guidelines and suggests patients may have used ezetimibe at an earlier treatment stage than is recommended in Swiss practice, noting it may be appropriate to start treatment at higher statins doses depending on an individual's cardiovascular risk.

Lastly, patients were generally assessed at university/academic hospitals and it was not reported whether patients were observed by a cardiologist, endocrinologist, nephrologist or general practitioner.

## 7.3.5 Results: Clinical Effectiveness

## Hypercholesterolaemia without ASCVD

*Table 8* provides a summary of the main pooled clinical effectiveness outcomes comparing ezetimibe monotherapy to statins or placebo and ezetimibe plus statins to statins. The 3- and 12-month time points were selected as representative timepoints for short- and long-term timepoints, respectively. There were no studies evaluating lipids outcomes beyond 3 months for comparisons involving ezetimibe monotherapy. A negative mean difference for LDL-c and total cholesterol and a positive mean difference for HDL-c indicates the results favour the intervention group (ezetimibe or ezetimibe plus statins). Triglyceride data was not pooled.

By 3 months, there were statistical differences between ezetimibe and placebo for absolute and percentage changes in LDL-c, HDL-c, total cholesterol and number of patients achieving LDL-c levels <130mg/dL, with the result favouring ezetimibe (orange shading).

By 3 months, there were statistically significant differences between ezetimibe and statins for absolute and percentage change in LDL-c, HDL-c and total cholesterol, and the number of patients achieving LDL-c levels <130mg/dL, with the result favouring statins (green shading).

Ezetimibe plus statins showed a significant difference to statins for absolute and percentage change in LDL-c, HDL-c, total cholesterol and number of patients achieving LDL-c goals at 3 months. The statistical difference for LDL-c and total cholesterol persisted to 12 months. The effect size increased for the absolute change and remained the same for the percentage change. There was no difference in HDL-c by 12 months. For additional information regarding each outcome, refer to the corresponding sections below.

# Table 8 Summary of meta-analyses results for patients with hypercholesterolaemia without ASCVD

Outcome	Mean difference (95% Cl) or risk ratio (95% Cl) p value													
	3 months	6 months	9 months	12 months	24 months									
Ezetimibe vs placebo														
LDL-c	-19.39% (-21.53, -17.25)	NR	NR	NR	NR									
	-46.68mg/dL (-53.46, -39.90)	NR	NR	NR	NR									
Achieving goals <sup>a</sup>	6.93 (3.66, 13.13)	NR	NR	NR	NR									
HDL-c	2.95% (2.04, 3.87)	NR	NR	NR	NR									
	1.72mg/dL (0.51, 2.94)	NR	NR	NR	NR									
Total cholesterol	-14.33% (-15.78, -12.87)	NR	NR	NR	NR									
	-56.24mg/dL (-63.03, -49.46)	NR	NR	NR	NR									
Ezetimibe v	s statins		1	•										
LDL-c	17.22% (11.23, 23.22)	NR	NR	NR	NR									
	10.77mg/dL (7.64, 13.90)	NR	NR	NR	NR									
Achieving goals <sup>a</sup>	0.38 (0.31, 0.47)	NR	NR	NR	NR									
HDL-c	-1.42% (-2.72, -0.12)	NR	NR	NR	NR									
	0.23mg/dL (-1.03, 1.50)	NR	NR	NR	NR									
Total cholesterol	12.40% (8.14, 16.66)	NR	NR	NR	NR									
	4.61mg/dL (-0.05, 9.27)	NR	NR	NR	NR									
Ezetimibe plus statins vs statins														
LDL- c	-16.14%	-16.14%	-15.35%	-14.24%	-16.50%									
	(-19.67, -12.60)	(-20.63, -11.65)	(-19.93, -10.78)	(-18.91, -9.57)	(-26.43, -6.57)									
	-16.72mg/dL (-22.34, -11.11)	NR	-31.13mg/dL (-45.96, -16.30)	NR	-51.40mg/dL (-65.14, -37.66)									
Outcome		Mean differe	nce (95% CI) or risk ı	ratio (95% CI)										
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		p value												
Achieving goals <sup>a</sup>	1.14	NA	NA	NA	NA									
-	(1.00, 1.10)													
HDL-c	1.22%	0.63%	0.75%	1.04%	2.40%									
	(0.45, 1.98)	(-0.64, 1.91)	(-1.22, 2.72)	(-0.43, 2.50)	(-0.24, 5.04)									
	3.82mg/dL	NR	0.19mg/dL	NR	0.20mg/dL									
	(1.37, 6.28)		(-4.54, 4.92)		(-4.40, 4.80)									
Total	-11.33%	-11.84%	-12.88%	-11.30%	-13.40%									
cholesterol	(-12.85, -9.82)	(-14.64, -9.05) (-15.98, -9.78		(-14.19, 8.40)	(-17.64, -9.16)									
	-18.02mg/dL	NR	-33.18mg/dL	NR	-53.30mg/dL									
	(-27.95, -8.09)		(-55.66, -10.70)		(-75.20, -31.40)									

## Abbreviations

CI = confidence interval, HDL-c = high density lipoprotein-cholesterol, LDL-c = low density lipoprotein-cholesterol, NA = not applicable, NR = not reported.

## <u>Notes</u>

For LDL-c and total cholesterol, negative mean difference favours intervention; positive mean difference favours comparators. For HDL-c, positive mean difference favours intervention; negative mean difference favours comparators.

For number of patients achieving LDL-c goals, a risk ratio >1 favours intervention; risk ratio <1 favours comparator.

No shading = no statistically significant difference between groups (p>0.05)

Green shading = statistically significant differences between groups (p<0.05) in favour of statins.

**Orange shading** = statistically significant differences between groups (p<0.05) in favour of ezetimibe or ezetimibe plus statins. **a** = risk ratio 95% CI of number of patients achieving LDL-c levels <130mg/dL.

### Ezetimibe vs placebo

No studies evaluated lipids levels beyond 3 months, MACE outcomes or markers of vascular damage.

#### LDL-c

#### Ezetimibe vs placebo, percentage change in LDL-c, 3 months

Thirteen studies provided evidence on the percentage change in LDL-c at 3 months. Eleven studies were included in the meta-analysis<sup>104 107 121 126-133</sup> and two were omitted owing to incomplete data.<sup>134 135</sup> Overall, there was a statistically significant difference between ezetimibe and placebo groups at 3 months (MD -19.39%; 95% CI -21.53, -17.25%; p<0.00001) (*Figure 17*), however, Chi<sup>2</sup> and I<sup>2</sup> statistics indicated considerable levels of heterogeneity and inconsistency (P<0.00001, I<sup>2</sup>=85%).

Ten studies evaluated ezetimibe in adults ( $\geq$ 18 years) with hypercholesterolaemia<sup>104 107 126-133</sup> and one study evaluated ezetimibe in children (6–10 years) with heterozygous FH.<sup>121</sup> Baseline LDL-c was higher among children compared to adults.

	Ez	tetimibe	Placebo				Mean Difference			Mean Difference		
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI		IV, Randor	m, 95% Cl	
Ballantyne 2003	-18.4	14.4	61	5.9	14.4	56	6.9%	-24.30 [-29.52, -19.08]				
Bays 2004	-18.9	14.6	148	-2.2	14.5	146	9.2%	-16.70 [-20.03, -13.37]				
Davidson 2002	-18.1	14.8	61	-1.3	1.7	70	8.7%	-16.80 [-20.54, -13.06]				
Dujovne 2002	-16.86	14.2	666	0.36	12.5	226	10.8%	-17.22 [-19.17, -15.27]		+		
Goldberg 2004	-19.8	10.5	89	2.7	13.3	92	9.0%	-22.50 [-25.98, -19.02]				
Kerzner 2003	-19.8	10.5	89	2.7	13.3	92	9.0%	-22.50 [-25.98, -19.02]				
Knopp 2003	-17.69	14.7	621	0.79	12.43	204	10.7%	-18.48 [-20.54, -16.42]		+		
Koren 2012	-18.6	13.65	77	-1.3	13.74	78	8.0%	-17.30 [-21.61, -12.99]				
Koren 2014	-17.59	2.48	43	-2.87	2.3	38	11.5%	-14.72 [-15.76, -13.68]		•		
Kusters 2015	-28	14.68	92	-0.95	13.52	45	7.2%	-27.05 [-32.01, -22.09]				
Melani 2003	-18.7	10.112	64	1.3	10.2	65	9.0%	-20.00 [-23.51, -16.49]				
Total (95% CI)			2011			1112	100.0%	-19.39 [-21.53, -17.25]		•		
Heterogeneity: Tau <sup>2</sup> = 10.06; Chi <sup>2</sup> = 65.71, df = 10 (P < 0.00001); l <sup>2</sup> = 85% Test for overall effect: Z = 17.77 (P < 0.00001)									⊢ -50	-25 0	) 25 Eavours Placebo	50
										r avours Ezetimite	avours ridcebu	

#### Figure 17 Forest plot indicating mean difference in LDL-c (percentage change) for ezetimibe

#### compared to placebo (3 months)

#### Abbreviations

**CI** = confidence interval, **SD** = standard deviation.

#### Ezetimibe vs placebo, absolute change in LDL-c, 3 months

Five studies provided evidence on the absolute change in LDL-c at 3 months. Three studies were included in the meta-analysis<sup>121</sup> <sup>134</sup> <sup>135</sup> and two were omitted owing to incomplete data.<sup>128</sup> <sup>133</sup> Overall, there was a statistically significant difference between ezetimibe and placebo groups at 3 months (MD -46.68mg/dL; 95% CI -53.46, -39.90 mg/dL; p<0.00001) (*Figure 18*). Chi<sup>2</sup> and I<sup>2</sup> statistics indicated moderate levels of heterogeneity and inconsistency (P=0.06, I<sup>2</sup>=65%).

Two studies evaluated ezetimibe in adults ( $\geq$ 18 years) with hypercholesterolaemia<sup>134 135</sup> and one study evaluated ezetimibe in children (6–10 years) with heterozygous FH.<sup>121</sup> Baseline LDL-c was higher among children compared to adults.



## Figure 18 Forest plot indicating mean difference in LDL-c (absolute change) for ezetimibe compared to placebo (3 months)

<u>Abbreviations</u> CI = confidence interval, SD = standard deviation.

#### Ezetimibe vs placebo, number of patients achieving LDL-c goals, 3 months

Six studies provided evidence on the number of patients achieving LDL-c goals at 3 months. All four studies were included in the meta-analyses with the analyses stratified according to treatment goals (<130mg/dL,<sup>107 127</sup> <70mg/dL<sup>127 132</sup> and <NCEP–ATP III goals<sup>128 130 133</sup>).

Overall, there were statistically significant differences between ezetimibe and placebo groups in the number of patients achieving LDL-c levels <130mg/dL (p<0.00001) and below NCEP-ATP III goals (p<0.00001) (*Table 9*). There was no statistically significant difference in the number of patients achieving LDL-c levels <70mg/dL (p=0.49). All LDL-c goals were subject to low levels of heterogeneity and inconsistency. For forest plots, refer to *Figure 82* to *Figure 84*.

All studies enrolled adult patients with hypercholesterolaemia.<sup>107 127 128 130 132 133</sup>

LDL-c goal	Number of studies	Heterogeneity	Ezetimibe n/N (%)	Placebo n/N (%)	Risk Ratio (95% Cl)
<130mg/dL	<b>2</b> 107 127	Chi <sup>2</sup> =0.85 P=0.36 I <sup>2</sup> =0%	71/235 (30.2%)	10/238 (4.2%)	6.93 (3.66, 13.13) p<0.00001
<70mg/dL	2127 132	NA	1/225 (0.04%)	0/224 (0.0%)	3.04 (0.13, 73.45) p=0.49
<ncep-atp iii<="" td=""><td><b>3</b>128 130 133</td><td>Chi<sup>2</sup>=0.39 P=0.82 I<sup>2</sup> =0%</td><td>77/194 (39.7%)</td><td>24/195 (12.3%)</td><td>3.15 (2.08, 4.76) p&lt;0.00001</td></ncep-atp>	<b>3</b> 128 130 133	Chi <sup>2</sup> =0.39 P=0.82 I <sup>2</sup> =0%	77/194 (39.7%)	24/195 (12.3%)	3.15 (2.08, 4.76) p<0.00001

Table 9 Ezetimibe compared to placebo: number of patients achieving LDL-c goals at 3 months

**Abbreviations** 

**CI** = confidence interval, **LDL-c** = low density lipoprotein-cholesterol, **n** = number of patients with event, **N** = total number of patients, **NCEP-ATP III** = national cholesterol education program-adult treatment panel III.

#### HDL-c

#### Ezetimibe vs placebo, percentage change in HDL-c, 3 months

Twelve studies provided evidence on the percentage change in HDL-c at 3 months. Ten studies were included in the meta-analysis<sup>104</sup> <sup>107</sup> <sup>121</sup> <sup>126-131</sup> <sup>133</sup> and two were omitted owing to incomplete data.<sup>134</sup> <sup>135</sup> Overall, there was a statistically significant difference between ezetimibe and placebo groups at 3 months (MD 2.95%; 95% CI 2.04, 3.87%; p<0.00001) (*Figure 19*). Chi<sup>2</sup> and I<sup>2</sup> statistics indicated low levels of heterogeneity and inconsistency (P<0.73, I<sup>2</sup>=0%).

Nine studies evaluated ezetimibe in adults (≥18 years) with hypercholesterolaemia<sup>104 107 126-131 133</sup> and one study evaluated ezetimibe in children (6–10 years) with heterozygous FH.<sup>121</sup> Baseline HDL-c was similar between adults and children.

	Ezetimibe Place			Placebo Mean Difference			Mean Difference	Mean Difference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Ballantyne 2003	4.2	11.2	61	3.7	11.1	56	5.1%	0.50 [-3.54, 4.54]	
Bays 2004	5	13.4	148	-0.3	13.3	146	9.0%	5.30 [2.25, 8.35]	
Davidson 2002	5.1	12.5	61	0.9	12.5	70	4.5%	4.20 [-0.09, 8.49]	
Dujovne 2002	1.31	12.6	666	-1.6	11	226	28.1%	2.91 [1.19, 4.63]	
Goldberg 2004	7	12.6	90	2.3	10.8	92	7.2%	4.70 [1.29, 8.11]	_ <del></del>
Kerzner 2003	3	8.19	67	0	7.75	60	10.9%	3.00 [0.23, 5.77]	
Knopp 2003	1.01	12.46	621	-1.26	11.14	204	25.4%	2.27 [0.45, 4.09]	
Koren 2012	-1.5	33.35	77	-5.3	30.64	78	0.8%	3.80 [-6.29, 13.89]	
Kusters 2015	2	19.57	85	1	18.82	42	1.7%	1.00 [-6.05, 8.05]	
Melani 2003	4.1	9.8	64	2	9.87	65	7.3%	2.10 [-1.29, 5.49]	+
Total (95% CI)			1940			1039	100.0%	2.95 [2.04, 3.87]	•
Heterogeneity: Tau <sup>2</sup> =	: 0.00; C	hi <b>²</b> = 6.1							
Test for overall effect:	Z = 6.33	8 (P ≤ 0.)	-20 -10 0 10 20 Eavours Placebo, Eavours Ezetimibe						

#### Figure 19 Forest plot indicating mean difference in HDL-c (percentage change) for ezetimibe

#### compared to placebo (3 months)

#### Abbreviations

CI = confidence interval, SD = standard deviation.

#### Ezetimibe vs placebo, absolute change in HDL-c, 3 months

Five studies provided evidence on the absolute change in HDL-c at 3 months. Three studies were included in the meta-analysis<sup>121</sup> <sup>134</sup> <sup>135</sup> and two were omitted owing to incomplete data.<sup>128</sup> <sup>133</sup> Overall, there was a statistically significant difference between ezetimibe and placebo groups at 3 months (MD 1.72mg/dL; 95% CI 0.51, 2.94mg/dL; p=0.006) (*Figure 20*). Chi<sup>2</sup> and I<sup>2</sup> statistics indicated low levels of heterogeneity and inconsistency (P=0.69, I<sup>2</sup>=0%).

Two studies evaluated ezetimibe in adults ( $\geq$ 18 years) with hypercholesterolaemia<sup>134 135</sup> and one study evaluated ezetimibe in children (6–10 years) with heterozygous FH.<sup>121</sup> Baseline HDL-c was similar between adults and children.



## Figure 20 Forest plot indicating mean difference in HDL-c (absolute change) for ezetimibe compared to placebo (3 months)

<u>Abbreviations</u> CI = confidence interval, SD = standard deviation.

#### **Total Cholesterol**

#### Ezetimibe vs placebo, percentage change in total cholesterol, 3 months

Eleven studies provided evidence on the percentage change in total cholesterol at 3 months. Nine studies were included in the meta-analysis<sup>107</sup> <sup>121</sup> <sup>126-131</sup> <sup>133</sup> and two were omitted owing to incomplete data.<sup>134</sup> <sup>135</sup> Overall, there was a statistically significant difference between ezetimibe and placebo groups at 3 months (MD -14.33%; 95% -15.78, -12.87%; p<0.00001) (*Figure 21*), however, Chi<sup>2</sup> and I<sup>2</sup> statistics indicated considerable levels of heterogeneity and inconsistency (P<0.003, I<sup>2</sup>=86%).

Eight studies evaluated ezetimibe in adults ( $\geq$ 18 years) with hypercholesterolaemia<sup>107 126-131 133</sup> and one study evaluated ezetimibe in children (6–10 years) with heterozygous FH.<sup>121</sup> Baseline total cholesterol was higher among children compared to adults.

	Ez	Ezetimibe Placebo				Mean Difference			Mean Difference			
Study or Subgroup	Mean	SD	Total	Mean	<b>SD</b>	Total	Weight	IV, Random, 95% CI		IV, Rando	m, 95% Cl	
Ballantyne 2003	-13.5	11.9	61	3.5	11.4	56	7.4%	-17.00 [-21.22, -12.78]				
Bays 2004	-13.3	10.9	148	-1.4	10.9	146	12.4%	-11.90 [-14.39, -9.41]				
Davidson 2002	-13.3	11.7	61	-0.6	11.7	70	7.9%	-12.70 [-16.72, -8.68]				
Dujovne 2002	-12.48	9.8	666	0.84	8.4	226	16.8%	-13.32 [-14.64, -12.00]		+		
Goldberg 2004	-13.7	7.9	90	2.2	9.9	92	12.1%	-15.90 [-18.50, -13.30]				
Kerzner 2003	-13	8.19	67	1	13.5	60	8.1%	-14.00 [-17.94, -10.06]				
Knopp 2003	-12.4	9.47	621	0.57	8.57	204	16.6%	-12.97 [-14.36, -11.58]		+		
Kusters 2015	-21	12.23	92	0.2	10.27	45	8.1%	-21.20 [-25.11, -17.29]				
Melani 2003	-13.2	8.76	64	0.2	8.83	65	10.6%	-13.40 [-16.44, -10.36]				
Total (95% CI)			1870			964	100.0%	-14.33 [-15.78, -12.87]		•		
Heterogeneity: Tau² = 2.84; Chi² = 22.94, df = 8 (P = 0.003); i² = 65% Test for overall effect: Z = 19.25 (P < 0.00001)										-25 Favours Ezetimibe	D 25 Favours Placebo	50

# Figure 21 Forest plot indicating mean difference in total cholesterol (percentage change) for ezetimibe compared to placebo (3 months)

#### Abbreviations

CI = confidence interval, SD = standard deviation.

#### Ezetimibe vs placebo, absolute change in total cholesterol, 3 months

Five studies provided evidence on the absolute change in total cholesterol at 3 months. Three studies were included in the meta-analysis<sup>121</sup> <sup>134</sup> <sup>135</sup> and two were omitted owing to incomplete data.<sup>128</sup> <sup>133</sup> Overall, there was a statistically significant difference between ezetimibe and placebo groups at 3 months (MD -56.24mg/dL; 95% CI -63.03, -49.46mg/dL; p<0.00001) (*Figure 22*), however, Chi<sup>2</sup> and I<sup>2</sup> statistics indicate considerable levels of heterogeneity and inconsistency (P<0.00001, I<sup>2</sup>=42%).

Two studies evaluated ezetimibe in adults (≥18 years) with hypercholesterolaemia<sup>134 135</sup> and one study evaluated ezetimibe in children (6–10 years) with heterozygous FH.<sup>121</sup> Baseline total cholesterol was higher among children compared to adults.



## Figure 22 Forest plot indicating mean difference in total cholesterol (absolute change) for

#### ezetimibe compared to placebo (3 months)

#### Abbreviations

CI = confidence interval, SD = standard deviation.

## Triglycerides

### Ezetimibe vs placebo, percentage change in triglycerides, 3 months

Eight studies provided evidence on percentage change in triglycerides at 3 months.<sup>107 121 127-129 131-133</sup> The results are described narratively rather than meta-analysed because it was unclear whether the results from each study were normally distributed.

Two studies reported statistically significant differences between the ezetimibe and placebo groups at 3 months (p<0.01; p=0.021)<sup>121 129</sup> and one study reported no significant differences (p=0.09) (*Table 10*).<sup>131</sup> Statistical differences were not reported in five studies, so it was unclear whether ezetimibe and placebo groups differed.<sup>107 127 128 132 133</sup>

Seven studies evaluated ezetimibe in adults ( $\geq$ 18 years) with hypercholesterolaemia<sup>107 127-129 131-133</sup> and one study evaluated ezetimibe in children (6–10 years) with heterozygous FH.<sup>121</sup> Baseline triglycerides were similar between adults and children.

Study	Ezetimibe at baseline, follow-up; n	Placebo at baseline follow-up; n	p value
Bays 2004 <sup>127 a</sup>	145.5 ± 79.1mg/dl	142.8 ± 62.6mg/dl	NR
	-10.7 ± 2.6%, n=148	-1.9 ± 2.6%, n=146	NR
Davidson 2002 <sup>128 a</sup>	190.3 ± 68.2mg/dl	170.9 ± 68.5mg/dl	NR
	-8.3 ± 3.0%, n=61	-0.6 ± 1.4%, n=70	NR
Dujovne 2002 <sup>129 b</sup>	174.8 ± NR mg/dl	169.0 ± NR mg/dl	NR
	-5.65 ± 1.31%, n=666	5.74 ± 1.97%, n=226	<0.01
Goldberg 2004 <sup>107</sup> c	163.0 ± 104.0mg/dl	162.0 ± 83.0mg/dl	NR
	-13.2 ± 27.8%, n=90	-2.2 ± 33.0%, n=92	NR
Knopp 2003 <sup>131 b</sup>	163.0 ± NR mg/dl	171.0 ± NR mg/dL	NR
	-1.7 ± 1.4%, n=621	2.4 ± 2.2%, n=204	0.09
Koren 2014 <sup>132 d</sup>	117.0mg/dl (90.0–159.0)	118.0mg/dl (86.0–179.0)	NR
	-2.4 ± 72.1%, n=77	2.0 ± 113.6%, n=78	NR
Kusters 2015 <sup>121 e</sup>	82.0 ± 30.0mg/dl	92.0 ± 61.0mg/dl	NR
	-6.0 ± 34.3%, n=85	8.0 ± 37.7% n=42	0.021
Melani 2003 <sup>133 b</sup>	168.3 ± NR mg/dl	159.4 ± NR mg/dl	NR
	-2.1 ± 3.8%, n=64	2.0 ± 3.8%, n=65	NR

Table 10 Ezetimibe compared to placebo: percentage change in triglycerides at 3 months

## Abbreviations

mg/dL = milligrams per decilitre, n = number of patients, NR = not reported.

#### <u>Notes</u>

 $\mathbf{a}$  = median ± standard error,  $\mathbf{b}$  = mean ± standard error,  $\mathbf{c}$  = median ± standard deviation,  $\mathbf{d}$  = median (interquartile range), mean ± standard deviation,  $\mathbf{e}$  = mean ± standard deviation.

### Ezetimibe vs placebo, absolute change in triglycerides, 3 months

Three studies provided evidence on the absolute change in triglycerides at 3 months.<sup>121 134 135</sup> The results are described narratively rather than meta-analysed because it was unclear whether the results from each study were normally distributed.

One study reported a statistically significant difference (p=0.021),<sup>121</sup> while two studies reported a lack of significant differences (p=NS) between ezetimibe and placebo groups at 3 months (*Table 11*).<sup>134 135</sup>

Two studies evaluated ezetimibe in adults ( $\geq$ 18 years) with hypercholesterolaemia<sup>134 135</sup> and one study evaluated ezetimibe in children (6–10 years) with heterozygous FH.<sup>121</sup> Baseline triglycerides were similar between adults and children.

Study	Ezetimibe at baseline	Placebo at baseline	p value
	follow-up, n	follow-up, n	
Krysiak 2011a <sup>134 a</sup>	122 ± 11mg/dL	119 ± 11mg/dL	NS
	112 ± 10mg/dL, n=41	127 ± 13mg/dL, n=40	NS
Krysiak 2011b <sup>135 a</sup>	118.9 ± 9.7mg/dL	120.2 ± 9.8mg/dL	NS
	113.6 ± 9.5mg/dL, n=23	122.9 ± 11.8mg/dL, n=23	NS
Kusters 2015 <sup>121 b</sup>	82 ± 30mg/dL	92 ± 61mg/dL	NR
	80 ± 40mg/dL, n=85	100 ± 64mg/dL, n=42	0.021

Table 11 Ezetimibe compared to placebo: absolute change in triglycerides at 3 months

#### **Abbreviations**

**mg/dL** = milligrams per decilitre, **n** = number of patients, **NR** = not reported, **NS** = not significant. **Notes** 

**a** = mean ± standard deviation, **b** = geometric mean ± standard deviation.

## Sub-groups analysis

## <u>Children</u>

In one study, there were statistical differences in favour of ezetimibe for the percentage change in LDLc (<0.001), total cholesterol (<0.001) and triglycerides (p=0.021) at 3 months.<sup>121</sup> There was no significant difference in the percentage change in HDL-c (p=0.81). The statistical difference was not reported for absolute change in lipid outcomes, so it is unclear whether the groups differed. For further information refer to **Section 15.4 Appendix D**, **Table 100**.

#### Ezetimibe vs statin

No studies evaluated lipids levels beyond 3 months, MACE outcomes or markers of vascular damage.

#### LDL-c

#### Ezetimibe vs statin, percentage change in LDL-c, 3 months

Seven studies provided evidence on the percentage change in LDL-c at 3 months. Five studies were included in the meta-analysis<sup>107 126-128 133</sup> and two were omitted owing to incomplete data.<sup>134 135</sup> Overall, there was a statistically significant difference between ezetimibe and statin groups at 3 months (MD 17.22%; 95% CI 11.23, 23.22%; p<0.00001) (*Figure 23*), however, Chi<sup>2</sup> and I<sup>2</sup> statistics indicated considerable levels of heterogeneity and inconsistency (P<0.00001, I<sup>2</sup>=95%).

All studies enrolled adult patients with hypocholesterolaemia.<sup>107 126-128 133</sup>



## Figure 23 Forest plot indicating mean difference in LDL-c (percentage change) for ezetimibe

## compared to statin (3 months)

#### Abbreviations

CI = confidence interval, LDL-c = low density lipoprotein-cholesterol, SD = standard deviation.

#### Ezetimibe vs statin, absolute change in LDL-c, 3 months

Four studies provided evidence on the absolute change in LDL-c at 3 months. Two studies were included in the meta-analysis<sup>134</sup> <sup>135</sup> and two were omitted owing to incomplete data.<sup>128</sup> <sup>133</sup> Overall, there was a statistically significant difference between ezetimibe and statin groups at 3 months (MD 10.77mg/dL; 95% CI 7.64, 13.90mg/dL; p<0.00001) (*Figure 24*). Chi<sup>2</sup> and I<sup>2</sup> statistics indicated low levels of heterogeneity and inconsistency (P=0.27, I<sup>2</sup>=17%).

All studies enrolled adult patients with hypocholesterolaemia.<sup>134 135</sup>

	Eze	Ezetimibe Statin				Mean Difference	Mean Difference		
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Krysiak 2011a	134	7	41	122	9	42	62.6%	12.00 [8.54, 15.46]	
Krysiak 2011b	129.3	7.3	22	120.6	9.1	24	37.4%	8.70 [3.95, 13.45]	
Total (95% CI)			63			66	100.0%	10.77 [7.64, 13.90]	•
Heterogeneity: Tau <sup>2</sup> =	0.95; Cł	ni² = 1 ZP ~	-50 -25 0 25 50						
restior overall ellect.	Z = 0.74	(F 5	0.0000						Favours Ezetimibe Favours Statin

# Figure 24 Forest plot indicating mean difference in LDL-c (absolute change) for ezetimibe compared to statins (3 months)

#### **Abbreviations**

CI = confidence interval, LDL-c = low density lipoprotein-cholesterol, SD = standard deviation.

## Ezetimibe vs statin, number of patients achieving LDL-c goals, 3 months

Four studies provided evidence on the number of patients achieving LDL-c goals at 3 months. All four studies were included in the meta-analyses with the analyses stratified according to treatment goals (<130mg/dL<sup>107 127</sup> and <NCEP–ATP III goals<sup>128 133</sup>).

Overall, there was a statistically significant difference between ezetimibe and statin groups in the number of patients achieving LDL-c levels <130mg/dL (p<0.00001) (*Table 12*). There was no statistically significant difference in the number of patients who achieved LDL-c levels below NCEP–ATP III goals (p=0.28). Both outcomes were subject to low levels of heterogeneity and inconsistency. For the forest plots, refer to *Figure 85* and *Figure 86*.

In one study, no patient achieved LDL-c levels <70mg/dL at 3 months in either the ezetimibe or statin groups.<sup>127</sup> All studies enrolled adult patients with hypocholesterolaemia.<sup>107 127 128 133</sup>

LDL-c goal	Number of studies	Heterogeneity	Ezetimibe n/N (%)	Statin n/N (%)	Risk Ratio (95% Cl)
<130mg/dL	2 <sup>107 127</sup>	Chi <sup>2</sup> =1.22	71/235	763/950	0.38 (0.31, 0.47)
		P=0.27	(30.2%)	(80.3%)	p<0.00001
		l²=18%			
<70mg/dL ª	1 <sup>127</sup>	NA	0/148	0/146	NA
			(0.0%)	(0.0%)	NR
<ncep-atp iii<="" td=""><td>2<sup>128 133</sup></td><td>Chi<sup>2</sup>=15.34</td><td>43/122</td><td>264/464</td><td>0.67 (0.35, 1.30)</td></ncep-atp>	2 <sup>128 133</sup>	Chi <sup>2</sup> =15.34	43/122	264/464	0.67 (0.35, 1.30)
		P<0.0001	(35.2%)	(57.0%)	p=0.28
		l²=93%			

### **Abbreviations**

**CI** = confidence interval, **LDL-c** = low density lipoprotein-cholesterol, **n** = number of patients with event, **N** = total number of patients, **NA** = not applicable, **NCEP-ATP III** = national cholesterol education program-adult treatment panel III, **NR** = not reported.

## <u>Notes</u>

**a** = Only one study per outcome so meta-analysis not performed. Statistical significance based on analysis performed in the study.

## HDL-c

## Ezetimibe vs statin, percentage change in HDL-c, 3 months

Seven studies provided evidence on the percentage change in HDL-c at 3 months. Five studies were included in the meta-analysis<sup>107 126-128 133</sup> and two were omitted owing to incomplete data.<sup>134 135</sup> Overall, there was a statistically significant difference between ezetimibe and statin groups at 3 months (MD - 1.42%; 95% CI -2.72, -0.12%; p=0.03) (*Figure 25*). Chi<sup>2</sup> and I<sup>2</sup> statistics indicated low levels of heterogeneity and inconsistency (P=0.79, I<sup>2</sup>=0%).

	Ez	etimib	е		Statin			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	<b>SD</b>	Total	Weight	IV, Random, 95% CI	IV, Random, 95% Cl
Ballantyne 2003	4.2	11.2	61	4.3	11.6	244	16.9%	-0.10 [-3.27, 3.07]	
Bays 2004	5	13.4	148	6.8	12.4	612	30.0%	-1.80 [-4.17, 0.57]	
Davidson 2002	5.1	12.5	61	6.9	13	263	13.7%	-1.80 [-5.31, 1.71]	
Goldberg 2004	7	12.6	90	7.6	11.9	345	20.2%	-0.60 [-3.49, 2.29]	
Melani 2003	4.1	9.8	64	6.7	12.81	205	19.1%	-2.60 [-5.57, 0.37]	
Total (95% CI)			424			1669	100.0%	-1.42 [-2.72, -0.12]	•
Heterogeneity: Tau² = Test for overall effect:	= 0.00; C : Z = 2.16	hi² = 1 5 (P = (	-20 -10 0 10 20 Favours Statin Favours Ezetimibe						

All studies enrolled adult patients with hypocholesterolaemia.<sup>107 126-128 133</sup>

# Figure 25 Forest plot indicating mean difference in HDL-c (percentage change) for ezetimibe compared to statin (3 months)

Abbreviations CI = confidence interval, HDL-c = high density lipoprotein-cholesterol, SD = standard deviation.

#### Ezetimibe vs statin, absolute change in HDL-c, 3 months

Four studies provided evidence on absolute change in HDL-c at 3 months. Two studies were included in the meta-analysis<sup>134</sup> <sup>135</sup> and two were omitted owing to incomplete data.<sup>128</sup> <sup>133</sup> Overall, there was no statistically significant difference between ezetimibe and statin groups at 3 months (MD 0.23mg/dL; 95% CI -1.03, 1.50mg/dL; p=0.72) (*Figure 26*). Chi<sup>2</sup> and I<sup>2</sup> statistics indicated low levels of heterogeneity and inconsistency (P=0.76, I<sup>2</sup>=0%).

Both studies enrolled adult patients with hypocholesterolaemia.134 135



### Figure 26 Forest plot indicating mean difference in HDL-c (absolute change) for ezetimibe

#### compared to statin (3 months)

#### **Abbreviations**

CI = confidence interval, HDL-c = high density lipoprotein-cholesterol, SD = standard deviation.

#### **Total Cholesterol**

## Ezetimibe vs statin, percentage change in total cholesterol, 3 months

Seven studies provided evidence on the percentage change in total cholesterol at 3 months. Five studies were included in the meta-analysis<sup>107 126-128 133</sup> and two were omitted owing to incomplete data.<sup>134 135</sup> Overall, there was a statistically significant difference between ezetimibe and statin groups at 3 months (MD 12.40%; 95% CI 8.14, 16.66%; p<0.00001) (*Figure 27*). However, Chi<sup>2</sup> and I<sup>2</sup> statistics indicated considerable levels of heterogeneity and inconsistency (P<0.00001, I<sup>2</sup>=93%).

All studies enrolled adult patients with hypocholesterolaemia.<sup>107 126-128 133</sup>

	Ezetimibe Statin						Mean Difference	Mean Difference
Study or Subgroup	Mean S	D Total	Mean	<b>SD</b>	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Ballantyne 2003	-13.5 11	.9 61	-32.1	11.7	244	19.2%	18.60 [15.27, 21.93]	_ <b>_</b>
Bays 2004	-13.3 10	.9 148	-27.7	12.4	612	20.7%	14.40 [12.39, 16.41]	
Davidson 2002	-13.3 11	.7 61	-25.8	11.4	263	19.3%	12.50 [9.26, 15.74]	
Goldberg 2004	-13.7 7	.9 90	-26.4	11.3	345	20.7%	12.70 [10.68, 14.72]	
Melani 2003	-13.2 8.7	6 64	-17.2	11.09	205	20.1%	4.00 [1.37, 6.63]	
Total (95% CI)		424			1669	100.0%	12.40 [8.14, 16.66]	•
Heterogeneity: Tau² = Test for overall effect:	= 21.72; Chi <del>"</del> : Z = 5.71 (P	-20 -10 0 10 20 Favours Ezetimibe Favours Statin						

#### Figure 27 Forest plot indicating mean difference in total cholesterol (percentage change) for

#### ezetimibe compared to statin (3 months)

#### Abbreviations

CI = confidence interval, SD = standard deviation.

#### Ezetimibe vs statin, absolute change in total cholesterol, 3 months

Four studies provided evidence on the absolute change in total cholesterol at 3 months. Two studies were included in the meta-analysis<sup>134</sup> <sup>135</sup> and two were omitted owing to incomplete data.<sup>128</sup> <sup>133</sup> Overall, there was a statistically significant difference between ezetimibe and statin groups at 3 months (MD 4.61mg/dL; 95% CI -0.05, 9.27mg/dL; p=0.05) (*Figure 28*). Chi<sup>2</sup> and I<sup>2</sup> statistics indicated low levels of heterogeneity and inconsistency (P=0.37, I<sup>2</sup>=0%).

Both studies enrolled adult patients with hypocholesterolaemia.



# Figure 28 Forest plot indicating mean difference in total cholesterol (absolute value) for ezetimibe compared to statins (3 months)

#### Abbreviations

CI = confidence interval, SD = standard deviation.

#### Triglycerides

#### Ezetimibe vs statin, percentage change in triglycerides, 3 months

Four studies provided evidence on percentage change in triglycerides at 3 months.<sup>107 127 128 133</sup> The results were described narratively rather than meta-analysed because it was unclear whether the results from each study were normally distributed.

The mean/median percentage change in the statin group was generally larger than in the ezetimibe group. However, the statistical difference was not reported in all studies, so it was unclear whether ezetimibe and statin groups differed (*Table 13*).<sup>107 127 128 133</sup>

All studies enrolled adult patients with hypocholesterolaemia.<sup>107 127 128 133</sup>

Study	Ezetimibe at baseline follow-up, n	Statin at baseline follow-up, n	p value
Bays 2004 <sup>127</sup> a	145.5 ± 79.1mg/dL	155.3 ± 75.3mg/dL	NR
	-10.7 ± 2.6%, n=148	-20.8 ± 1.2%, n=612	NR
Davidson 2002128 b	190.3 ± 68.2mg/dL	168.7 ± 59.8mg/dL	NR
	-8.3 ± 3.0%, n=61	-16.6 ± 1.4%, n=263	NR
Goldberg 2004 <sup>107</sup> c	163.0 ± 104.0mg/dL	167.0 ± 89.0mg/dL	NR
	-13.2 ± 27.8%, n=90	-15.2 ± 34.1%, n=345	NR
Melani 2003 <sup>133 b</sup>	168.3 ± NR mg/dL	177.2 ± NR mg/dL	NR
	-2.1 ± 3.8%, n=64	-7.6 ± 2.1%, n=205	NR

## Table 13 Ezetimibe compared to statins: percentage change in triglycerides at 3 months

## **Abbreviations**

mg/dL = milligram per decilitre, n = number of patients, NR = not reported.

Notes

a = median ± standard error, b = mean ± standard error, c = median ± standard deviation.

## Ezetimibe vs statin, absolute triglyceride values, 3 months

Two studies provided evidence on the absolute change in triglycerides at 3 months.<sup>134</sup> <sup>135</sup> The results were described narratively rather than meta-analysed because it was unclear whether the results from each study were normally distributed.

Both studies reported no statistically significant differences between the ezetimibe and statins groups at 3 months (p=NS) (*Table 14*).<sup>134 135</sup>

Both studies enrolled adult patients with hypocholesterolaemia.<sup>134 135</sup>

Table 14 Ezetimibe compared to statins: abso	olute change in triglycerides at 3 months
----------------------------------------------	-------------------------------------------

Study	Ezetimibe at baseline follow-up, n	Statin at baseline follow-up, n	p value
Krysiak 2011a <sup>134</sup> a	122.0 ± 11.0mg/dL	120.0 ± 12.0mg/dL	NS
	112.0 ± 10.0mg/dL, n=41	111.0 ± 14.0mg/dL, n=42	NS
Krysiak 2011b <sup>135 a</sup>	118.9 ± 9.7mg/dL	121.6 ± 10.2mg/dL	NS
	113.6 ± 9.5mg/dL, n=23	112.4 ± 10.8mg/dL, n=24	NS

## Abbreviations

**mg/dL** = milligrams per decilitre, **n** = number of patients, **NS** = not significant. **Notes** 

**a** = mean ± standard deviation.

## Sub-group analysis

## Statin type

#### Percentage change in LDL-c, HDL-c, total cholesterol and triglycerides

Five studies were included in this sub-group analysis. However, only studies evaluating simvastatin were meta-analysed.<sup>107 127 128</sup> The remaining statin types were described narratively rather than meta-analysed owing to insufficient study numbers.<sup>126 133</sup>

#### Atorvastatin

In one study, atorvastatin (10–80mg) reported a greater reduction in LDL-c, total cholesterol and triglycerides with similar increases in HDL-c compared to ezetimibe. However, the statistical difference was not reported, so it was unclear whether the groups differed.<sup>126</sup>

#### Pravastatin

In one study, pravastatin (10–40mg) reported a greater reduction in LDL-c, total cholesterol and triglycerides with similar increases in HDL-c compared to ezetimibe. However, the statistical difference was not reported, so it was unclear whether groups differed.<sup>133</sup>

#### Simvastatin

Overall, there was a statistically significant difference between ezetimibe and simvastatin groups for percentage change in LDL-c (p<0.00001) and total cholesterol (p=0.05) with the result favouring simvastatin. There was no significant difference in HDL-c (p=0.09) (*Table 15*).

Ezetimibe resulted in a greater reduction in triglycerides compared to statins in two studies, and there was no difference between the groups in one study. However, the statistical difference was not reported, so it was unclear whether the groups differed.

The dose of simvastatin ranged from 10mg to 80mg.<sup>107 127 128</sup>

## Table 15 Ezetimibe compared to statins: percentage change in LDL-c, HDL-c and total

Statin type	LDL-c mean difference (95% CI)	HDL-c mean difference (95% CI)	Total cholesterol mean difference (95% CI)
Overall			
All statins	17.22% (11.23, 23.22)	-1.42%, (-2.72, -0.12)	12.40%, (8.14, 16.66)
	p<0.00001	p=0.03	p<0.00001
Sub-groups			
Atorvastatin <sup>126 a</sup>	20.53% (18.72, 22.35)	-1.42% (-3.05, 0.20)	13.38% (12.08, 14.69)
(10–80mg)	p=NR	p=NR	p=NR
Pravastatin <sup>133 a</sup>	5.60% (2.50, 8.70)	-2.60% (-5.57, 0.37)	4.00% (1.37, 6.63)
(10–40mg)	p=NR	p=NR	p=NR
Simvastatin <sup>107 127 128</sup>	19.17% (17.47, 20.86)	-0.10% (-3.27, 3.07)	18.60% (15.27, 21.93)
(10–80mg)	p<0.00001	p=0.09	p=0.05

## cholesterol at 3 months according to statin type

#### Abbreviations

CI = confidence interval, HDL-c = high density lipoprotein, LDL-c = low density lipoprotein, NR = not reported. Notes

**a** = Only one study in the sub-group so meta-analysis not performed. Statistical significance based on analysis performed in the study.

Absolute change in LDL-c, HDL-c, total cholesterol and triglycerides

The absolute change in lipids and triglycerides could not be determined owing to insufficient study numbers.

#### Ezetimibe plus statin vs statin

## MACE

One study provided evidence on MACE outcomes at 24 months post-intervention.<sup>120</sup> The number of MACE events was similar between the ezetimibe plus statin and the statin group. Statistical difference was not reported by the study authors, so it was unclear whether the groups differed (*Table 16*).

Outcome	Ezetimibe plus statin	Statin
MACE (all)	10/357 (2.8%) patients	7/363 (1.9%) patients
3P-MACE ª	6 events	4 events
Non-fatal MI	3 events	2 events
Non-fatal stroke	1 event	1 event
Cardiovascular death	2 events	1 event
Non-cardiovascular death	NR	NR
Coronary revascularisation	6 events	5 events
Unstable angina	NR	NR

Table 16 Ezetimibe plus statin compared to statin: MACE outcomes at 24 months

#### **Abbreviations**

**MACE** = major adverse cardiac event, **MI** = myocardial infarction.

#### **Notes**

**a** = 3P-MACE includes non-fatal MI, stroke and cardiovascular death. Unclear if patients experienced multiple events. **Source** 

Kastelein (2008)<sup>120</sup>

#### LDL-c

#### Ezetimibe plus statin vs statin, percentage change in LDL-c, 3-24 months

Seventeen studies provided evidence on the percentage change in LDL-c from 3 to 24 months. Fourteen studies were included in the meta-analysis<sup>106 107 109 120 122 126-128 133 136-140</sup> and three were omitted owing to incomplete data.<sup>134 135 141</sup> Overall, there were statistically significant differences between ezetimibe plus statin and statin groups at all timepoints (*Figure 29*). At 3 months the mean difference was 16.14% (95% CI -19.67, -12.60%; p<0.01) and by 12 months, the difference was -14.24% (95% CI -18.91, - 9.57%; p<0.01). However, Tau<sup>2</sup> and I<sup>2</sup> statistics indicated considerable levels of heterogeneity and inconsistency within the meta-analysis model.

The included studies evaluated ezetimibe plus statins in adults with hypercholesterolaemia in 12 studies,<sup>106 107 109 126-128 133 136-140</sup> adults with FH in 1 study,<sup>120</sup> and adolescents (10–17 years) with heterozygous FH in 1 study.<sup>122</sup> Baseline LDL-c was higher among adolescents and adults with FH compared to adults with other types of hypercholesterolaemia.

	Ezetir	nibe+Stati	n Arm	S	tatin Arm				
Study	Mean	SD	Total	Mean	SD	Total		Weight(%)	MD, 95%CI
3 Months									
Alvarezsala.2008	-49.90	21.80	37.00	-35.20	19.50	39.00	<b>⊢</b> ∎–	2.04	-14.70 [-24.02, -5.38]
Ballantyne.2003	-54.50	14.80	249.00	-42.40	18.80	244.00	. ⊦∎∣	3.60	-12.10 [-15.09, -9.11]
Bays.2004	-53.00	14.70	604.00	-39.00	14.80	612.00	H I	3.83	-14.00 [-15.66, -12.34]
Davidson.2002	-49.90	14.90	274.00	-36.10	14.60	263.00	i i i i i i i i i i i i i i i i i i i	3.70	-13.80 [-16.30, -11.30]
Goldberg.2004	-53.20	17.20	353.00	-38.50	14.20	345.00		3.73	-14.70 [-17.04, -12.36]
Kastelein.2008	-58.76	13.14	357.00	-43.11	16.57	363.00		3.75	-15.65 [-17.83, -13.47]
Masana.2005	-24.37	18.65	355.00	3.49	15.00	78.00	∎	3.40	-27.86 [-31.71, -24.01]
Melani.2003	-37.70	13.55	204.00	-24.30	13.58	205.00	· · ·  =	3.67	-13.40 [-16.03, -10.77]
Robinson.2014	-23.30	33.49	55.00	0.80	33.86	55.00		1.46	-24.10 [-36.69, -11.51]
Mixed-effect Model, (p	< 0.01)						$\diamond$		-16.14 [-19.67, -12.60]
6 Months							· ·		
Ballantyne 2004b	-51 80	13 60	201 00	-37 40	10 60	45 00	<b>-</b>	3 46	-14 40 [-18 02 -10 78]
Bavs.2008	-50.60	13.44	201.00	-40.34	4.62	45.00	, _ ,   <b>=</b>	3.74	-10.26 [-12.56, -7.96]
Kastelein 2008	-59.08	12 78	338.00	-43 72	19 29	342 00	,—,   <b>_</b>	3 71	-15 36 [-17 82 -12 90]
Masana 2005	-24 24	19 49	355.00	2.34	14 59	78.00	,-, 	3 41	-26 58 [-30 40 -22 76]
Ose 2007	-53 70	13.03	539.00	-38.80	13.27	559.00	,-, <u> </u>	3.85	-14 90 [-16 46 -13 34]
Mixed-effect Model, (p	< 0.01)	10.00	000.00	00.00	10.27	000.00	$\sim$	0.00	-16.14 [-20.63, -11.65]
							~		
9 Months	50.00					15.00	1 - 1		
Ballantyne.2004b	-50.39	17.40	201.00	-38.10	13.60	45.00	┝┻┤	3.20	-12.29 [-16.93, -7.65]
Bays.2008	-50.34	14.67	201.00	-41.90	6.94	45.00	. <b> </b> ■	3.63	-8.44 [-11.31, -5.57]
Kastelein.2008	-59.40	12.78	338.00	-43.90	16.09	342.00		3.75	-15.50 [-17.68, -13.32]
Masana.2005	-26.32	17.67	355.00	-1.59	13.51	78.00	∎  i	3.48	-24.73 [-28.25, -21.21]
Vandergraff.2008	-53.99	15.82	126.00	-38.14	15.66	120.00	∎-	3.38	-15.85 [-19.78, -11.92]
Mixed-effect Model, (p	< 0.01)						$\diamond$		-15.35 [-19.93, -10.78]
12 Months									
Ballantyne.2004b	-48.40	18.80	201.00	-38.60	12.40	45.00	-∎-	3.25	-9.80 [-14.26, -5.34]
Bays.2008	-51.03	12.21	201.00	-40.00	5.78	45.00	∎	3.72	-11.03 [-13.42, -8.64]
Kastelein.2008	-58.57	15.99	338.00	-43.64	16.08	342.00		3.71	-14.93 [-17.34, -12.52]
Masana.2005	-24.54	17.67	355.00	-4.29	12.80	78.00	∎	3.51	-20.25 [-23.63, -16.87]
Strony.2008	-44.40	14.20	87.00	-29.12	15.40	22.00		2.56	-15.28 [-22.37, -8.19]
Mixed-effect Model, (p	< 0.01)						$\diamond$		-14.24 [-18.91, -9.57]
15 Months							Ť		
Bays 2008	-48 90	14 67	201.00	-38 50	8 10	45.00	L=-1	3 57	-10 40 [-13 52 -7 28]
Kastelein 2008	-58.60	9.59	338.00	-43.67	16.08	342.00		3.79	-14 93 [-16 92 -12 94]
Rastelein.2006	-38.00	9.59	330.00	-43.07	10.00	342.00		3.79	-14.95 [-10.92, -12.94]
Mixed-effect Model, (p	< 0.01)						$\sim$		-12.73 [-19.78, -5.68]
18 Months									
Kastelein.2008	-57.76	15.99	338.00	-42.25	19.29	342.00	<b>₽</b>	3.67	-15.51 [-18.17, -12.85]
Mixed-effect Model, (p	< 0.01)						$\bigcirc$		-15.51 [-25.50, -5.52]
21 Months									
Kastelein.2008	-58.37	15.99	338.00	-43.01	16.08	342.00	<b> =</b>	3.71	-15.36 [-17.77, -12.95]
Mixed-effect Model, (p	< 0.01)						$\bigcirc$		-15.36 [-25.28, -5.44]
24 Months							-		
Kastelein.2008	-55.60	18.72	322.00	-39.10	12.43	320.00	<b> </b> ■	3.71	-16.50 [-18.96, -14.04]
Mixed-effect Model, (p	< 0.01)						$\bigcirc$		-16.50 [-26.43, -6.57]
Overall heterogeneity:	(p < 0.01.	τ <sup>2</sup> = 24.11. Ι	<sup>2</sup> = 91.93%)				$\checkmark$		
Moderator significance	: (p < 0.01	$\chi^2(df = 8)$	= 249.98)				< Favours Ezetimibe+Statin	Favours Statin>	
						Г	<del>-</del> -		
						-60	-50 -40 -30 -20 -10 0	10	
							Mean Difference (95% CI)		

## Figure 29 Forest plot indicating mean difference in LDL-c (percentage change) for ezetimibe

## plus statin compared to statin (3-24 months)

## **Abbreviations**

**CI** = confidence interval, **LDL-c** = low density lipoprotein-cholesterol, **MD** = mean difference, **SD** = standard deviation. **Notes** 

Horizontal and vertical bars around the estimate (black square) depict the bounds of the confidence intervals.

#### Ezetimibe plus statin vs statin, absolute change in LDL-c, 3-24 months

Thirteen studies provided evidence on the absolute change in LDL-c at 3 to 24 months. Nine studies were included in the meta-analysis<sup>106 109 120 122 134 135 141-143</sup> and four were omitted owing to incomplete data.<sup>128 133 137 140</sup> Overall, there were statistically significant differences between ezetimibe plus statin and statin groups (*Figure 30*). Specifically, at 3 months the mean difference was -16.72mg/dL (95% CI -22.34, -11.11mg/dL; p<0.001). By 15 months, the difference was -18.70mg/dL (95% CI -32.59, -4.81mg/dL; p<0.01). However, Tau<sup>2</sup> and I<sup>2</sup> statistics indicated moderate levels of heterogeneity and inconsistency within the meta-analysis model.

The included studies evaluated ezetimibe plus statins in adults with hypercholesterolaemia in seven studies,<sup>106</sup> <sup>109</sup> <sup>134</sup> <sup>135</sup> <sup>141-143</sup> adults with FH in one study<sup>120</sup> and adolescents (10–17 years) with heterozygous FH in one study.<sup>122</sup> Baseline LDL-c was higher among adolescents and adults with FH compared to adults with other types of hypercholesterolaemia.

	Ezetin	nibe+Stati	n Arm	S	tatin Arm						
Study	Mean	SD	Total	Mean	SD	Total				Weight (%)	MD, 95%Cl
Baseline											
Bays.2008	174.00	27.07	201.00	174.00	27.07	45.00		<b>⊢</b> −		5.93	0.00 [ -8.75, 8.75]
Florentin.2011	178.00	31.00	50.00	172.00	31.00	50.00		H		4.34	6.00 [ -6.15, 18.15]
Kastelein.2008	319.00	65.00	357.00	317.80	66.10	363.00			<b>-</b>	5.50	1.20 [ -8.38, 10.78]
Krysiak.2011a	182.00	8.00	42.00	183.00	10.00	44.00		H	H	8.74	-1.00 [ -4.82, 2.82]
Krysiak.2011b	181.70	10.20	25.00	182.00	10.50	25.00		H		7.67	-0.30 [ -6.04, 5.44]
Liberopoulos.2013	3 177.00	32.00	25.00	176.00	48.00	25.00				1.82	1.00 [-21.61, 23.61]
Moutzouri.2011	177.00	33.00	53.00	176.00	34.00	55.00		F		4.15	1.00 [-11.64, 13.64]
Robinson.2014	119.30	28.10	55.00	123.70	47.90	55.00		⊢		3.45	-4.40 [-19.08, 10.28]
Vandergraff.2008	225.63	43.33	126.00	219.27	43.27	120.00		H		4.90	6.36 [ -4.46, 17.18]
Mixed-effect Model,	(p = 0.71)							<	>		0.94 [ -4.03, 5.90]
3 Months											
Florentin.2011	90.00	20.00	50.00	97.00	23.00	50.00		⊢_∎	H H	6.10	-7.00 [-15.45. 1.45]
Krysiak.2011a	95.00	6.00	39.00	122.00	9.00	42.00		H <b>e</b> H		8.99	-27.00 [-30.31, -23.69]
Krysiak.2011b	100.20	6.90	24.00	120.60	9.10	24.00				8.34	-20.40 [-24.97, -15.83]
Liberopoulos.2013	3 92.00	19.00	25.00	97.00	28.00	25.00		· · ·		3.92	-5.00 [-18.26, 8.26]
Moutzouri.2011	91.00	20.00	53.00	99.00	26.00	55.00				5.94	-8.00 [-16.73, 0.73]
Robinson.2014	96.70	31.40	55.00	124.80	53.10	55.00	H	• 1		3.00	-28.10 [-44.40, -11.80]
Mixed-effect Model,	(p < 0.01)							$\diamond$			-16.72 [-22.34, -11.11]
9 Months											
Vandorgraff 2008	103 47	40.07	126.00	134 60	40.42	120.00				5.21	21 12 [ /1 20 20 06]
vanuergran.2000	103.47	40.97	120.00	134.00	40.42	120.00				J.2 I	-31.13 [-41.30, -20.90]
Mixed-effect Model,	(p < 0.01)						<				-31.13 [-45.96, -16.30]
15 Months											
Bays.2008	85.70	27.07	201.00	104.40	27.07	45.00		⊢■		5.93	-18.70 [-27.45, -9.95]
Mixed-effect Model,	(p < 0.01)						-	$\bigcirc$			-18.70 [-32.59, -4.81]
24 Months											
Kastelein.2008	141.30	52.60	338.00	192.70	60.30	342.00 ⊦				6.07	-51.40 [-59.90, -42.90]
Mixed-effect Model,	(p < 0.01)					$\langle$	$\bigcirc$				-51.40 [-65.14, -37.66]
Overall heterogeneit	ty: (p < 0.01	, τ <sup>2</sup> = 30.32	2, $I^2 = 66.7$	1%)							
Moderator significan	ice: (p < 0.0	$1, \chi^2(df =$	5) = 111.83	3)			< Favour	s Ezetimibe + Statin	Favours	Statin>	
						-					
						-61	0 -40	-20	0 10 20	30	
						-01	Mear	Difference (QF	% CI)	00	
							mean	Difference (30			

## Figure 30 Forest plot indicating mean difference in LDL-c (absolute change) for ezetimibe plus

## statin compared to statin (3–24 months)

## Abbreviations

CI = confidence interval, LDL-c = low density lipoprotein-cholesterol, MD = mean difference, SD = standard deviation.

#### <u>Notes</u>

Horizontal and vertical bars around the estimate (black square) depict the bounds of the confidence intervals.

#### Ezetimibe plus statin vs statin, number of patients achieving LDL-c goals, 3-15 months

Ten studies provided evidence on the number of patients achieving LDL-c goals at 3 months.<sup>106 107 122</sup> <sup>126-128 133 136 138 139</sup> Seven studies were included in the meta-analyses with the analyses stratified according to treatment goals (<130mg/dL<sup>107 127</sup> and <NCEP–ATP III goals<sup>126 128 133 136 138</sup>).

Overall, there were statistically significant differences between ezetimibe plus statin and statin groups in the number of patients achieving LDL-c values <130mg/dL (p<0.00001) and <NCEP-ATP goals (p<0.00001) at 3 months (*Table 17*). The outcomes were subject to low levels of heterogeneity and inconsistency. For the forest plots, refer to *Figure 85* and *Figure 86*.

Treatment goals at 6<sup>139</sup> to 15<sup>106</sup> months were informed by one study each (*Table 17*). At 6, 9 and 12 months, there were statistically significant differences between ezetimibe plus statin and statin groups in the number of patients achieving LDL-c goals <130mg/dL, <70mg/dL and <NCEP–ATP goals. At 15 months, there was statistically significant differences in the number of patients achieving LDL-c goals <130mg/dL (p<0.001) but not <130mg/dL (p=0.45).

The included studies evaluated ezetimibe plus statins in adults with hypercholesterolaemia in nine studies,<sup>106 107 126-128 133 136 138 139</sup> and adolescents (10–17 years) with heterozygous FH in one study.<sup>122</sup>

Length of follow-up LDL-c goal	Number of studies	Heterogeneity	Ezetimibe plus statins n/N (%)	Statins n/N (%)	Risk Ratio (95% Cl)
3 months					
<130mg/dL	2 107 127	Chi <sup>2</sup> =1.45 P=0.23 I <sup>2</sup> =31%	877/954 (91.9%)	763/950 (80.3%)	1.14 (1.09, 1.19) p<0.00001
<70mg/dL ª	1 <sup>127</sup>	NA	234/604 (38.7%)	43/612 (7.0%)	5.51 (4.06, 7.48) p<0.001
<ncep-atp iii<="" td=""><td>5126 128 133 136 138</td><td>Chi<sup>2</sup>=1.04 P=0.90 I<sup>2</sup>=0%</td><td>738/1014 (72.9%)</td><td>482/800 (60.3%)</td><td>1.73 (1.52, 1.96) p&lt;0.00001</td></ncep-atp>	5126 128 133 136 138	Chi <sup>2</sup> =1.04 P=0.90 I <sup>2</sup> =0%	738/1014 (72.9%)	482/800 (60.3%)	1.73 (1.52, 1.96) p<0.00001
6 months					
<130mg/dL ª	1 <sup>139</sup>	NA	508/539 (94.2%)	453/553 (87.3%)	1.15 (1.10, 1.20) p<0.001
<70mg/dL ª	1 <sup>139</sup>	NA	164/539 (30.4%)	39/559 (7.0%)	4.36 (3.14, 6.06) p<0.001
9 months					
<130mg/dL ª	<b>1</b> <sup>122</sup>	NA	97/126 (77.0%)	64/120 (53.3%)	1.44 (1.19, 1.75) p<0.01

Table 17 Ezetimibe plus statin compared to statin: number of patients achieving LDL-c goals (3– 15 months)

Length of follow-up LDL-c goal	Number of studies	Heterogeneity	Ezetimibe plus statins n/N (%)	Statins n/N (%)	Risk Ratio (95% Cl)
12 months					
<ncep-atp iii<="" td=""><td>1<sup>137</sup></td><td>NA</td><td>183/201</td><td>35/45</td><td>2.48 (1.23, 5.01)</td></ncep-atp>	1 <sup>137</sup>	NA	183/201	35/45	2.48 (1.23, 5.01)
а			(91.0%)	(77.8%)	p=0.02
15 months					
<130mg/dL ª	1 <sup>106</sup>	NA	359/397	196/227	1.05 (0.99, 1.11)
			(90.4%)	(86.3%)	p=0.45
<70mg/dL ª	1106	NA	137/399	11/227	7.09 (3.92, 12.81)
			(34.3%)	(4.9%)	p<0.001

### **Abbreviations**

**CI** = confidence interval, **LDL-c** = low density lipoprotein-cholesterol, **n** = number of patients with event, **N** = total number of patients.

#### Notes

**a** = Only one study per outcome so meta-analysis not performed. Statistical significance was based on analysis performed in the study.

#### HDL-c

#### Ezetimibe plus statin vs statin, percentage change in HDL-c, 3-12 months

Sixteen studies provided evidence on the percentage change in HDL-c from 3 to 24 months. Thirteen studies were included in the meta-analysis<sup>107</sup> <sup>109</sup> <sup>120</sup> <sup>122</sup> <sup>126-128</sup> <sup>133</sup> <sup>136-140</sup> and three were omitted owing to incomplete data.<sup>134</sup> <sup>135</sup> <sup>141</sup> Overall, there was a statistically significant difference between ezetimibe plus statin and statin groups at 3 months but not at any other timepoint (*Figure 31*). At 3 months the mean difference was 1.22% (95% CI 0.45, 1.98%; p<0.01). By 12 months, the difference was 1.04% (95% CI -0.43, 2.50%; p=0.17). Tau<sup>2</sup> and l<sup>2</sup> statistics indicated low levels of heterogeneity and inconsistency within the model.

The included studies evaluated ezetimibe plus statins in adults with hypercholesterolaemia in 11 studies,<sup>107</sup> <sup>109</sup> <sup>126-128</sup> <sup>133</sup> <sup>136-140</sup> adults with FH in 1 study<sup>120</sup> and adolescents (10–17 years) with heterozygous FH in 1 study.<sup>122</sup> Baseline HDL-c was slightly lower among adolescents and adults with FH compared to adults with other types of hypercholesterolaemia.

	Arm	Stat	in Arm						
Study	Mean	SD	Total	Mean	SD	Total		Weight(%)	MD, 95%CI
3 Months									
Alvarezsala 2008	0 10	25 40	37 00	-2 40	13 90	39.00	L	0.31	2 50 [-6 77 11 77]
Ballantyne 2003	7.30	11 50	249.00	4 30	11 60	244 00		6 45	3.00[0.96 5.04]
Bave 2004	7.00	12 30	604.00	6.80	12.40	612.00		13 92	0.40 [-0.99 1.79]
Davidson 2002	9.20	13.20	274.00	6.90	12.40	263.00		5.46	2 40 [ 0.33, 1.73]
Goldberg 2004	8.20	13 10	353.00	7.60	11 90	345.00		7 79	0.60 [-1.26, -2.46]
Kastelein 2008	9.86	15.10	357.00	9.45	15.62	363.00		5.26	0.00 [-1.20, 2.40]
Masana 2005	2.00	20.70	355.00	-0.60	14 10	78.00		1.86	2 60 [-1 20 6 40]
Melani 2003	8 10	12 77	204.00	6 70	12.81	205.00		1.86	1 40 [-1.20, 0.40]
Robinson 2014	-0.40	14.76	55.00	0.00	15 14	55.00		4.86	-0.40[-5.99, 5.19]
100113011.2014	-0.40	14.70	55.00	0.00	13.14	55.00		0.00	-0.40 [-0.00, 0.10]
Mixed-effect Model, (p <	: 0.01)						$\diamond$		1.22 [ 0.45, 1.98]
6 Months									
Kastelein.2008	10.68	14.89	338.00	10.44	16.09	342.00	┝──┥	4.94	0.24 [-2.09, 2.57]
Ose.2007	6.40	13.03	539.00	5.60	12.67	559.00	<b>∔∎</b> -	11.60	0.80 [-0.72, 2.32]
Mixed-effect Model, (p =	: 0.33)						$\diamond$		0.63 [-0.64, 1.91]
9 Months									
Kastelein 2008	9 93	15 99	338 00	9 29	15 53	342 00		4 78	0 64 [-1 73 3 01]
Vandergraff 2008	4.67	14.26	126.00	3.68	14.02	120.00		2.15	0.99 [-2.54, 4.52]
Mixed-effect Model (n =	0.46)								0 75 [-1 22 2 72]
mixed-effect model, (p =	0.40)						$\sim$		0.75 [-1.22, 2.72]
12 Months									
Ballantyne.2004b	6.30	13.40	201.00	5.40	3.13	45.00	┝╧┳╌┥	6.28	0.90 [-1.17, 2.97]
Kastelein.2008	10.68	16.54	338.00	10.28	14.98	342.00	<b>⊢</b> ∎−-	4.76	0.40 [-1.97, 2.77]
Strony.2008	7.20	10.60	87.00	3.40	9.00	22.00	<b>⊢</b> −−−−	1.40	3.80 [-0.57, 8.17]
Mixed-effect Model, (p =	0.17)						$\diamond$		1.04 [-0.43, 2.50]
15 Months									
Bays 2008	7.70	13.40	201.00	7.70	13.30	45.00	L	1.45	0.00 [-4.30, 4.30]
Kastelein 2008	9.76	16.54	338.00	10.19	18.30	342.00		3.90	-0.43 [-3.05, 2.19]
Mixed affect Model (n =	0.78)								0.31[.2.55, 1.93]
Mixed-enect Model, (p =	0.70)								-0.51 [-2.55, 1.85]
18 Months									
Kastelein.2008	10.60	15.44	338.00	10.14	17.75	342.00		4.29	0.46 [-2.04, 2.96]
Mixed-effect Model, (p =	0.72)						$\langle \rangle$		0.46 [-2.04, 2.96]
21 Months									
Kastelein 2008	11.24	16.54	338.00	9.33	16.64	342.00	<b>⊨</b> ∎	4.31	1.91 [-0.58, 4.40]
Mixed-effect Model, (p =	0.13)								1.91 [-0.58, 4.40]
24 Mantha							Ţ,		
∠4 WOTUIS Kastelein 2008	10.20	17 9/	322.00	7 80	16 10	320.00		3 86	2 40 [-0 24 5 04]
Nastelein.2000	10.20	17.54	522.00	7.00	10.10	520.00		5.00	2.40 [-0.24, 5.04]
wixed-effect Model, (p =	0.07	0 00 1 <sup>2</sup> -	0.00%)				$\sim$		2.40 [-0.24, 5.04]
Moderator significance:	$(p = 0.02, \chi^2)$	df = 8) =	18.85)						
						<	-avours Statin - Pavours Ezetimibe	++-518[II>	
						-10	-5 0 5	10 15	
							Mean Difference (95% CI	)	

# Figure 31 Forest plot indicating mean difference in HDL-c (percentage change) for ezetimibe plus statin compared to statin (3–24 months)

## Abbreviations

**CI** = confidence interval, **HDL-c** = high density lipoprotein-cholesterol, **MD** = mean difference, **SD** = standard deviation. **Notes** 

Horizontal and vertical bars around the estimate (black square) depict the bounds of the confidence intervals.

#### Ezetimibe plus statin vs statin, absolute change in HDL-c, 3-24 months

Twelve studies provided evidence on the absolute change in HDL-c from 3 to 24 months. Eight studies were included in the meta-analysis<sup>106</sup> <sup>120</sup> <sup>122</sup> <sup>134</sup> <sup>135</sup> <sup>141-143</sup> and four were omitted owing to incomplete data.<sup>128</sup> <sup>133</sup> <sup>137</sup> <sup>140</sup> Overall, there was a statistically significant difference between ezetimibe plus statin and statin groups at 3 months but not at any other timepoint (*Figure 32*). At 3 months, the mean difference was 3.82mg/dL (95% CI 1.37, 6.28mg/dL; p<0.01). By 15 months, the difference was 3.87mg/dL (95% CI -1.67, 9.41mg/dL; p=0.17). Tau<sup>2</sup> and I<sup>2</sup> statistics indicated considerable levels of heterogeneity and inconsistency within the model.

The included studies evaluated ezetimibe plus statins in adults with hypercholesterolaemia in six studies,<sup>106 134 135 141-143</sup> adults with FH in one study<sup>120</sup> and adolescents (10–17 years) with heterozygous FH in one study.<sup>122</sup> Baseline HDL-c was slightly lower among adolescents and adults with FH compared to adults with other types of hypercholesterolaemia.

	Ezetimi	be+Stati	n Arm	5	Statin Arm				
Study	Mean	SD	Total	Mean	SD	Total	١	Weight (%)	MD, 95%CI
Baseline									
Bays.2008	50.27	11.60	201.00	46.40	11.60	45.00	<b>—</b>	5.56	3.87 [ 0.12, 7.62]
Florentin.2011	59.00	14.00	50.00	60.00	13.00	50.00	<b>⊢</b>	3.82	-1.00 [ -6.30, 4.30]
Kastelein.2008	46.70	11.30	357.00	47.40	13.20	363.00	<b>⊢</b> ∎1	8.59	-0.70 [ -2.49, 1.09]
Krysiak.2011a	45.00	3.00	42.00	44.00	3.00	44.00	k <mark>-∎-</mark> i	9.35	1.00 [ -0.27, 2.27]
Krysiak.2011b	46.20	3.60	25.00	46.40	4.20	25.00	⊢-■1	7.99	-0.20 [ -2.37, 1.97]
Liberopoulos.201	3 59.00	11.00	25.00	62.00	12.00	25.00	<b>⊢</b>	2.97	-3.00 [ -9.38, 3.38]
Moutzouri.2011	60.00	12.00	53.00	58.00	13.00	55.00	<b>⊢</b>	4.38	2.00 [ -2.72, 6.72]
Vandergraff.2008	46.27	9.20	126.00	45.96	9.20	120.00	<b>⊢−</b> −1	7.78	0.31 [ -1.99, 2.61]
Mixed-effect Model,	(p = 0.65)								0.43 [-1.41, 2.27]
3 Months									
Florentin.2011	59.00	14.00	50.00	60.00	13.00	50.00	<b>├────</b> ──┤	3.82	-1.00 [ -6.30, 4.30]
Krysiak.2011a	54.00	3.00	39.00	47.00	4.00	42.00	⊢∎⊣	8.99	7.00 [ 5.47, 8.53]
Krysiak.2011b	54.50	3.80	24.00	48.20	3.00	24.00	-∎	8.37	6.30 [ 4.36, 8.24]
Liberopoulos.201	3 60.00	11.00	25.00	64.00	12.00	25.00	<b>├</b> ─── <b>⋼</b> ───┤	2.97	-4.00 [-10.38, 2.38]
Moutzouri.2011	61.00	12.00	53.00	59.00	14.00	55.00	<b>⊢</b>	4.18	2.00 [ -2.91, 6.91]
Mixed-effect Model,	(p < 0.01)						$\bigcirc$		3.82 [ 1.37, 6.28]
9 Months									
Vandergraff.2008	47.66	9.65	126.00	47.47	9.53	120.00	<b>⊢</b> ∎−-1	7.62	0.19 [ -2.21, 2.59]
Mixed-effect Model,	(p = 0.94)								0.19 [-4.54, 4.92]
15 Months									
Bays.2008	54.14	11.60	201.00	50.27	11.60	45.00	<b>—</b> — <b>—</b> ———————————————————————————————	5.56	3.87 [ 0.12, 7.62]
Mixed-effect Model,	(p = 0.17)								3.87 [-1.67, 9.41]
24 Months									
Kastelein.2008	50.90	12.80	322.00	50.70	14.70	320.00	<b>⊢₽</b> −1	8.05	0.20 [ -1.93, 2.33]
Mixed-effect Model,	(p = 0.93)								0.20 [-4.40, 4.80]
Overall heterogenei	ity: (p < 0.0*	1, τ <sup>2</sup> = 4.3	2, I <sup>2</sup> = 70.7	(5%)					
Moderator significar	nce: (p = 0.0	04, χ <sup>2</sup> (df :	= 5) = 11.4	4)			<favours ezetimibe+statin="" favours="" statin=""></favours>		
							-12 -5 0 5 10		
							Mean Difference (95% CI)		

## Figure 32 Forest plot indicating mean difference in HDL-c (absolute change) for ezetimibe plus

## statin compared to statin (3–24 months)

## **Abbreviations**

CI = confidence interval, HDL-c = high density lipoprotein-cholesterol, MD = mean difference, SD = standard deviation. Notes

Horizontal and vertical bars around the estimate (black square) depict the bounds of the confidence intervals.

## Ezetimibe plus statin vs statin, percentage change in total cholesterol, 3-24 months

Sixteen studies provided evidence on the percentage change in total cholesterol from 3 to 24 months. Thirteen studies were included in the meta-analysis<sup>106 107 109 120 122 126-128 133 136 138-140</sup> and three were omitted owing to incomplete data.<sup>134 135 141</sup> Overall, there were statistically significant differences between ezetimibe plus statin and statin groups at all timepoints (*Figure 33*). At 3 months the mean difference was -11.33% (95% CI -12.85, -9.82%; p<0.001) and at 12 months, the difference was -11.30% (95% CI -12.85, -9.82%; p<0.001) and I<sup>2</sup> statistics indicated considerable levels of heterogeneity and inconsistency within the model.

The included studies evaluated ezetimibe plus statins in adults with hypercholesterolaemia in eleven studies,<sup>106 107 109 126-128 133 136 138-140</sup> adults with FH in one study<sup>120</sup> and adolescents (10–17 years) with heterozygous FH in one study.<sup>122</sup> Baseline total cholesterol was higher among adolescents and adults with FH compared to adults with other types of hypercholesterolaemia.

	Ezetin	nibe+Sta	tin Arm	Stat	in Arm				
Study	Mean	SD	Total	Mean	SD	Total		Weight(%	5) MD, 95%Cl
2 Months									
Alverezeele 2008	20.20	14.40	27.00	27 50	14.05	20.00		1 74	10 70 [ 17 10 4 20]
Alvalezsala.2000	-30.20	14.40	37.00	-27.50	14.05	39.00	· · · · · · · · · · · · · · · · · · ·	1.74	-10.70 [-17.10, -4.30]
Ballantyne.2003	-41.10	11.70	249.00	-32.10	11.70	244.00		5.42	-9.00 [-11.07, -0.93]
Bays.2004	-37.60	12.30	604.00	-27.70	12.40	612.00		6.26	-9.90 [-11.29, -8.51]
Davidson.2002	-36.60	11.60	274.00	-25.80	11.40	263.00		5.57	-10.80 [-12.75, -8.85]
Goldberg.2004	-37.70	13.30	353.00	-26.40	11.30	345.00	<b></b>	5.72	-11.30 [-13.13, -9.47]
Kastelein.2008	-48.03	11.90	357.00	-35.12	12.00	363.00	F <b>■</b> -1	5.83	-12.91 [-14.66, -11.16]
Masana.2005	-15.90	22.60	355.00	2.50	15.90	78.00	<b>⊢−</b> ●−−1	3.03	-18.40 [-22.64, -14.16]
Melani.2003	-27.10	11.06	204.00	-17.20	11.09	205.00	. ⊢■	5.31	-9.90 [-12.05, -7.75]
Robinson.2014	-11.30	14.57	55.00	1.40	14.95	55.00	<b>—</b>	2.16	-12.70 [-18.22, -7.18]
Mixed-effect Model, (p < 0.0	01)						$\diamond$		-11.33 [-12.85, -9.82]
6 Months									
Kastelein.2008	-48.44	13.97	338.00	-35.15	11.84	342.00	-∎	5.57	-13.29 [-15.24, -11.34]
Ose.2007	-38.40	10.07	539.00	-27.80	10.25	559.00		6.47	-10.60 [-11.809.40]
Mixed-effect Model, (p < 0.0	01)								-11.84 [-14.64, -9.05]
							$\checkmark$		
9 Months	1000 100-0								
Kastelein.2008	-48.47	13.97	338.00	-35.81	9.43	342.00	. ⊢	5.77	-12.66 [-14.45, -10.87]
Vandergraff.2008	-42.45	12.91	126.00	-29.25	12.81	120.00		4.01	-13.20 [-16.41, -9.99]
Mixed-effect Model, (p < 0.0	01)						$\bigcirc$		-12.88 [-15.98, -9.78]
12 Months									
Ballantyne.2004b	-35.40	14.00	201.00	-27.50	10.40	45.00	<b>⊢</b> ■	3.61	-7.90 [-11.50, -4.30]
Kastelein.2008	-48.00	14.15	338.00	-35.20	11.65	342.00	⊢	5.57	-12.80 [-14.75, -10.85]
Strony.2008	-32.40	10.60	87.00	-19.20	12.70	22.00	· · ·	2.03	-13.20 [-18.96, -7.44]
Mixed-effect Model, (p < 0.0	01)								-11.30 [-14.19, -8.40]
							$\checkmark$		
15 Months									
Bays.2008	-36.20	14.00	201.00	-28.10	10.40	45.00	. <b>⊢_</b> ■	3.61	-8.10 [-11.70, -4.50]
Kastelein.2008	-48.02	13.91	338.00	-35.48	11.65	342.00	├─■─┤	5.59	-12.54 [-14.47, -10.61]
Mixed-effect Model, (p < 0.0	01)						$\bigcirc$		-10.80 [-14.00, -7.60]
18 Months									
Kastelein.2008	-47.29	11.77	338.00	-34.12	14.05	342.00	∎	5.57	-13.17 [-15.12, -11.22]
Mixed-effect Model, (p < 0.0	01)								-13.17 [-17.28, -9.06]
21 Months									
Kastelein 2008	-47.44	6.99	338.00	-35.16	14.05	342.00	┝╼┻╾┥	5.93	-12.28 [-13.95, -10.61]
Mixed-effect Model, (p < 0.0	01)								-12.28 [-16.26, -8.30]
24 Months									
Kastelein.2008	-45.30	14.36	322.00	-31.90	14.31	320.00	∎	5.22	-13.40 [-15.62, -11.18]
Mixed-effect Model, (p < 0.0	01)								-13.40 [-17.64, -9.16]
Overall heterogeneity: (p <	0.01, τ <sup>2</sup> =	3.40, I <sup>2</sup> =	71.24%)						
Moderator significance: (p <	< 0.01, χ <sup>2</sup> (	df = 8) =	567.61)				< Favours Fzatimika+Statin	Favoure St	atin>
						I			
						-2	5 -20 -15 -10 -5	D	
							Mean Difference (95% CI)		

## Figure 33 Forest plot indicating mean difference in total cholesterol (percentage change) for

## ezetimibe plus statin compared to statin (3–24 months)

## Abbreviations

CI = confidence interval, MD = mean difference, SD = standard deviation.

<u>Notes</u>

Horizontal and vertical bars around the estimate (black square) depict the bounds of the confidence intervals.

#### Ezetimibe plus statin vs statin, absolute change in total cholesterol, 3-24 months

Twelve studies provided evidence on the absolute change in total cholesterol from 3 to 24 months. Eight studies were included in the meta-analysis.<sup>106</sup> <sup>120</sup> <sup>122</sup> <sup>134</sup> <sup>135</sup> <sup>141-143</sup> and four were omitted owing to incomplete data.<sup>128</sup> <sup>133</sup> <sup>137</sup> <sup>140</sup> Overall, there were statistically significant differences between ezetimibe plus statin and statin groups at 3, 6, 9 and 24 months (*Figure 34*). Specifically, at 3 months the mean difference was -18.02mg/dL (95% CI -27.95, -8.09mg/dL; p<0.01). By 15 months, the difference was -19.32mg/dL (95% CI -41.16, 2.52mg/dL; p=0.08). However, Tau<sup>2</sup> and I<sup>2</sup> statistics indicated considerable levels of heterogeneity and inconsistency within the model.

The included studies evaluated ezetimibe plus statins in adults with hypercholesterolaemia in six studies,<sup>106 134 135 141-143</sup> adults with FH in one study<sup>120</sup> and adolescents (10–17 years) with heterozygous FH in one study.<sup>122</sup> Baseline total cholesterol was higher among adolescents and adults with FH compared to adults with other types of hypercholesterolaemia.

	Ezetimibe + Statin Arm		Statin Arm		m				
	Mean	SD	Total	Mean	SD	Total		Weight(%	) MD, 95%CI
Baseline									
Bays.2008	259.10	30.93	201.00	259.10	30.93	45.00	⊢.	6.49	0.00 [-10.00, 10.00]
Florentin.2011	264.00	37.00	50.00	254.00	37.00	50.00	⊢∔-	5.31	10.00 [ -4.50, 24.50]
Kastelein.2008	400.00	67.50	357.00	400.00	68.30	363.00	⊢ <b>≑</b> -	- 6.51	0.00 [ -9.92, 9.92]
Krysiak.2011a	255.00	12.00	42.00	259.00	13.00	44.00	⊢∎∔	7.60	-4.00 [ -9.28, 1.28]
Krysiak.2011b	249.50	12.70	25.00	255.00	13.80	25.00	⊢∎∔I	7.16	-5.50 [-12.85, 1.85]
Liberopoulos.2013	253.00	53.00	25.00	266.00	38.00	25.00		3.07	-13.00 [-38.56, 12.56]
Moutzouri.2011	263.00	39.00	53.00	256.00	41.00	55.00	⊢ <u></u>	<b>-</b> 5.16	7.00 [-8.09, 22.09]
Vandergraff.2008	292.43	45.46	126.00	285.47	45.46	120.00	⊢ <del>∔</del> -	<b>■</b> 6.13	6.96 [-4.40, 18.32]
Mixed-effect Model, (p =	0.91)						$\sim$	>	0.47 [ -7.77, 8.71]
2 Months									
5 Wonths	170.00	24.00	50.00	174.00	27.00	50.00		6.40	4 00 [ 14 01 6 01]
Knysick 2011a	157.00	24.00	20.00	101.00	10.00	42.00		7 0.49	24.00 [-14.01, 0.01]
Krysiak.2011a	162.70	10.00	39.00	191.00	19.00	42.00		7.30	-34.00 [-40.70, -27.30]
Kryslak.2011D	160.00	20.00	24.00	197.50	10.70	24.00	F=	7.40	-33.60 [-39.66, -27.94]
Moutzouri 2011	171.00	29.00	25.00	175.00	21.00	25.00		5.05	-0.00 [-21.53, 9.53]
Moulzoun.2011	171.00	24.00	55.00	176.00	31.00	55.00		7 0.30	-5.00 [-15.43, 5.43]
Mixed-effect Model, (p <	0.01)						$\langle \rangle$		-18.02 [-27.95, -8.09]
9 Months									
Vandergraff.2008	167.02	42.09	126.00	200.20	41.51	120.00	⊢-∎1	6.38	-33.18 [-43.63, -22.73]
Mixed-effect Model, (p <	0.01)								-33.18 [-55.66, -10.70]
15 Months	100.00	~~ ~~				15.00		0.75	
Bays.2008	166.28	30.93	201.00	185.60	27.07	45.00	■1	6.75	-19.32 [-28.31, -10.33]
Mixed-effect Model, (p =	0.08)								-19.32 [-41.16, 2.52]
24 Months									
Kastelein.2008	217.30	56.40	322.00	270.60	61.50	320.00	⊢■→	6.72	-53.30 [-62.43, -44.17]
Mixed-effect Model, (p <	0.01)								-53.30 [-75.20, -31.40]
Overall heterogeneity: (p	< 0.01, τ <sup>2</sup> =	103.15,	l <sup>2</sup> = 81.96	%)					
Moderator significance: (	(p < 0.01, χ <sup>2</sup>	<sup>2</sup> (df = 5) =	= 46.80)				< Favours Ezatimiha+Statio	Favours Statin>	
							-70 -50 -30 -10 0	10 20 30	
							Mean Difference (95% (	20 00	
							Mean Difference (3070 C	.,	

## Figure 34 Forest plot indicating mean difference in total cholesterol (absolute change) for

## ezetimibe plus statin compared to statin (3–24 months)

## Abbreviations

**CI** = confidence interval, **MD** = mean difference, **SD** = standard deviation.

<u>Notes</u>

Horizontal and vertical bars around the estimate (black square) depict the bounds of the confidence intervals.

## Triglycerides

#### Ezetimibe plus statin vs statin, percentage change in triglycerides, 3-24 months

Twelve studies provided evidence on the percentage change in triglycerides from 3 to 24 months.<sup>106 107</sup> <sup>109 120 122 127 128 133 136-139</sup> The results were described narratively rather than meta-analysed because it was unclear whether the results from each study were normally distributed.

At 3 months, there were statistically significant differences favouring ezetimibe plus statin in five studies,<sup>107 127 128 133 138</sup> no difference in one study<sup>136</sup> and statistical differences were not reported in one study (*Table 18*).<sup>109</sup> There were significant differences favouring ezetimibe plus statin at 6 to 24 months in all studies.<sup>106 120 122 137 139</sup>

The included studies evaluated ezetimibe plus statins in adults with hypercholesterolaemia in 10 studies,<sup>106 107 109 127 128 133 136-139</sup> adults with FH in 1 study<sup>120</sup> and adolescents (10–17 years) with heterozygous FH in 1 study.<sup>122</sup> Baseline triglycerides were similar between adolescents and adults with FH compared to adults with other types of hypercholesterolaemia.

Study	Ezetimibe plus statin at baseline	Statin at baseline	p value		
	follow-up, n	follow-up, n			
3 months					
Alvarez-Sala 2008136	150.58 ± 26.57mg/dL	141.72 ± 62.00mg/dL	0.30		
а	-21.00 ± 24.90%, n=37	-3.8 ± 35.10%, n=39	0.20		
Bays 2004 <sup>127 b</sup>	153.3 ± 83.3mg/dL	155.3 ± 75.3mg/dL	NR		
	-24.3 ± 1.1%, n=604	-20.8 ± 1.2%, n=612	<0.001		
Davidson 2002 <sup>128 c</sup>	178.8 ± 65.1mg/dL	168.7 ± 59.8mg/dL	NR		
	-24.1 ± 1.4%, n=274	-16.6 ± 1.4%, n=263	<0.01		
Goldberg 2004 <sup>107</sup> a	169 ± 93mg/dL	167 ± 89mg/dL	NR		
	-28.0 ± 28.0%, n=353	-15.2 ± 34.1%, n=345	<0.001		
Masana 2005 <sup>138 c</sup>	131 ± 4.1mg/dL	128 ± 8.5mg/dL	NR		
	-8.2 ± 1.7%, n=350	5.4 ± 3.4%, n=788	<0.001		
Melani 2003 <sup>133 c</sup>	177.15 ± NR mg/dL	177.15 ± NR mg/dL	NR		
	-17.6 ± 2.1%, n=204	-7.6 ± 2.1%, n=205	<0.01		
Robinson 2014 <sup>109 d</sup>	123 (89 –158)	114 (85–154)	NR		
	-5.8 (-19.0–24.9), n=55	1.6 (-17.7–32.9), n=55	NR		
6 months					
Ose 2007 <sup>139 a, e</sup>	150.58 ± 79.72mg/dL	150.58 ± 79.72mg/dL	NR		
	-24.6% (-26.6, -22.7), n=539	-20.2% (-22.4, -17.9), n=559	<0.001		

Table 18 Ezetimibe plus statin compared to statin: percentage change in triglycerides at 3–24 months

Study	Ezetimibe plus statin at baseline follow-up, n	Statin at baseline follow-up, n	p value			
9 months						
Van der Graff 2008 <sup>122</sup>	89 ± 49.3mg/dL	88 ± 38.84mg/dL	0.88			
а	-20 ± 23.76%, n=126	76%, n=126 -13.04 ± 39%, n=120				
12 months						
Ballantyne 2004b137 d	159.43 (124–212.58)	159.43 (115.15–203.70)	NR			
	-29.6% (-40.3, -15.1), n=201	16.9% (-30.7, 5.2), n=45	<0.01			
15 months						
Bays 2008 <sup>106 d</sup>	168.3 ± 88.57mg/dL	168.3 ± 97.43mg/dL	NR			
	-25.4% (-28.0, -22.9), n=201	-18.4% (-22.1, -14.2), n=45	<0.001			
24 months						
Kastelein 2008120 d	157mg/dL (113–217)	160mg/dL (114–227)	0.84			
	-29.8% (-43.5–11.5), n=357	-23.2% (-37.0–1.7), n=363	<0.01			

## Abbreviations

mg/dL = milligram per decilitre, n = number of patients, NR = not reported.

<u>Notes</u>

 $\mathbf{a}$  = median  $\pm$  standard deviation,  $\mathbf{b}$  = median  $\pm$  standard error,  $\mathbf{c}$  = mean  $\pm$  standard error,  $\mathbf{d}$  = median interquartile range,  $\mathbf{e}$ 

= median (95% confidence interval).

## Ezetimibe plus statin vs statin, absolute change in triglycerides, 3-24 months

Eight studies provided evidence on absolute change in triglycerides from 3 to 24 months.<sup>106 120 122 134 135</sup> <sup>141-143</sup> The results were described narratively rather than meta-analysed because it was unclear whether the results from each study were normally distributed.

There were no statistically significant differences between ezetimibe plus statin and statin groups for absolute change in triglycerides at 3<sup>134 135 141-143</sup> and 15 months (*Table 19*).<sup>106</sup> At 9 and 24 months, there were statistically significant differences in favour of ezetimibe plus statin.<sup>120 122</sup>

The included studies evaluated ezetimibe plus statins in adults with hypercholesterolaemia in six studies,<sup>106 134 135 141-143</sup> adults with FH in one study<sup>120</sup> and adolescents (10–17 years) with heterozygous FH in one study.<sup>122</sup> Baseline triglycerides were similar between adolescents and adults with FH compared to adults with other types of hypercholesterolaemia.

## Table 19 Ezetimibe plus statin compared to statin: absolute change in triglycerides at 3-24

Study	Ezetimibe plus statin at baseline	Statin at baseline	p value			
3 months	ronow-up, n	ronow-up, n				
5 11011015		T				
Florentin 2011 <sup>141 a</sup>	117mg/dL (48–237)	111mg/dL (58–241)	NS			
	95mg/dL (41–173), n=50	92mg/dL (48–200), n=50	NS			
Krysiak 2011a <sup>134 b</sup>	124 ± 12mg/dL	120 ± 12mg/dL	NS			
	109 ± 11mg/dL, n=39	111 ± 14mg/dL, n=42	NS			
Krysiak 2011b <sup>135 b</sup>	119.2 ± 12mg/dL	121.6 ± 10.2mg/dL	NS			
	107.9 ± 12.8mg/dL, n=24	112.4 ± 10.8mg/dL, n=24	NS			
Liberopoulos 2013 <sup>142</sup> a	109mg/dL (58–194)	104mg/dL (73–210)	NS			
	92mg/dL (58–166), n=166	94mg/dL (61–160), n=25	NS			
Moutzouri 2011 <sup>143</sup> a	123mg/dL (48–237)	111mg/dL (55–241)	NS			
	94mg/dL (41–174), n=41	93mg/dL (54–200), n=55	NS			
9 months	-					
Van der Graff 2008 <sup>122 c</sup>	89.0 ± 49.3mg/dL	88.0 ± 38.84mg/dL	0.88			
	71.0 ± 38.14mg/dL, n=126	81.0± 39.07mg/dL, n=120	0.01			
15 months						
Bays 2008 <sup>106 c</sup>	168.3 ± 88.57mg/dL	168.3 ± 97.43mg/dL	NR			
	124.0 ± 62.0mg/dL, n=201	132.86 ± 70.86mg/dL, n=45	NR			
24 months						
Kastelein 2008120 d	157mg/dL (113–217)	160mg/dL (114–227)	0.84			
	108mg/dL (82–148)	120mg/dL (89–164)	<0.01			

## months

## Abbreviations

**n** = number of patients, **NR** = not reported, **NS** = not significant.

## Notes

 $\mathbf{a}$  = median (range),  $\mathbf{b}$  = mean  $\pm$  standard deviation,  $\mathbf{c}$  = median  $\pm$  standard deviation,  $\mathbf{d}$  = median interquartile range.

## Ezetimibe plus statin vs statin, change in markers of vascular damage, 24 months

One study provided evidence on markers of vascular damage, as measured by intima-media thickness at 24 months post-intervention.<sup>120</sup> Overall, there were no statistically significant differences between ezetimibe plus statin and statin groups in markers of vascular damage when assessing the carotid artery or femoral artery or when averaging both together (*Table 20*).

Outcome	Timepoint	Ezetimibe plus statin	Statin	p value		
Mean intima-media th	nickness of carotid arter	ry (mm)				
Common carotid	Baseline	0.67 ± 0.16	0.68 ± 0.16	0.45		
artery	24 months	0.68 ± 0.16	0.68 ± 0.15	0.93		
Carotid bulb	Baseline	0.79 ± 0.22	0.80 ± 0.20	0.51		
	24 months	0.81 ± 0.23	0.81 ± 0.22	0.37		
Internal carotid artery	Baseline	0.62 ± 0.17	0.61 ± 0.17	0.42		
	24 months	0.64 ± 0.17	0.62 ± 0.17	0.21		
Femoral artery (mm)						
Mean intima-media thickness	Baseline	0.77 ± 0.30	0.80 ± 0.39	0.14		
	24 months	0.79 ± 0.33	0.80 ± 0.37	0.16		
Carotid and femoral artery (mm)						
Average	Baseline	0.73 ± 0.19	0.75 ± 0.22	0.18		
	24 months	0.75 ± 0.22	0.76 ± 0.23	0.15		

# Table 20 Ezetimibe plus statin compared to statin: intima-media thickness in carotid and femoral arteries at 24 months

Source

Kastelein (2008)120

#### Sub-groups analysis

## Statin type

Percentage change in LDL-c, HDL-c, total cholesterol and triglycerides

#### Atorvastatin

In one study, ezetimibe plus atorvastatin (10–80mg) showed significant differences to atorvastatin (10– 80mg) in LDL-c, HDL-c and total cholesterol and triglycerides at 3 and 12 months (p<0.01 for all outcomes).<sup>126 137</sup> The results favoured ezetimibe plus atorvastatin.

#### Fluvastatin

In one study, ezetimibe plus fluvastatin (80mg) showed significant differences to fluvastatin (80mg) in LDL-c and total cholesterol at 3 months (p<0.001 for both outcomes).<sup>136</sup> The results favoured ezetimibe plus fluvastatin. There was no difference in HDL-c or triglycerides (p=NS).

#### Pravastatin

In one study, ezetimibe plus pravastatin (10–40mg) showed significant differences to pravastatin (10–40mg) in LDL-c, HDL-c, total cholesterol and triglycerides at 3 months (p<0.01 for all outcomes).<sup>133</sup> The results favoured ezetimibe plus pravastatin.

#### Simvastatin

For ezetimibe plus simvastatin compared to simvastatin there were significant differences in LDL-c and total cholesterol at 3, 9, 12 and 24 months as inferred by meta-analyses. At 3 months the difference in LDL-c was -17.04% (95% CI -22.02, -12.05; p<0.0001) and at 12 months the difference was -15.32% (95% CI -21.10, -9.54, p<0.0001). The mean difference in total cholesterol at 3 months was -12.04% (95% CI -13.94, -10.14; p<0.001) and at 12 months it was -12.91% (95% CI -16.45, -9.37, p<0.001). There were statistically significant differences in HDL-c at 3 months (MD 0.88%, 95% CI 0.00, 1.77; p<0.05) but not at any other timepoints (e.g. 12 months [MD 1.17%; 95% CI -0.91, 3.26; p>0.05]). The Tau<sup>2</sup> and l<sup>2</sup> statistics indicated considerable levels of heterogeneity for all outcomes.

The percentage change in triglycerides was not meta-analysed because it was unclear whether triglyceride scores were normally distributed across the included studies. However, there were significant differences between ezetimibe plus simvastatin and simvastatin in triglycerides at 3, 6, 15 and 24 months.<sup>106 107 120 122 127 128 138 139</sup>

Dose of simvastatin was 10mg,<sup>140</sup> 40mg,<sup>122</sup> 80mg<sup>120</sup> or 10–80mg<sup>106</sup> <sup>107</sup> <sup>120</sup> <sup>122</sup> <sup>127</sup> <sup>128</sup> <sup>138-140</sup> in the intervention and comparator arms. Ezetimibe was fixed at 10mg in all studies.

For further information regarding sub-group analysis refer to Section 15.4.3 (Appendix D), Table 102.

Absolute change in LDL-c, HDL-c, total cholesterol and triglycerides

#### Atorvastatin

In one study, ezetimibe plus atorvastatin (10mg) compared to atorvastatin (10mg) showed no significant differences to atorvastatin (10mg) in LDL-c at 3 months (p=NS). Changes in HDL-c and total cholesterol were not reported by the study.<sup>109</sup>

#### Simvastatin

For ezetimibe plus simvastatin compared to simvastatin there were significant differences in LDL-c at 3, 9, 15 and 24 months, as inferred by meta-analyses.<sup>106 120 122 134 135 141 143</sup> At 3 months the difference was -15.58mg/dL (95% CI -21.63, -9.52; p<0.001). By 15 months the difference was -18.70mg/dL (95% CI - 32.97, -4.43; p=0.05). The Tau<sup>2</sup> and I<sup>2</sup> statistics indicated considerable levels of heterogeneity for all outcomes.

HDL-c, total cholesterol and triglycerides were not analysed because all of the included studies utilised ezetimibe plus simvastatin.

The dose of simvastatin was 40mg,<sup>122 134 135 141 143</sup> 80mg<sup>120</sup> and between 10–80mg<sup>106</sup> in the intervention and comparator arms. Ezetimibe was fixed at 10mg in all studies.

For further information regarding sub-group analysis refer to Section 15.4.3 (Appendix D), Table 103.

#### **Adolescents**

In one study, there were statistical differences in favour of ezetimibe plus statin in the absolute and percentage changes in LDL-c, total cholesterol and triglycerides at 6 months (p<0.01 for all outcomes).<sup>122</sup> There was no difference in the absolute or percentage change in HDL-c (p>0.05 for both outcomes). For further information regarding sub-group analysis refer to **Section 15.4 Appendix D**, **Table 101**.

## Hypercholesterolaemia with ASCVD

*Table 21* provides a summary of the main pooled clinical effectiveness outcomes comparing ezetimibe plus statins to statin monotherapy. The 3- and 12-month timepoints were selected as representative timepoints for short- and long-term timepoints, respectively. A negative mean difference for LDL-c and total cholesterol and a positive mean difference for HDL-c indicates the results favour the intervention group.

By 3 months, there were statistically significant differences (orange shading) between ezetimibe plus statins and statin in the number of patients achieving LDL-c goals and absolute and percentage changes in LDL-c and total cholesterol. There was no difference in HDL-c. At 12 months, the statistical effect persisted for the absolute change in LDL-c and total cholesterol but not for the percentage change. The absolute change in lipids at 12 months was mainly driven by the IMPROVE-IT trial.<sup>52</sup>

The results for MACE were not pooled. However, in one study of 18,144 patients, there was a statistically significant difference in incidence of 3P-MACE (p=0.003), non-fatal MI (p=0.002) and ischaemic stroke (p=0.008) between ezetimibe plus simvastatin and simvastatin groups, with a lower incidence in the ezetimibe plus simvastatin group.<sup>52</sup> There were no differences in cardiovascular death (p=1.00), coronary revascularisation (p=0.11) and unstable angina (p=0.62).

Outcome	Mean difference (95% CI) or risk ratio (95% CI)							
	3 months	6 months	9 months	12 months	24 months			
LDL-c	-13.41%	-9.66%	NR	-9.60%	NR			
	(-19.26, -7.56)	(-18.96, -0.37)		(-27.33, 8.13)				
	-17.22mg/dL	-10.23mg/dL	-6.17mg/dL	-16.82mg/dL	-15.00mg/dL			
	(-24.23, -10.22)	(-33.25, 12.79)	(-25.78, 13.44)	(-22.51, -11.12)	(-45.21, 15.21)			
Achieving	1.91	2.59	NR	NR	NR			
goals <sup>a</sup>	(1.43, 2.53)	(1.62, 4.16)						
HDL-c	1.01%	2.89%	NR	-2.50%	NR			
	(-1.56, 3.58)	(-0.66, 6.44)		(-13.52, 8.52)				
	0.42mg/dL	NR	14.83mg/dL	0.59mg/dL	2.00mg/dL			
	(-1.82, 2.67)		(0.18, 29.48)	(-0.38, 1.56)	(-7.80, 11.80)			
Total	-8.31%	-7.01%	NR	-7.90%	NR			
cholesterol	(-13.33, -3.29)	(-14.77, 0.75)		(-20.22, 4.22)				
	-21.18mg/dL	NR	-4.70mg/dL	-17.84mg/dL	-16.00mg/dL			
	(-28.93, -13.34)		(-24.46, 15.06)	(-24.12, -11.56)	(-50.30, 18.30)			

Table 21 Summary of meta-analyses results for patients with hypercholesterolaemia with ASCVD

Abbreviations

CI = confidence interval, HDL-c = high density lipoprotein-cholesterol, LDL-c = low density lipoprotein-cholesterol, NA = not applicable, NR = not reported.
#### <u>Notes</u>

For LDL-c and total cholesterol, negative mean difference favours intervention, positive mean difference favours comparators. For HDL-c, positive mean difference favours intervention, negative mean difference favours comparators. For number of patients achieving LDL-c goals, risk ratio >1 favours intervention, risk ratio <1 favours comparator. **No shading** = no statistically significant difference between groups (p>0.05) **Orange shading** = statistically significant difference between groups (p<0.05) in favour of ezetimibe or ezetimibe plus statins **a** = risk ratio 95% CI of number of patients achieving <100mg/dL.

#### Ezetimibe plus statin vs statin

#### MACE

Three studies provided evidence on MACE outcomes from one to seven years.<sup>52 144 145</sup> The studies were described narratively rather than meta-analysed owing to the different lengths of follow-up (*Table 22*).

At 12 months, there was no difference in the incidence of 4P-MACE (cardiovascular death, non-fatal MI, ischaemic stroke, unstable angina) between ezetimibe plus statin and statin groups (p=0.11).<sup>144</sup> Statistical difference was not reported for the remaining MACE outcomes at 1 or 2 years so it is unclear whether ezetimibe plus statin and statin groups differed.<sup>144 145</sup>

At seven years, there were statistically significant differences in favour of ezetimibe plus simvastatin with respect to 5P-MACE (cardiovascular death, major coronary event and non-fatal stroke; p=0.016), 3P-MACE (cardiovascular death, MI and ischaemic stroke; p=0.001), MI (p=0.002) and ischaemic stroke (p=0.008).<sup>52</sup> There were no statistical differences in cardiovascular death (p=1.00), non-cardiovascular death (p=0.79), coronary revascularisation (p=0.11) and unstable angina (p=0.62) between ezetimibe plus simvastatin and simvastatin.

	1 year			2 years			7 years			
Outcome	Ezetimibe plus statin n/N (%)	Statin n/N (%)	p value	Ezetimibe plus statin n/N (%)	Statin n/N (%)	p value	Ezetimibe plus statin n/N (%)	Statin n/N (%)	HR (95% Cl) p value	
5P-MACE <sup>a</sup>	NR	NR	NA	NR	NR	NA	2,572/9,067 (32.7%)	2,742/9,077 (34.7%)	0.93 (0.89, 0.99) p=0.016	
4P-MACE b	9/126 (7.1%)	18/136 (13.2%)	p=0.11	NR	NR	NR	NR	NR	NR	
3P-MACE °	1/126 (0.79%)	7/136 (5.1%)	NR	4/18 (22.2%)	2/16 (12.5%)	NR	1,718/9,067 (18.9%)	1,918/9,077 (21.1%)	0.90 (0.84, 0.96) p=0.003	
Non-fatal MI	0/126 (0.0%)	1/136 (0.7%)	NR	NR	NR	NA	945/9,067 (12.8%)	1,083/9,077 (14.4%)	0.87 (0.80, 0.95) p=0.002	
Ischaemic stroke	1/126 (0.8%)	1/136 (0.7%)	NR	NR	NR	NA	236/9,067 (3.4%)	297/9,077 (4.1%)	0.79 (0.67, 0.94) p=0.008	
Cardiovascular death	0/126 (0.0%)	5/136 (3.7%)	NR	NR	NR	NA	537/9,067 (6.9%)	538/9,077 (6.8%)	1.00 (0.89, 1.13) p=1.00	
Non-cardiovascular death	NR	NR	NA	NR	NR	NA	232/9,067 (2.6%)	238/9,077 (2.6%)	0.98 (0.81, 1.17) p=0.79	
Coronary	NR	NR	NA	NR	NR	NA	1,690/9,067	1,793/9,077	0.95	

Table 22 Ezetimibe plus statin vs statin: MACE at 1–7 years

	1 year			2 years			7 years			
Outcome	Ezetimibe plus statin n/N (%)	Statin n/N (%)	p value	Ezetimibe plus statin n/N (%)	Statin n/N (%)	p value	Ezetimibe plus statin n/N (%)	Statin n/N (%)	HR (95% Cl) p value	
revascularisation							(21.8%)	(23.4%)	(0.89, 1.01) p=0.11	
Hospitalised for unstable angina	1/126 (0.8%)	2/136 (1.5%)	NR	NR	NR	NA	156/9,067 (2.1%)	148/9,077 (1.9%)	1.06 (0.85, 1.33) p=0.62	

#### **Abbreviations**

CI = confidence interval, HR = hazard ratio, MACE = major adverse cardiac event, MI = myocardial infarction, NA = not applicable, NR = not reported.

# Notes

1 year = ezetimibe (10mg) plus rosuvastatin (10mg) vs rosuvastatin (10mg); 2 and 7 years = ezetimibe (10mg) plus simvastatin (40mg) vs simvastatin (40mg)

Non-cardiovascular death = death from any cause – (cardiovascular causes and coronary heart disease).

a = 5P-MACE includes death from cardiovascular causes, major coronary event (MI, hospitalisation for unstable angina or coronary revascularisation within 30 days) and non-fatal stroke

**b** = 4P-MACE includes death from cardiac causes, non-fatal MI, ischaemic stroke and unstable angina.

c = 3P MACE includes cardiovascular death, non-fatal MI and ischaemic stroke.

For the hazard ratio, numbers >1 indicate risks were lower in the statin group (higher event rate in the ezetimibe plus statin group), numbers <1 indicate risks were lower in the ezetimibe plus statin group (higher event rate in the statin group).

# Source

One-year data obtained from Kouvelos (2013),<sup>144</sup> two-year data obtained from West (2011)<sup>145</sup> and seven-year data obtained from Cannon (2015).<sup>52</sup>

#### LDL-c

#### Ezetimibe plus statin vs statin, percentage change in LDL-c, 3-12 months

Twelve studies provided evidence on the percentage change in LDL-c from 3 to 12 months. Eleven studies were included in the meta-analysis<sup>146-156</sup> and one was omitted owing to incomplete data.<sup>157</sup> Overall, there were statistically significant differences between ezetimibe plus statin and statin groups at 3 and 6 months but not at any other timepoint (*Figure 35*). At 3 months, the mean difference was - 13.41% (95% CI -19.26, -7.56; p<0.01) and by 12 months, the difference was -9.60% (95% CI -27.33, 8.13; p=0.29). However, Tau<sup>2</sup> and I<sup>2</sup> statistics indicated considerable levels of heterogeneity and inconsistency within the model.

The trial population was heterogeneous and included patients with hypercholesterolaemia and established CHD (or its risk equivalent),<sup>146 150 152 155 156</sup> patients with hypercholesterolaemia at high or very high risk of ASCVD who were already receiving statins,<sup>147-149</sup> patients with hypercholesterolaemia with CHD and/or type 2 diabetes,<sup>154</sup> and those with established ASCVD<sup>153</sup> or who had had a recent MI.<sup>151</sup>

	Ezetim	ibe+Statir	Arm	5	Statin Arm	1			
Study	Mean	SD	Total	Mean	SD	Total		Weight(%)	MD, 95%CI
3 Months									
Ballantyne.2004a	-50.20	12.60	250.00	-44.30	14.10	246.00	HEH	7.71	-5.90 [ -8.25, -3.55]
Ballantyne.2019	-23.20	20.40	86.00	1.80	21.40	41.00	⊢-∎1	6.39	-25.00 [-32.84, -17.16]
Bays.2015	-29.70	21.70	46.00	-8.50	29.40	53.00	⊢_∎	5.69	-21.20 [-31.30, -11.10]
Farnier.2016	-19.30	38.10	50.00	-17.10	28.40	48.00	H	- 4.74	-2.20 [-15.47, 11.07]
McKenney2006	-57.00	14.61	67.00	-53.00	14.94	70.00	<b>⊢</b> ∎-1	7.21	-4.00 [ -8.95, 0.95]
Nicholl.2017	-27.30	22.03	91.00	0.04	14.60	40.00	⊢∎-1	6.82	-27.34 [-33.74, -20.94]
Roetersvanlennep.2008	-29.10	13.60	178.00	-11.50	16.77	189.00	H∎H	7.59	-17.60 [-20.72, -14.48]
Stein.2004	-33.20	15.81	278.00	-20.30	16.16	290.00	HEH	7.67	-12.90 [-15.53, -10.27]
Zieve.2010	-23.00	28.97	516.00	-18.00	34.53	509.00	⊦∎⊣	7.44	-5.00 [ -8.90, -1.10]
Mixed-effect Model, (p < 0	.01)						$\diamond$		-13.41 [-19.26, -7.56]
4.5 Months									
Ballantyne.2004a	-55.60	9.30	242.00	-49.10	13.90	237.00	Here in the second seco	7.74	-6.50 [ -8.624.38]
Mixed-effect Model, (p = 0	.44)							-	-6.50 [-22.97, 9.97]
6 Months									
Ballantyne.2004a	-59.40	10.70	232.00	-52.50	15.10	228.00	HEH	7.70	-6.90 [ -9.30, -4.50]
Bays.2015	-22.60	29.20	46.00	-5.00	33.50	53.00	⊢∎	5.01	-17.60 [-29.95, -5.25]
Farnier.2016	-11.00	50.90	50.00	-16.30	28.40	48.00	<b>⊢</b>	3.96	5.30 [-10.94, 21.54]
Feldman.2004	-53.00	12.50	108.00	-38.00	12.50	246.00	H∎H	7.64	-15.00 [-17.83, -12.17]
Mixed-effect Model, (p = 0	.04)						$\diamond$		-9.66 [-18.96, -0.37]
12 Months									
Hougaard.2017	-62.00	19.20	39.00	-52.40	10.90	41.00	⊢-∎1	6.68	-9.60 [-16.49, -2.71]
Mixed-effect Model, (p = 0	.29)								-9.60 [-27.33, 8.13]
Overall heterogeneity: (p <	0.01, τ <sup>2</sup> = 6	69.45, I <sup>2</sup> =	93.87%)						
Moderator significance: (p	< 0.01, χ <sup>2</sup> (	df = 4) = 2	6.04)				< Equoure Exetimited Statin	Envoure Statio	
						-6	0 -40 -20 0	10 20 30	
							Mean Difference (95% C	1)	

#### Figure 35 Forest plot indicating mean difference in LDL-c (percentage change) for ezetimibe

#### plus statin compared to statin (3-12 months)

#### **Abbreviations**

CI = confidence interval, LDL-c = low density lipoprotein-cholesterol, MD = mean difference, SD = standard deviation. Notes

#### Ezetimibe plus statin vs statin, absolute change in LDL-c, 3-24 months

Nine studies provided evidence on the absolute change in LDL-c from 3 to 24 months. Eight studies were included in the meta-analysis<sup>52</sup> <sup>111</sup> <sup>144</sup> <sup>145</sup> <sup>151</sup> <sup>158-160</sup> and one was omitted owing to incomplete data.<sup>161</sup> Overall, there were statistically significant differences between ezetimibe plus statin and statin groups at 3 and 12 months but not at any other timepoint (*Figure 36*). At 3 months, the mean difference was -17.22mg/dL (95% CI -24.23, -10.22mg/dL; p<0.01) and by 12 months, the difference was -16.82mg/dL (95% CI -22.51, -11.12mg/dL; p<0.01). However, Tau<sup>2</sup> and I<sup>2</sup> statistics indicated considerable levels of heterogeneity and inconsistency within the model.

The trial population was heterogeneous and included patients with ACS,<sup>52</sup> recent MI,<sup>151</sup> coronary artery disease,<sup>158</sup> peripheral artery disease,<sup>145</sup> chronic kidney disease,<sup>160</sup> hypercholesterolaemia with CHD or risk equivalent,<sup>159</sup> and patients who had had a recent coronary event<sup>111</sup> or undergone vascular surgery.<sup>144</sup>

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	Ezetim	ibe+Stati	n Arm		Statin Arr	n			
Study	Mean	SD	Total	Mean	SD	Total		Weight(%)	MD, 95%CI
Baseline									
Cannon.2015	95.00	22.96	8990.00	95.00	23.11	9009.00	÷	14.69	0.00 [ -0.67, 0.67]
Hougaard.2017	143.08	27.07	43.00	158.55	34.80	44.00	<b>⊢</b>	4.02	-15.47 [-28.55, -2.39]
Jackowska.2019	110.70	30.49	20.00	111.85	20.22	20.00		2.94	-1.15 [-17.18, 14.88]
Kouvelos.2013	148.20	58.10	126.00	143.00	54.10	136.00		3.78	5.20 [ -8.42, 18.82]
Reckless.2008	95.90	19.70	201.00	89.33	19.40	195.00	<b>-</b>	12.01	6.57 [ 2.72, 10.42]
Stojakovic.2010	112.00	25.00	56.00	102.00	23.00	28.00		5.27	10.00 [ -0.74, 20.74]
West.2011	118.00	38.18	18.00	118.00	40.00	16.00	L	1.24	0.00 [-26.37, 26.37]
Zinellu.2016	165.00	47.00	10.00	164.00	34.00	10.00		0.70	1.00 [-34.95, 36.95]
Mixed-effect Model,	(p = 0.41)						· .		1.94 [ -2.66, 6.53]
3 Months									
Pockloss 2008	67.20	10 70	201.00	85.85	10.40	105.00	Lal	12.01	18 56 [ 22 /1 1/ 71]
Reckless.2000	61.00	19.70	201.00	76.00	19.40	195.00		12.01	15.00 [-22.41, -14.71]
Stojakovic.2010	61.00	18.00	56.00	76.00	18.00	28.00		1.23	-15.00 [-23.17, -6.83]
Mixed-effect Model,	(p < 0.01)						$\langle \rangle$		-17.22 [-24.23, -10.22]
4 Months									
Zinellu.2016	141.85	26.21	10.00	163.44	23.64	10.00	· · · · · · · · · · · · · · · · · · ·	1.74	-21.59 [-43.47, 0.29]
Mixed-effect Model,	(p = 0.07)								-21.59 [-44.88, 1.70]
6 Months									
lackowska 2019	73.96	38 68	20.00	84 19	30.52	20.00		178	-10 23 [-31 82 11 36]
Jackowska.2015	10.00	50.00	20.00	04.15	00.02	20.00		1.70	-10.20 [-01.02, 11.00]
Mixed-effect Model,	(p = 0.38)							-	-10.23 [-33.25, 12.79]
9 Months									
Zinellu.2016	151.10	22.61	10.00	157.27	17.99	10.00		2.45	-6.17 [-24.08, 11.74]
Mixed-effect Model,	(p = 0.54)							-	-6.17 [-25.78, 13.44]
12 Months									
Cannon.2015	55.04	75.51	6864.00	71.80	76.50	6939.00	<b>⊞</b>	13.44	-16.76 [-19.30, -14.22]
Hougaard.2017	51.14	30.94	39.00	77.34	19.34	41.00	⊢_∎	4.89	-26.20 [-37.57, -14.83]
Kouvelos.2013	75.90	31.60	126.00	87.20	31.70	136.00	⊢-∎	7.70	-11.30 [-18.97, -3.63]
West.2011	67.00	29.70	18.00	91.00	32.00	16.00	<b>⊢</b> • – –	1.90	-24.00 [-44.84, -3.16]
Zinellu.2016	152.13	28.78	10.00	155.21	32.89	10.00		1.18	-3.08 [-30.17, 24.01]
Mixed-effect Model,	(p < 0.01)						$\diamond$		-16.82 [-22.51, -11.12]
24 Months									
West.2011	68.00	42.42	18.00	83.00	44.00	16.00		- 1.03	-15.00 [-44.13, 14.13]
Mixed-effect Model,	(p = 0.33)							~	-15.00 [-45.21, 15.21]
Overall heterogenei	ty: (p < 0.01,	$\tau^2 = 16.6$	$1, I^2 = 57.64^\circ$	%)					-
woderator significar	ice: (p < 0.0	i, χ (af =	() = 02.79)				< Favours Ezetimibe+Statin	Favours Statin>	
						-50	-40 -30 -20 -10 0 10	0 20 30 40 4 CD	
							wean Difference (95%	~ CI)	

# Figure 36 Forest plot indicating mean difference in LDL-c (absolute change) for ezetimibe plus

### statin compared to statin (3–24 months)

# **Abbreviations**

CI = confidence interval, LDL-c = low density lipoprotein-cholesterol, MD = mean difference, SD = standard deviation. Notes

#### Ezetimibe plus statin vs statin, number of patients achieving LDL-c goals, 3 months

Nine studies provided evidence on the number of patients achieving LDL goals at 3 to 6 months.<sup>111 147-</sup><sup>150 154-157</sup> All nine studies were included in the meta-analysis.

Overall, there was a statistically significant difference between the groups in the number of patients achieving LDL-c <70mg/dL at 3 months (p=0.008) and <100mg/dL at 3 (p<0.00001) and 6 (p<0.0001) months (*Table 23*). There was no difference in the number of patients achieving LDL-c <70mg/dL at 6 months (p=0.11) Timepoints and goals were subject to moderate to considerable levels of heterogeneity and inconsistency. For the forest plots, refer to *Figure 89* to *Figure 92*.

The trial population was heterogeneous and included patients with hypercholesterolaemia and established CHD (or its risk equivalent),<sup>150 155-157</sup> patients with hypercholesterolaemia at high or very high risk of ASCVD who were already receiving statins,<sup>147-149</sup> patients with hypercholesterolaemia with CHD and/or type 2 diabetes,<sup>154</sup> and patients who had had a recent coronary event.<sup>111</sup>

Table 23 Ezetimibe plus statin compared to statin: number of patients achieving LDL-c goals from 3–6 months

Length of follow-up	Number of studies	Heterogeneity	Ezetimibe plus Statin n/N (%)	Statin n/N (%)	Risk Ratio (95% Cl)
LDL <100mg/dL					
3 months	6111 147 154-157	Chi <sup>2</sup> =114.3 P<0.00001 I <sup>2</sup> =95%	528/1,496 (35.3%)	834/1,525 (54.7%)	1.73 (1.32, 2.26) p<0.00001
6 months	2148 150	Chi <sup>2</sup> =2.34 P=0.13 I <sup>2</sup> =57%	130/299 (43.5%)	126/161 (78.3%)	2.59 (1.62, 4.16) p<0.0001
LDL <70mg/dL					
3 months	<b>5</b> 111 147 154 156 157	Chi <sup>2</sup> =99.39 P<0.00001 I <sup>2</sup> =96%	621/1,220 (50.9%)	311/1,180 (26.4%)	3.41 (1.66, 7.01) p=0.0008
6 months	2148 149	Chi <sup>2</sup> =4.27 P=0.04 I <sup>2</sup> =77%	47/100 (47.0%)	23/101 (22.8%)	2.09 (0.85, 5.14) p=0.11

# Abbreviations

CI = confidence interval, LDL-c = low density lipoprotein-cholesterol, n = number of patients with event, N = total number of patients, NA = not applicable.

#### Ezetimibe plus statin vs statin, percentage change in HDL-c, 3-12 months

Ten studies provided evidence on the percentage change in HDL-c from 3 to 12 months. Nine studies were included in the meta-analysis<sup>146</sup> <sup>149-156</sup> and one was omitted owing to incomplete data.<sup>157</sup> Overall, there were no statistically significant differences between ezetimibe plus statin and statin groups at any timepoints (*Figure 37*). At 3 months the mean difference was 1.01% (95% CI -1.56; 3.58%; p=0.54). By 12 months, the difference was -2.50% (95% CI -13.52, 8.52%; p=0.76). Tau<sup>2</sup> and I<sup>2</sup> statistics indicated considerable levels of heterogeneity and inconsistency within the model.

The trial population was heterogeneous and included patients with hypercholesterolaemia and established CHD (or its risk equivalent),<sup>146 150 152 155 156</sup> patients with hypercholesterolaemia with CHD and/or type 2 diabetes,<sup>154</sup> patients with established ASCVD<sup>153</sup> and who had recently had an MI.<sup>151</sup>

	Ezet	imibe+St	atin Arm	Statin Arm								
Study	Mean	SD	Total	Mean	SD	Total					Weight	(%) MD, 95%CI
3 Months												
Ballantyne.2004a	9.00	14.20	250.00	6.90	14.10	246.00				<b>⊢∎</b> 1	11.70	2.10 [ -0.39, 4.59]
McKenney2006	8.00	14.61	67.00	7.00	14.94	70.00					7.40	1.00 [ -3.95, 5.95]
Nicholl.2017	-2.20	59.00	91.00	2.20	24.50	40.00 ⊢			•		1.60	-4.40 [-18.70, 9.90]
Roetersvanlennep.2008	-2.60	15.48	178.00	1.00	14.16	189.00			<b>—</b>	4	10.67	-3.60 [ -6.64, -0.56]
Stein.2004	3.70	13.95	293.00	1.00	14.25	303.00				⊢∎⊣	12.12	2.70 [ 0.44, 4.96]
Zieve.2010	2.00	17.38	516.00	-1.00	17.26	509.00				⊨∎→	12.37	3.00 [ 0.88, 5.12]
Mixed-effect Model, (p = 0.5	4)								-			1.01 [ -1.56, 3.58]
4.5 Months												
Ballantyne.2004a	11.40	10.90	242.00	7.80	15.40	237.00				⊢-∎1	11.88	3.60 [ 1.21, 5.99]
Mixed-effect Model, (p = 0.6	0)								-			3.60 [ -1.97, 9.17]
6 Months												
Ballantyne.2004a	12.30	10.70	232.00	6.50	15.10	228.00				⊢∎→	11.88	5.80 [ 3.40, 8.20]
Farnier.2016	-1.80	16.30	50.00	1.70	16.60	48.00		H	-	<u> </u>	5.44	-3.50 [-10.02, 3.02]
Feldman.2004	8.00	10.40	109.00	5.10	11.00	248.00				<b>⊢</b> ∎1	11.90	2.90 [ 0.52, 5.28]
Mixed-effect Model, (p = 0.6	1)									<>		2.89 [ -0.66, 6.44]
12 Months												
Hougaard.2017	-3.60	25.80	39.00	-1.10	18.10	41.00		L			3.03	-2.50 [-12.31, 7.31]
Mixed-effect Model, (p = 0.7	6)						-					-2.50 [-13.52, 8.52]
Overall heterogeneity: (p < 0 Moderator significance: (p =	$0.01, \tau^2 = 0.01$	$44.87, I^2$	= 94.99%)									
moderator significance. (p =	σ.στ, χ (	(ui - +) =	1.00)					<fav< td=""><td>ours Statin</td><td>Favours Ezetimibe</td><td>+Statin&gt;</td><td></td></fav<>	ours Statin	Favours Ezetimibe	+Statin>	
							1			1 1		
						-20	-15	-10	-5	0 5 1	0 15	
								Mean	Differenc	e (95% CI)		

### Figure 37 Forest plot indicating mean difference in HDL-c (percentage change) for ezetimibe

#### plus statin compared to statin (3–12 months)

#### **Abbreviations**

CI = confidence interval, HDL-c = high density lipoprotein-cholesterol, MD = mean difference, SD = standard deviation. Notes

#### Ezetimibe plus statin vs statin, absolute change in HDL-c, 3-24 months

Eight studies provided evidence on the absolute change in HDL-c from 3 to 24 months. Seven studies were included in the meta-analysis<sup>52</sup> <sup>111</sup> <sup>144</sup> <sup>145</sup> <sup>151</sup> <sup>159</sup> <sup>160</sup> and one was omitted owing to incomplete data.<sup>161</sup> Overall, there were statistically significant differences between ezetimibe plus statin and statin groups at 4 and 9 months but not at any other timepoint (*Figure 38*). At 3 months, the mean difference was 0.42mg/dL (95% CI -1.82, 2.67mg/dL; p=0.71). By 12 months, the difference was 0.59mg/dL (95% CI - 0.38, 1.56mg/dL; p=0.23). Tau<sup>2</sup> and I<sup>2</sup> statistics indicated low levels of heterogeneity and inconsistency within the model.

The trial population was heterogeneous and included patients with ACS,<sup>52</sup> recent MI,<sup>151</sup> peripheral artery disease,<sup>145</sup> chronic kidney disease,<sup>160</sup> hypercholesterolaemia with CHD (or risk equivalent)<sup>159</sup> and those who had had a recent coronary event<sup>111</sup> or undergone vascular surgery.<sup>144</sup>

	Ezetimibe+Statin Arm Statin Arm								
Study	Mean	SD	Total	Mean	SD	Total		Weight(%)	MD, 95%CI
Baseline									
Cannon.2015	40.00	11.85	8929.00	40.00	11.85	8930.00		83.22	0.00 [ -0.35, 0.35]
Hougaard.2017	42.54	11.60	43.00	42.54	11.60	44.00	<b>⊢</b>	0.42	0.00 [ -4.88, 4.88]
Kouvelos.2013	40.90	12.80	126.00	41.30	11.00	136.00	<b>⊢</b> •	1.20	-0.40 [ -3.30, 2.50]
Reckless.2008	41.76	12.44	201.00	41.38	12.25	195.00	⊢ <del>•</del> ⊣	1.70	0.38 [ -2.05, 2.81]
Stojakovic.2010	41.00	10.00	56.00	44.00	11.00	28.00	┝━━╪┤	0.43	-3.00 [ -7.84, 1.84]
West.2011	48.00	16.97	18.00	45.00	16.00	16.00	<b>⊢</b>	0.08	3.00 [ -8.09, 14.09]
Zinellu.2016	57.00	19.00	10.00	44.00	8.00	10.00	j(	0.06	13.00 [ 0.22, 25.78]
Mixed-effect Model	(p = 1.00	))					<b>•</b>		-0.00 [-0.34, 0.34]
3 Months									
Reckless.2008	46.02	12.44	201.00	44.47	12.25	195.00	<del>↓ • .  </del>	1.70	1.55 [ -0.88, 3.98]
Stojakovic.2010	39.00	10.00	56.00	45.00	14.00	28.00	<b>⊢_</b> ∎į́	0.30	-6.00 [-11.81, -0.19]
Mixed-effect Model	(p = 0.71	1)					$\diamond$		0.42 [-1.82, 2.67]
4 Months									
Zinellu.2016	60.35	18.65	10.00	44.93	9.99	10.00	•	0.06	15.42 [ 2.31, 28.53]
Mixed-effect Model	(p = 0.02)	2)							15.42 [ 2.31, 28.53]
	u								
9 Months									
Zinellu.2016	60.06	21.88	10.00	45.23	8.96	10.00	j I	0.05	14.83 [ 0.18, 29.48]
Mixed-effect Model	(p = 0.05	5)							14.83 [ 0.18, 29.48]
12 Months									
Cannon 2015	48 51	32 99	6871 00	47 83	32 95	6942 00		8.31	0.68[-0.42 1.78]
Hougaard.2017	42.54	11.60	39.00	42.54	11.60	41.00		0.39	0.00 [ -5.09, 5.09]
Kouvelos.2013	44.70	9.50	126.00	44.70	10.20	136.00	 ⊢+-1	1.77	0.00 [ -2.39, 2.39]
West.2011	42.00	12.72	18.00	46.00	12.00	16.00	<u>⊢</u>	0.15	-4.00 [-12.31, 4.31]
Zinellu.2016	62.41	17.47	10.00	44.35	7.93	10.00	· · · · · · · · · · · · · · · · · · ·	0.07	18.06 [ 6.17, 29.95]
Mixed-effect Model	(p = 0.23	3)					•		0.59 [-0.38, 1.56]
24 Months									
West.2011	46.00	12.72	18.00	44.00	16.00	16.00	<b>⊢</b>	0.10	2.00 [ -7.80, 11.80]
Mixed-effect Model	(p = 0.69	<del>)</del> )							2.00 [-7.80, 11.80]
Overall heterogene	ity: (p = 0.	.03, τ <sup>2</sup> = 0	$0.00, I^2 = 0$	.00%)					
Moderator signification	nce: (p =	0.09, χ <sup>2</sup> (α	df = 6) = 10	0.99)			<favours ezetimibe+statin="" favours="" statin=""></favours>		
						4	20 -10 0 10 20 30		
							Mean Difference (95% CI)		

#### Figure 38 Forest plot indicating mean difference in HDL-c (absolute change) for ezetimibe plus

#### statin compared to statin (3-24 months)

#### Abbreviations

CI = confidence interval, HDL-c = high density lipoprotein-cholesterol, MD = mean difference, SD = standard deviation. Notes

#### Ezetimibe plus statin vs statin, percentage change in total cholesterol, 3-12 months

Eight studies provided evidence on the percentage change in total cholesterol from 3 to 12 months. Seven studies were included in the meta-analysis<sup>146</sup> <sup>147</sup> <sup>150</sup> <sup>151</sup> <sup>154-156</sup> and one was omitted owing to incomplete data.<sup>157</sup> Overall, there was a statistically significant difference between ezetimibe plus statin and statin groups at 3 months but not at any other timepoints (*Figure 39*). At 3 months, the mean difference was -8.31% (95% CI -13.33, -3.29%; p<0.01). By 12 months, the difference was -7.90% (95% CI -20.22, 4.42%; p=0.21). However, Tau<sup>2</sup> and I<sup>2</sup> statistics indicated considerable levels of heterogeneity and inconsistency within the model.

The trial population was heterogeneous and included patients with hypercholesterolaemia and established CHD (or its risk equivalent),<sup>146 150 155 156</sup> patients with hypercholesterolaemia at high or very high risk of ASCVD,<sup>147</sup> patients with hypercholesterolaemia with CHD and/or type 2 diabetes,<sup>154</sup> and patients who had recently had an MI.<sup>151</sup>

	Ezetimibe+Statin Arm			s	Statin Ar	m			
Study	Mean	SD	Total	Mean	SD	Total	Weig	ght(%)	MD, 95%CI
3 Months									
Ballantyne.2004a	-36.50	9.50	250.00	-33.10	9.40	246.00	■ 1	1.76	-3.40 [ -5.06, -1.74]
Ballantyne.2019	-16.00	16.70	109.00	0.70	18.54	55.00	⊢	9.33	-16.70 [-22.52, -10.88]
Roetersvanlennep.2008	-17.70	11.20	178.00	-6.60	11.00	189.00	<b>■</b> 1	1.53	-11.10 [-13.37, -8.83]
Stein.2004	-26.10	13.95	278.00	-16.00	14.25	290.00	H 1	1.51	-10.10 [-12.42, -7.78]
Zieve.2010	-14.00	17.38	516.00	-12.00	17.26	509.00	<b>■</b> 1	1.59	-2.00 [ -4.12, 0.12]
Mixed-effect Model, (p < 0.01)							$\diamond$		-8.31 [-13.33, -3.29]
4.5 Months	10 50	7.00	0.40.00	07.00	10.00	007.00	_		
Ballantyne.2004a	-40.50	7.80	242.00	-37.00	10.80	237.00	1	1.75	-3.50[-5.19, -1.81]
Mixed-effect Model, (p = 0.53)									-3.50 [-14.43, 7.43]
6 Months									
Ballantyne.2004a	-43.30	7.60	232.00	-40.20	10.60	228.00	∎ 1	1.75	-3.10 [ -4.79, -1.41]
Feldman.2004	-38.00	9.40	109.00	-27.00	11.00	248.00	<b>H</b> 1	1.54	-11.00 [-13.23, -8.77]
Mixed-effect Model. (p = 0.08)							$\sim$		-7.01 [-14.77. 0.75]
, , ,							~		
12 Months									
Hougaard.2017	-46.80	16.40	39.00	-38.90	9.70	41.00	⊢1	9.24	-7.90 [-13.84, -1.96]
Mixed-effect Model, (p = 0.21)									-7.90 [-20.22, 4.42]
Overall heterogeneity: (p < 0.0	01, τ <sup>2</sup> = 30.3	33, I <sup>2</sup> = 9	5.86%)						
Moderator significance: (p < 0.	.01, χ²(df =	= 4) = 15.	66)				< Favours Ezetimibe+Statin Favours Compoarator	>	
						I			
						-6	0 -40 -20 0 10 30		
							Mean Difference (95% CI)		

#### Figure 39 Forest plot indicating mean difference in total cholesterol (percentage change) for

#### ezetimibe plus statin compared to statin (3–12 months)

#### **Abbreviations**

CI = confidence interval, MD = mean difference, SD = standard deviation. Notes

#### Ezetimibe plus statin vs statin, absolute change in total cholesterol, 3-24 months

Eight studies provided evidence on the absolute total cholesterol values from 3 to 24 months. Seven studies were included in the meta-analysis<sup>52</sup> <sup>111</sup> <sup>144</sup> <sup>145</sup> <sup>151</sup> <sup>159</sup> <sup>160</sup> and one was omitted owing to incomplete data.<sup>161</sup> Overall, there were statistically significant differences between the groups at 3, 4 and 12 months but not at any other timepoint (*Figure 40*). At 3 months, the mean difference was -21.18mg/dL (95% CI -28.93, -13.43mg/dL; p<0.01). By 12 months, the difference was -17.84mg/dL (95% CI -24.12, -11.56mg/dL; p<0.01). Tau<sup>2</sup> and l<sup>2</sup> statistics indicated moderate levels of heterogeneity and inconsistency within the model.

The trial population was heterogeneous and included patients with ACS,<sup>52</sup> recent MI,<sup>151</sup> peripheral artery disease,<sup>145</sup> chronic kidney disease,<sup>160</sup> or hypercholesterolaemia with CHD (or risk equivalent)<sup>159</sup> and patients who had had a recent coronary event<sup>111</sup> or undergone vascular surgery.<sup>144</sup>

	Ezetim	nibe+Sta	tin Arm	S	tatin Arı	n			
Study	Mean	SD	Total	Mean	SD	Total		Weight(%	) MD, 95%Cl
Baseline									
Cannon.2015	162.40	27.41	8998.00	162.40	27.41	9000.00		16.65	0.00 [ -0.80, 0.80]
Hougaard.2017	204.95	34.80	43.00	220.40	38.67	44.00	<b>⊢</b> •	3.82	-15.45 [-30.90, 0.00]
Kouvelos.2013	243.30	63.80	126.00	239.30	63.20	136.00	<b>⊢</b>	3.84	4.00 [-11.39, 19.39]
Reckless.2008	168.20	21.59	201.00	161.64	21.27	195.00	<b>⊦</b> ∎-1	13.40	6.56 [ 2.34, 10.78]
Stojakovic.2010	222.00	38.00	56.00	205.00	26.00	28.00		4.50	17.00 [ 3.15, 30.85]
West.2011	189.00	42.43	18.00	194.00	44.00	16.00	<b>⊢</b>	1.28	-5.00 [-34.14, 24.14]
Zinellu.2016	254.00	53.00	10.00	232.00	34.00	10.00	F	0.74	22.00 [-17.03, 61.03]
Mixed-effect Model, (p =	0.26)						$\diamond$		2.95 [ -2.21, 8.12]
3 Months									
Reckless.2008	140.76	21.59	201.00	159.70	21.27	195.00	┝═┥	13.40 -	18.94 [-23.16, -14.72]
Stojakovic.2010	138.00	26.00	56.00	164.00	23.00	28.00	<b>⊢</b> ∎−-	6.23 -	26.00 [-36.91, -15.09]
Mixed-effect Model, (p <	0.01)						$\diamond$		21.18 [-28.93, -13.43]
4 Months									
Zinellu.2016	142.09	25.07	10.00	165.07	24.03	10.00	<b>⊢−−−−</b> −	2.21	-22.98 [-44.50, -1.46]
Mixed-effect Model, (p =	0.05)								-22.98 [-46.08, 0.12]
9 Months									
Zinellu.2016	150.97	21.94	10.00	155.67	18.77	10.00	<b>⊢</b>	3.02	-4.70 [-22.60, 13.20]
Mixed-effect Model, (p =	0.64)								-4.70 [-24.46, 15.06]
12 Months									
Cannon.2015	128.68	96.90	6878.00	148.02	95.06	6950.00	⊦ <del>∎</del> -	14.66	19.34 [-22.54, -16.14]
Hougaard.2017	112.14	38.67	39.00	135.34	27.07	41.00	<b>⊢</b> −−−1	4.12	-23.20 [-37.90, -8.50]
Kouvelos.2013	154.10	35.80	126.00	167.60	36.40	136.00	<b>⊢</b> ∎→	8.04	-13.50 [-22.25, -4.75]
West.2011	135.00	38.18	18.00	162.00	40.00	16.00	<b>⊢</b> ŧ	1.54	-27.00 [-53.37, -0.63]
Zinellu.2016	152.53	27.17	10.00	155.15	32.91	10.00	<b>⊢</b>	1.53	-2.62 [-29.07, 23.83]
Mixed-effect Model, (p <	0.01)						$\diamond$		17.84 [-24.12, -11.56]
24 Months									
West.2011	136.00	50.91	18.00	152.00	48.00	16.00	<b>├</b> ─── <b>।</b>	1.00	-16.00 [-49.26, 17.26]
Mixed-effect Model, (p =	0.36)								-16.00 [-50.30, 18.30]
Overall heterogeneity: (p	< 0.01, τ <sup>2</sup>	= 18.27,	$ ^2 = 54.60\%)$						
Moderator significance: (	p < 0.01, 🤉	$\chi^2(df = 6)$	= 65.82)				< Favours Ezetimibe+Statin Favours Statin>		
						_			
						ا مہر	) -40 -20 0 10 30	50 70	
							wean Difference (95% CI)		

# Figure 40 Forest plot indicating mean difference in total cholesterol (absolute change) for

# ezetimibe plus statin compared to statin (3-24 months)

# **Abbreviations**

**CI** = confidence interval, **MD** = mean difference, **SD** = standard deviation.

#### <u>Notes</u>

### Ezetimibe plus statin vs statin, percentage change in triglycerides, 3-6 months

Seven studies provided evidence on the percentage change in triglycerides from 3 to 6 months.<sup>146 149 150</sup> <sup>152 154-156</sup> The results were described narratively rather than meta-analysed because it was unclear whether the results from each study were normally distributed.

At 3 months, there were statistically significant differences between the groups in one study,<sup>155</sup> no difference in three studies<sup>146 154 156</sup> and one study did not report the statistical difference (*Table 24*).<sup>152</sup> There were no significant differences between the groups at 4.5 months<sup>146</sup> and limited differences at 6 months.<sup>146 149 150</sup>

# Table 24 Ezetimibe plus statin compared to statin: percentage change in triglycerides at 3–6 months

Study	Ezetimibe plus statin at baseline follow-up, n	Statin at baseline follow-up, n	p value
3 months			
Ballantyne 2004a <sup>146</sup>	174.5 ± 93.5mg/dL	171.5 ± 94.0mg/dL	NR
a, b	-27.7 ± 1.9%, n=250	-28.4 ± 1.7%, n=246	NS
McKenney 2006 <sup>152</sup>	164 ± NR mg/dL	157.0 ± NR mg/dL	NR
c, d	-23.0% (-29.0, -17.0), n=67	-19.0% (-24.0, -13.0), n=70	NR
Roeters van	132.9 ± 53.1mg/dL	141.7 ± 62.0mg/dL	NR
Lennep 2008 <sup>154 a, e</sup>	-0.1 ± 53.6%, n=178	-2.8 ± 32.4%, n=189	NS
Stein 2004155 b	117.3 ± 3.9mg/dL	118.8 ± 4.2mg/dL	NR
	-9.3 ± 1.7%, n=293	-3.9 ± 1.7%, n=290	<0.01
Zieve 2010 <sup>156 a, d</sup>	113 ± 54mg/dL	117 ± 62mg/dL	NR
	-12.0% (-14.0, -9.0), n=516	-9.0% (-11.0, -7.0), n=509	0.15
4.5 months			
Ballantyne 2004a <sup>146</sup>	174.5 ± 93.5mg/dL	171.5 ± 94.0mg/dL	NR
a, b	-32.0 ± 1.3%, n=242	-31.2 ± 1.8%, n=237	NS
6 months			
Ballantyne 2004a <sup>146</sup>	174.5 ± 93.5mg/dL	171.5 ± 94.0mg/dL	NR
a, b	-35.3 ± 1.2%, n=232	-34.8 ± 1.9%, n=228	NS
Farnier 2016 <sup>149 a, f</sup>	127.0mg/dL (95.0–163.5)	116.0mg/dL (91.0–179.0)	NR
	-11.1 ± 30.4%, n=50	-1.8 ± 31.18%, n=48	NR
Feldman 2004150 a,	177.0 ± 87.4mg/dL	169.5 ± 88.8mg/dL	NR
b	-25.0 ± 28.2%, n=109	-19.0 ± 29.9%, n=248	<0.05

# Abbreviations

**mg/dL** = milligram per decilitre, **n** = number of patients, **NR** = not reported, **NS** = not significant. **Notes** 

 $\overline{\mathbf{a}}$  = median ± standard deviation,  $\mathbf{b}$  = median ± standard error,  $\mathbf{c}$  = median,  $\mathbf{d}$  = median (95% confidence),  $\mathbf{e}$  = mean ± standard error,  $\mathbf{f}$  = median (interquartile range).

### Ezetimibe plus statin vs statin, absolute change in triglycerides, 3-24 months

Five studies provided evidence on absolute change in triglycerides from 3 to 24 months.<sup>52 111 145 159 160</sup> The results were described narratively rather than meta-analysed because it was unclear whether the results from each study were normally distributed.

There were limited significant differences between ezetimibe plus statin and statin groups from 3 to 24 months (*Table 25*).

Study	Ezetimibe plus statin at baseline follow-up, n	Statin at baseline follow-up, n	p value
3 months			
Reckless 2008 <sup>111 a</sup>	136.4 ± 4.43mg/dL	140.83 ± 4.43mg/dL	NR
	122.23 ± 5.31mg/dL, n=201	124.9 ± 5.31mg/dL, n=195	0.55
Stojakovic 2010 <sup>159 b</sup>	180 ± 177mg/dL	155 ± 91mg/dL	NS
	132 ± 72mg/dL, n=56	142 ± 88mg/dL, n=28	0.008
4 months			
Zinellu 2012 <sup>160 b</sup>	151 ± 80mg/dL	141 ± 70mg/dL	NR
	112.88 ± 69.7mg/dL, n=10	140.15 ± 62.88mg/dL, n=10	NR
9 months	·		
Zinellu 2012 <sup>160 b</sup>	151 ± 80mg/dL	141 ± 70mg/dL	NR
	134.09 ± 56.82mg/dL, n=10	121.97 ± 68.18mg/dL, n=10	NR
12 months			
Cannon 2015 <sup>52 c</sup>	120mg/dL (85–172)	121mg/dL (85–172)	NR
	104mg/dL (77–143), n=6,878	116mg/dL (84–165), n=6,950	<0.001
West 2011 <sup>145 d</sup>	130 ± 21mg/dL	227 ± 47mg/dL	NS
	126 ± 18mg/dL, n=18	173 ± 27mg/dL, n=16	NS
Zinellu 2012 <sup>160 b</sup>	151 ± 80mg/dL	141 ± 70mg/dL	NR
	118.18 ± 75.00mg/dL, n=10	113.64 ± 42.42mg/dL, n=10	NR
24 months			
West 2011145 d	130 ± 21mg/dL	227 ± 47mg/dL	NS
	119 ± 20mg/dL, n=18	171 ± 30mg/dL, n=16	NS

Table 25 Ezetimibe	plus	statin	compared	to	statin:	absolute	change	in	triglycerides	at	3–24
months											

Abbreviations

n = number of patients, NR = not reported, NS = not significant.

Notes

 $a = median \pm standard deviation$ ,  $b = mean \pm standard deviation$ , c = median interquartile range,  $d = mean \pm standard error$ .

## Ezetimibe plus statin vs statin, change in markers of vascular damage, 12-24 months

Two studies provided evidence on markers of vascular damage at 12 and 24 months post-intervention as measured by atheroma, and vessel and lumen volume.<sup>145</sup><sup>151</sup> There were no statistically significant differences between ezetimibe plus statin and statin groups in markers of vascular damage when evaluated by IVUS<sup>151</sup> or MRI<sup>145</sup> at any timepoint (*Table 26*).

Table 26 Ezetimibe plus statin compared to statin: intima-media thickness in carotid and femoral

Outcome	Follow-up	Ezetimibe plus Statin	Statin mean ± SD	p value
		mean ± SD		
IVUS <sup>151 a</sup>				
Total atheroma	Baseline	200 ± 294.9	218.4 ± 244.4	0.63
volume (mm <sup>3</sup> )	12 months	189.3 ± 238.7	212.2 ± 414.4	0.39
Vessel volume (mm <sup>3</sup> )	Baseline	513.7 ± 541.7	533.8 ± 596.5	0.93
	12 months	491.4 ± 348.3	529.5 ± 577.5	0.57
Lumen volume (mm <sup>3</sup>	Baseline	311.5 ± 259.0	324.6 ± 396.8	0.85
	12 months	293.2 ± 265.0	326 ± 338.6	0.80
MRI <sup>145</sup>				
Plaque volume (cm3)	Baseline	11.5 ± 5.9	11.0 ± 6.0	NS
	12 months	11.1 ± 5.9	10.3 ± 6.0	NS
	24 months	10.5 ± 5.5	10.5 ± 5.6	NS
Total vessel volume	Baseline	17.5 ± 10.2	17.7 ± 10	NS
(cm <sup>3</sup> )	12 months	16.9 ± 10.2	16.9 ± 10	NS
	24 months	16.3 ± 10.2	17.2 ± 10.4	NS
Lumen volume (cm <sup>3</sup> )	Baseline	5.9 ± 4.7	6.7 ± 4.8	NS
	12 months	5.8 ± 4.7	6.5 ± 4.8	NS
	24 months	5.9 ± 5.5	6.7 ± 5.2	NS

#### arteries at 12-24 months

#### **Abbreviations**

cm<sup>3</sup> = centimetres cubed, IVUS = intravascular ultrasound, MRI = magnetic resonance imaging, NS = not significant, SD = standard deviation.

#### Notes

**a** = entire pullback reported

#### Sub-groups analysis

Four sub-groups were assessed – statin type, older adults, individuals with diabetes, and low, intermediate and high cardiovascular risk groups. The results from the sub-group analyses of older adults, individuals with diabetes and individuals with low, intermediate and high cardiovascular risk are predominately informed by secondary analyses of the IMPROVE-IT trial.<sup>52</sup>

#### Statin type

Percentage change in LDL-c, HDL-c, total cholesterol and triglycerides

#### Atorvastatin

Six studies compared ezetimibe plus atorvastatin to atorvastatin.<sup>148 151 153 155 156 158</sup> At 3 months, there were significant differences between the groups in LDL-c (-16.16%, 95% CI -25.89, -6.42; p<0.01) and HDL-c (2.78%, 95% CI 1.24, 4.31; p<0.001) with the result favouring ezetimibe plus atorvastatin. There was no difference in total cholesterol at 3 months (-6.04%, 95% CI, -13.97, 1.90%; p=0.14), or in LDL-c (-9.60%, 95% CI -29.31, -10.11; p>0.05) and HDL-c (-2.50%, 95% CI -12.31, 7.31; p>0.05) at 12 months. Total cholesterol was not meta-analysed at 12 months owing to insufficient study numbers. The Tau<sup>2</sup> and I<sup>2</sup> statistics indicated considerable levels of heterogeneity for all outcomes.

The percentage change in triglycerides was not meta-analysed because it was unclear whether the results from each study were normally distributed. At 3 months, there was a statistically significant difference between ezetimibe plus atorvastatin and atorvastatin groups in one study.<sup>155</sup> There was no difference in another study.<sup>156</sup>

Atorvastatin dose was 20mg,<sup>155</sup> 40mg<sup>148</sup> <sup>153</sup> <sup>156</sup> <sup>158</sup> and 80mg<sup>151</sup> in the intervention and comparator arms. Ezetimibe was fixed at 10mg in all studies.

#### Rosuvastatin

In one study, ezetimibe plus rosuvastatin (10mg) reported lower LDL-c, HDL-c and total cholesterol, and higher triglycerides at 6 months compared to rosuvastatin (10mg).<sup>149</sup> The statistical difference was not reported at any timepoint, so it was unclear whether ezetimibe and rosuvastatin groups differed.

#### Simvastatin

In one study, ezetimibe plus simvastatin (80mg) significantly differed to simvastatin (80mg) with respect to LDL-c (p<0.001), HDL-c (p<0.05), total cholesterol (p<0.001) and triglycerides (p<0.05) at 3 months.<sup>150</sup>

For further information regarding sub-group analysis refer to Section 15.4.3 (Appendix D), Table 107.

#### Absolute change in LDL-c, HDL-c, total cholesterol and triglycerides

Two trials were not utilised in the sub-group analysis as the comparator statin differed from the intervention statin (i.e. ezetimibe plus simvastatin vs rosuvastatin or atorvastatin).<sup>146 152</sup>

#### Atorvastatin

In one study, ezetimibe plus atorvastatin (20mg) showed no significant differences to atorvastatin (40mg) in LDL-c at 3 months.<sup>158</sup> At 12 months, ezetimibe plus atorvastatin (80mg) significantly differed to atorvastatin (80mg) with respect to LDL-c (p<0.001) and total cholesterol (p<0.001) but not HDL-c (p=0.48).<sup>151</sup>

#### Fluvastatin

In one study, ezetimibe plus fluvastatin (80mg) significantly differed to fluvastatin (80mg) with respect to LDL-c (p<0.001), total cholesterol (p<0.001) and triglycerides (p=0.008) at 3 months. There was no difference in HDL-c (p=0.08).<sup>159</sup>

#### Rosuvastatin

In one study, ezetimibe plus rosuvastatin (10mg) significantly differed to rosuvastatin (10mg) with respect to LDL-c (p=0.005) and total cholesterol (p=0.004) at 12 months. There was no difference in HDL-c (p=0.98) and triglycerides (p=0.50).<sup>144</sup>

#### Simvastatin

For ezetimibe plus simvastatin compared to simvastatin there were significant differences in LDL-c and total cholesterol at 12 months but not at any other timepoint as inferred by meta-analyses.<sup>52 145 160</sup> At 3 months the mean difference in LDL-c was -21.59mg/dL (95% CI -43.47, 0.29mg/dL; p=0.10) and by 12 months the difference was -16.75mg/dL (95% CI -19.25, -14.24mg/dL; p<0.001). The mean difference in total cholesterol at 3 months was -22.98mg/dL (95% CI -44.50, -1.46mg/dL; p<0.05) and by 12 months it was -19.21mg/dL (95% CI -22.37, -16.06mg/dL; p<0.001). There were no statistically significant differences in HDL-c at any timepoint (p>0.05). Tau<sup>2</sup> and I<sup>2</sup> statistic indicated considerable level of heterogeneity for all outcomes. The absolute change in triglycerides was not meta-analysed because it was unclear whether the results from each study were normally distributed. The included studies reported opposing results. There was a significant difference in one study,<sup>52</sup> no difference in one study,<sup>145</sup> and one study did not report the statistics.<sup>160</sup>

The dose of simvastatin was 40mg<sup>52 145 160</sup> or 80mg<sup>52</sup> in the intervention and comparator arm. Ezetimibe was fixed at 10mg in all studies.

For further information regarding sub-group analysis of statin types refer to Section 15.4.3 (Appendix

#### D), Table 106.

#### Low-, intermediate- and high-risk groups

Bohula (2017) stratified patients into groups of low, intermediate and high risk using the thrombolysis in MI risk score for secondary prevention (TIMI TRS  $2^{\circ}P$ ).<sup>162</sup> Risk factors included coronary heart failure, hypertension, age  $\geq$ 75 years, diabetes mellitus, prior stroke, coronary bypass graft, peripheral artery disease, estimated glomerular filtration rate (eGFR) <60 and smoking. Patients with three or more risk factors were deemed high-risk, those with two risk factors were deemed intermediate-risk and patients with one to zero factors were considered low-risk.

Overall, there were statistically significant differences between the risk categories with respect to 3P-MACE (p=0.01) and MI (p=0.01) with lower hazard ratios observed amongst high-risk patients. There were no differences in cardiovascular death (p=0.93), ischaemic stroke (p=0.075), coronary revascularisation (p=0.14) or unstable angina (p=0.80) at seven years (*Table 108*).

The absolute risk reduction in 3P-MACE was 6.3% (95% CI 2.9, 9.7%) for high-risk groups, 2.2% (95% CI -0.3, 4.6%) for intermediate-risk and -0.9% (95% CI -2.5, 0.7%) for low-risk groups (p=0.01). The absolute risk reduction in MI was 5.9% (95% CI 2.9, 9.1%) for high-risk groups, 1.5% (95% CI -0.5, 3.7%) for intermediate-risk and -0.4% (95% CI -1.8, 1.1%) for low-risk groups (p=0.01) (*Table 108*).

The statistical difference was not reported for changes in lipids and triglycerides, so it was unclear whether the risk categories differed (*Table 109*). However, the authors reported that LDL-c values at 12 months were similar across risk categories by treatment.

#### **Older Adults**

Bach (2019) stratified patients into those younger than 65 years, those 65 to 74 and those older than 75.<sup>163</sup> Individuals 75 years and older reported greater prevalence of hypertension, cardiovascular disease and peripheral vascular disease compared to younger adults. This potentially confounds the results because this group may be at an inherently higher cardiovascular risk.

Overall, there was a statistically significant interaction between age and treatment effect with respect to 5P-MACE (p=0.02), with a lower hazard ratio observed among individuals 75 years and older (HR 0.80, 95% CI 0.70, 0.90) compared to individuals younger than 65 (HR 0.97, 95% CI 0.90, 1.05) and those 65 to 74 (HR 0.96, 95% CI 0.87, 1.06). There were no statistically significant interactions for 3P-MACE (p=0.39), cardiovascular death (p=0.12), MI (p=0.15) or ischaemic stroke (p=0.11). There were no differences in LDL-c at 12 months between age groups (p>0.05). The statistical difference was not reported for HDL-c, total cholesterol and triglycerides.

The study authors further stratified patients by TIMI TRS 2°P risk scores. There was no statistically significant interaction between treatment, age or risk group (p=0.09). However, there were significant reductions in MACE following ezetimibe plus statin treatment compared to statin in high-risk adults younger than 75 (HR 0.85 95% CI, 0.74, 0.98; p=0.03) and older than 75 (HR 0.75, 95% CI 0.63, 0.89; p=0.001).

Two additional RCTs evaluated ezetimibe plus statin exclusively in older adults (age >65 years).<sup>156 157</sup> One did not report the standard deviation or statistical significance between treatment groups, so it was unclear whether ezetimibe plus statin and statin groups differed (*Table 112*).<sup>157</sup> The other reported statistically significant differences between ezetimibe and statin groups for LDL-c (p=0.001), HDL-c (p<0.01) and total cholesterol (p=0.029) but not for triglycerides (p=0.15), with the results favouring ezetimibe plus statin at 3 months.<sup>156</sup>

#### **Diabetes**

Giugliano (2018) stratified patients based on diabetes status.<sup>116</sup> Overall, there were statistically significant interactions between diabetes status and treatment group for 5P-MACE (p=0.023), 3P-MACE (p=0.016), MI (p=0.028) and ischaemic stroke (p=0.031), with a lower hazard ratio observed among individuals with diabetes compared to individuals without diabetes (*Table 113*). There were no statistically significant interactions for cardiovascular death (p=0.57), coronary revascularisation (p=0.51) or unstable angina (p=0.94) at seven years. There was no significant difference in reduction in LDL-c at 12 months between individuals with and without diabetes (p =0.12) (*Table 114*).

There were statistically significant baseline differences between the patient groups, for example, individuals with diabetes had a higher risk score (mean 2.8 additional risk factors, TIMI RS 2°P) compared to patients without diabetes (mean 1.4 additional risk factors). Additional differences included medical history, medications before admission and lipid values (p<0.001 for all outcomes). For this reason, the study authors stratified patients by TIMI TRS 2°P risk scores. In patients without diabetes there was a statistically significant interaction between risk group and treatment group (p=0.034), with high-risk individuals who received ezetimibe plus statin reporting a greater reduction in 3P-MACE compared to the statin group at seven years. By contrast, in individuals with diabetes there was no statistically significant interaction between risk groups and treatment (p=0.59).

### Hyperlipidaemia without ASCVD

**Table 27** provides a summary of the main pooled clinical effectiveness outcomes comparing ezetimibe monotherapy and ezetimibe plus fenofibrate to fenofibrate. No studies evaluated MACE outcomes or markers of vascular damage. Further, comparisons involving ezetimibe compared to placebo or statins and ezetimibe plus statins to statins could not be meta-analysed owing to insufficient study numbers. A negative mean difference for LDL-c and total cholesterol and a positive mean difference for HDL-c indicates results favouring the intervention group.

There were no differences between ezetimibe and fenofibrate for percentage change in LDL-c, total cholesterol or the number of patients achieving LDL-c levels <130mg/dL at 3 months. There was a statistically significant difference in HDL-c, with the results favouring fenofibrate (green shading).

By 3 months, there were statistically significant differences (orange shading) between ezetimibe plus fenofibrate and fenofibrate for percentage change in LDL-c and total cholesterol and number of patients achieving LDL-c levels <130mg/dL, with the results in favour of ezetimibe plus fenofibrate. There were no differences in HDL-c.

# Table 27 Summary of meta-analyses results for patients with hyperlipidaemia without ASCVD at3 months

Outcomes	Length of follow-up Mean difference (95% CI) or risk ratio (95% CI)											
	Ezetimibe vs placebo	Ezetimibe vs statins	Ezetimibe plus statin vs statin	Ezetimibe vs fenofibrate	Ezetimibe plus fenofibrate vs fenofibrate							
LDL-c	NA	NA	NA	-9.72% (-27.85, 8.41)	-19.94% (-31.80, -8.09)							
Achieving goals <sup>a</sup>	NA	NA	NA	1.61 (1.18, 2.20)	2.48 (1.92, 3.19)							
HDL-c	NA	NA	NA	-10.75% (-19.72, -1.78)	0.92% (-2.06, 3.91)							
Total cholesterol	NA	NA	NA	0.30% (-2.44, 3.03)	-10.40% (-12.94, -7.86)							

### Abbreviations

**CI** = confidence interval, **HDL-c** = high density lipoprotein-cholesterol, **LDL-c** = low density lipoprotein-cholesterol, **NA** = not applicable.

#### Notes

For LDL-c and total cholesterol, negative mean difference favours intervention, positive mean difference favours comparators.

For HDL-c, positive mean difference favours intervention, negative mean difference favours comparators.

For number of patients achieving LDL-c goals, risk ratio >1 favours intervention, risk ratio <1 favours comparator.

No shading = no statistically significant difference between groups (p>0.05)

Green shading = statistically significant differences between groups (p<0.05) in favour of fenofibrate.

**Orange shading** = statistically significant differences between groups (p<0.05) in favour of ezetimibe plus fenofibrate.

a = risk ratio 95% CI of number of patients achieving <130mg/dL.

#### Ezetimibe vs placebo

Two studies provided evidence on lipids and triglyceride levels at 3 months (*Table 28*).<sup>164 165</sup> The studies were not meta-analysed owing to different methods of reporting the outcomes (percentage<sup>165</sup> and absolute change<sup>164</sup>). There were statistically significant differences between ezetimibe and placebo groups regarding the absolute change in LDL-c and total cholesterol (p<0.0001 for both outcomes). There were no statistical differences for absolute change in HDL-c (p=0.40) or triglycerides (p=0.10).<sup>164</sup>

The percentage change in LDL-c, total cholesterol and triglycerides in the ezetimibe group was generally larger than in the placebo group. However, the statistical difference was not reported in all studies, so it was unclear whether ezetimibe and placebo groups differed.<sup>165</sup>

Table 28 Ezetimibe compared to placebo: percentage and absolute change in lipids and triglycerides at 3 months

Outcomes	Follow-up	Ezetimibe mean ± SD	Placebo mean ± SD	p value
LDL-c				
Percentage change	Baseline	158.6 ± 21.3mg/dL	162.4 ± 27.1mg/dL	NR
165	3 months	-13.4 ± 17.0%	0.2 ± 16.2%	NR
Absolute values <sup>164</sup>	Baseline	127.6 ± 36.0mg/dL	127.6 ± 36.0mg/dL	NA
	3 months	102.1 ± 21.3mg/dL	133.0 ± 41.0mg/dL	<0.0001
Achieving goals <sup>165</sup>	3 months	75/187 (40.1%)	7/64 (10.9%)	NR
HDL-c				
Percentage change	Baseline	42.5 ± 7.7mg/dL	42.5 ± 7.7mg/dL	NR
165	3 months	3.9 ± 15.8%	3.2 ± 27.1%	NR
Absolute values <sup>164</sup>	Baseline	39.1 ± 9.3mg/dL	39.1 ± 9.3mg/dL	NR
	3 months	40.6 ± 9.3mg/dL	39.8 ± 10.4mg/dL	0.4
Total cholesterol				
Percentage change	Baseline	259.1 ± 30.9mg/dL	259.1 ± 31.0mg/dL	NR
165	3 months	-11.8 ± 11.1%	0.2 ± 11.2%	NR
Absolute values <sup>164</sup>	Baseline	204.6 ± 39.8mg/dL	204.6 ± 39.8mg/dL	NR
	3 months	178.3 ± 29.7mg/dL	208.4 ± 42.2mg/dL	<0.0001
Triglycerides				
Percentage change <sup>a</sup>	Baseline	274.6 ± 106.3mg/dL	256.9 ± 79.7mg/dL	NR
165	3 months	-11.1 ± 31.2%	-9.2 ± 38.5%	NR
Absolute values <sup>164</sup>	Baseline	199.3 ± 59.4mg/dL	199.3 ± 59.4mg/dL	NA
	3 months	176.3 ± 62.9mg/dL	200.2 ± 77.1%	0.1

### Abbreviations

HDL-c = high density lipoprotein-cholesterol, LDL-c = low density lipoprotein-cholesterol, mg/dL = milligrams per decilitre, NCEP-ATP III = national cholesterol education program-adult treatment panel III, NR = not reported, SD = standard deviation. Notes

**a** = median ± standard deviation.

#### Ezetimibe vs statins

One study provided evidence on lipids and triglyceride levels at 3 months.<sup>125</sup> Overall, there were statistically significant differences between ezetimibe and statin groups with respect to number of patients achieving LDL-c levels <NCEP-ATP III goals and percentage change in LDL-c, total cholesterol and triglycerides (p<0.001 or p<0.0001 for all outcomes). There was no statistical difference in HDL-c (p>0.05) (*Table 29*).

# Table 29 Ezetimibe compared to statin: absolute and percentage change in lipids and triglycerides at 3 months

Outcomes	Follow-up	Ezetimibe mean ± SD	Statin mean ± SD	p value	
LDL-c					
Absolute change	Baseline	176.2 ± 40.0mg/dL	174.2 ± 48.0mg/dL		
	3 months	161.5 ± 18.6mg/dL	114.5 ± 21.7mg/dL	NR	
Percentage change		-15.6 ± NR	-32.8 ± NR	<0.0001	
Achieving goals (NCEP–ATP III)	3 months	19/66 (28.8%)	41/69 (59.4%)	<0.001	
HDL-c	•			·	
Percentage change	Baseline	52.4 ± 15.1mg/dL	53.6 ± 14.4mg/dL	NR	
	3 months	3.28 ± 6.9%	2.74 ± 7.58%	>0.05	
Total cholesterol	•			·	
Percentage change	Baseline	268.7 ± 43.7mg/dL	262.9 ± 53.6mg/dL	NR	
	3 months	-10.38 ± 10.89%	-23.24 ± 9.29%	<0.0001	
Triglycerides <sup>a</sup>					
Percentage change	Baseline	197.0 ± 104.6mg/dL	175.5 ± 82.4mg/dL	NR	
	3 months	-20.45 ± 10.57%	-16.49 ± 8.31%	<0.0001	

#### Abbreviations

HDL-c = high density lipoprotein-cholesterol, LDL-c = low density lipoprotein-cholesterol, mg/dL = milligrams per decilitre, NR = not reported, SD = standard deviation.

<u>Notes</u>

**a** = median ± standard deviation.

Source

Stein (2008)125

#### Ezetimibe plus statin vs statins

One study provided evidence on lipids and triglyceride levels at 3 months.<sup>125</sup> The mean percentage change in LDL-c, total cholesterol and triglycerides in the ezetimibe plus statin group was generally lower than in the statin group. The statistical difference was not reported, so it was unclear whether ezetimibe plus statin and statin groups differed (*Table 30*).

# Table 30 Ezetimibe plus statin compared to statin: absolute and percentage change in lipids andtriglycerides at 3 months

Outcomes	Follow-up	Ezetimibe plus statin Mean ± SD	Statin Mean ± SD	p value
LDL-c	•			•
Absolute change	Baseline	172.90 ± 44.1mg/dL	174.2 ± 48mg/dL	NR
	3 months	89.7 ± 19.6mg/dL	114.5 ± 21.7mg/dL	NR
Percentage change	3 months	-46.1 ± NR	-32.8 ± NR	NR
Achieving goals (NCEP–ATP III)	3 months	54/64 (84.4%)	41/69 (59.4%)	NR
HDL-c				
Percentage change	Baseline	55.2 ± 15.3mg/dL	53.6 ± 14.4mg/dL	NR
	3 months	7.60 ± 7.47%	2.74 ± 7.58%	NR
Total cholesterol				
Percentage change	Baseline	265.60 ± 47.20mg/dL	262.9 ± 53.6mg/dL	NR
	3 months	-31.11 ± 10.86%	-23.24 ± 9.29%	NR
Triglycerides <sup>a</sup>				
Percentage change	Baseline	188.4 ± 100.9mg/dL	175.5 ± 82.4mg/dL	NR
	3 months	-20.45 ± 10.57%	-16.49 ± 8.31%	NR

#### **Abbreviations**

HDL-c = high density lipoprotein cholesterol, LDL-c = low density lipoprotein-cholesterol, mg/dL = milligrams per decilitre, NR = not reported, SD = standard deviation.

#### <u>Notes</u>

**a** = median ± standard deviation.

Source

Stein (2008)125

### LDL-c

#### Ezetimibe vs fenofibrate, percentage change in LDL-c, 3 months

Two studies provided evidence on the percentage change in LDL-c at 3 months.<sup>165 166</sup> Both studies were included in the meta-analysis. Overall, there was no statistically significant difference between ezetimibe and fenofibrate groups at 3 months (MD -9.72%; 95% CI -27.85, 8.41%; p=0.29) (*Figure 41*). Chi<sup>2</sup> and I<sup>2</sup> statistics indicated considerable levels of heterogeneity and inconsistency (P<0.00001, I<sup>2</sup>=98%).



# Figure 41 Forest plot indicating mean difference in LDL-c (percentage change) for ezetimibe compared to fenofibrate (3 months)

#### **Abbreviations**

CI = confidence interval, LDL-c = low density lipoprotein-cholesterol, SD = standard deviation.

#### Ezetimibe vs fenofibrate, number of patients achieving LDL-c goals, 3 months

Two studies provided evidence on the number of patients achieving LDL-c goals at 3 months. Both studies were included in the meta-analysis.<sup>165</sup> <sup>166</sup> Overall, there was a statistically significant difference between ezetimibe and fenofibrate groups at 3 months (RR 1.61; 95% CI 1.18, 2.20; p=0.003) (*Figure* **42**). Chi<sup>2</sup> and I<sup>2</sup> statistics indicated low levels of heterogeneity and inconsistency (P=0.29, I<sup>2</sup>=12%).

Both studies reported NCEP-ATP III goal.<sup>165 166</sup>

	Ezetim	ibe	Fenofib	rate		Risk Ratio Risk			Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl		M-H, Rand	om, 95% Cl	
Ansquer 2009	17	60	14	60	24.5%	1.21 [0.66, 2.24]		_		
Farnier 2005b	75	187	43	189	75.5%	1.76 [1.29, 2.42]			-	
Total (95% CI)		247		249	100.0%	1.61 [1.18, 2.20]			•	
Total events	92		57							
Heterogeneity: Tau <sup>2</sup> = Test for overall effect:	i <sup>2</sup> = 1.10 (P = 0.0	3, df = 1 (1 103)	P = 0.29	8); I² = 129	χ.	0.01 Fa	0.1 vours Fenofibrate	1 10 Favours Ezetimibe	100	

### Figure 42 Forest plot indicating the risk ratio in the number of patients below NCEP-ATP goals

#### for ezetimibe compared to fenofibrate (3 months)

#### **Abbreviations**

CI = confidence interval, LDL-c = low density lipoprotein-cholesterol, SD = standard deviation.

#### HDL-c

#### Ezetimibe vs fenofibrate, percentage change in HDL-c, 3 months

Two studies provided evidence on the percentage change in HDL-c at 3 months.<sup>165 166</sup> Both studies were included in the meta-analysis. Overall, there was a statistically significant difference between ezetimibe and fenofibrate groups at 3 months (MD -10.75%; 95% CI -19.72, -1.78%; p=0.02) (*Figure 43*). Chi<sup>2</sup> and I<sup>2</sup> statistics indicated considerable levels of heterogeneity and inconsistency (P=0.06, I<sup>2</sup>=71%).

	Eze	etimibe	e	Fen	ofibrat	te		Mean Difference	Mean Difference	
Study or Subgroup	Mean	<b>SD</b>	Total	Mean	<b>SD</b>	Total	Weight	IV, Random, 95% CI	I IV, Random, 95% CI	
Ansquer 2009	2.2	17.9	56	7.9	17.9	58	45.1%	-5.70 [-12.27, 0.87]	ŋ <b>──</b> ─	
Farnier 2005b	3.9	15.8	173	18.8	16.4	179	54.9%	-14.90 [-18.26, -11.54]	] —	
Total (95% CI)			229			237	100.0%	-10.75 [-19.72, -1.78]		
Heterogeneity: Tau <sup>2</sup> = 35.22; Chi <sup>2</sup> = 5.96, df = 1 (P = 0.01); I <sup>2</sup> = 83% Test for overall effect: Z = 2.35 (P = 0.02)									-50 -25 0 25 5 Favours Fenofibrate Favours Ezetimibe	

# Figure 43 Forest plot indicating mean difference in HDL-c (percentage change) for ezetimibe

#### compared to fenofibrate (3 months)

#### **Abbreviations**

CI = confidence interval, HDL-c = high density lipoprotein-cholesterol, SD = standard deviation.

#### **Total Cholesterol**

#### Ezetimibe vs fenofibrate, percentage change in total cholesterol, 3 months

Two studies provided evidence on the percentage change in total cholesterol at 3 months.<sup>165</sup> <sup>166</sup> Both studies were included in the meta-analysis. Overall, there was no statistically significant difference between ezetimibe and fenofibrate groups at 3 months (MD 0.30%; 95% CI -2.44, 3.03%; p=0.83) (*Figure 44*). Chi<sup>2</sup> and I<sup>2</sup> statistics indicated low levels of heterogeneity and inconsistency (P=0.27, I<sup>2</sup>=18%).

	Ezetimibe Fenofibrate				Mean Difference			Mean Difference			
Study or Subgroup	Mean	SD	Total	Mean	<b>SD</b>	Total	Weight	IV, Random, 95% CI		IV, Random, 95% CI	
Ansquer 2009	-17.1	10.1	56	-18.9	9.9	58	46.3%	1.80 [-1.87, 5.47]			
Farnier 2005b	-11.8	11.1	173	-10.8	19.9	179	53.7%	-1.00 [-4.35, 2.35]			
Total (95% CI)			229			237	100.0%	0.30 [-2.44, 3.03]		•	
Heterogeneity: Tau <sup>2</sup> = 0.70; Chi <sup>2</sup> = 1.22, df = 1 (P = 0.27); i <sup>2</sup> = 18%								-50	-25 0 25	50	
Test for overall effect:	Z = 0.21	(P = 0	).83)							Favours Ezetimibe Favours Fenofibrate	

#### Figure 44 Forest plot indicating mean difference in total cholesterol (percentage change) for

#### ezetimibe compared to fenofibrate (3 months)

#### **Abbreviations**

CI = confidence interval, SD = standard deviation.

### Ezetimibe vs fenofibrate, percentage change in triglycerides, 3 months

Two studies provided evidence on the percentage change in triglycerides at 3 months.<sup>165 166</sup> The results were described narratively rather than meta-analysed because it was unclear whether the results from each study were normally distributed. One study reported no significant differences between ezetimibe and fenofibrate groups<sup>166</sup> and the other did not report statistics comparing the two groups (*Table 31*).<sup>165</sup>

Table 31 Ezetimibe compared to fenofibrate: percentage change in triglycerides at 3 months

Study	Follow-up	Ezetimibe median ± SD, n	Fenofibrate median ± SD, n	p value
Ansquer 2009 <sup>166</sup>	Baseline	212 ± NR mg/dL	223 ± NR mg/dL	NR
	3 months	-10.4 ± 24.6%, n=56	-38.3 ± 24.7%, n=58	NR
Farnier 2005b <sup>165</sup>	Baseline	274.4 ± 106.3mg/dL	283.4 ± 88.6mg/dL	NR
	3 months	-11.1 ± 31.2%, n=56	-43.2 ± 27.0%, n=58	NS

Abbreviations

mg/dL = milligrams per decilitre, n = number of patients, NR = not reported, NS = not significant, SD = standard deviation.

#### Ezetimibe plus fenofibrate vs fenofibrate

#### LDL-c

#### Ezetimibe plus fenofibrate vs fenofibrate, percentage change in LDL-c, 3 to 12 months

Two studies provided evidence on the percentage change in LDL-c at 3 months.<sup>165 166</sup> Both studies were included in the meta-analysis. Overall, there was a statistically significant difference between ezetimibe plus fenofibrate and fenofibrate groups at 3 months (MD -19.94%; 95% CI -31.80, -8.09%; p=0.001) (*Figure 45*). However, Chi<sup>2</sup> and I<sup>2</sup> statistics indicated considerable levels of heterogeneity and inconsistency (P<0.00001, I<sup>2</sup>=94%).

	Ezetimibe + Fenofibrate Fenofibrate				te		Mean Difference	Mean Difference		
Study or Subgroup	Mean	<b>SD</b>	Total	Mean	<b>SD</b>	Total	Weight	IV, Random, 95% CI	IV, Random, 95% Cl	
Ansquer 2009	-36.2	12.5	59	-22.4	12.6	58	49.2%	-13.80 [-18.35, -9.25]		
Farnier 2005b	-20.4	16	175	5.5	17.1	179	50.8%	-25.90 [-29.35, -22.45]		
Total (95% CI)			234			237	100.0%	-19.94 [-31.80, -8.09]		
Heterogeneity: Tau² = 68.96; Chi² = 17.26, df = 1 (P < 0.0001); l² = 94% Test for overall effect: Z = 3.30 (P = 0.0010)									-50 -25 0 25 Favours Ezetimibe + Feno Favours Fenofibrate	50

#### Figure 45 Forest plot indicating mean difference in LDL-c (percentage change) for ezetimibe

#### plus fenofibrate compared to fenofibrate (3 months)

#### **Abbreviations**

CI = confidence interval, LDL-c = low density lipoprotein-cholesterol, SD = standard deviation.

One study provided evidence on the percentage change in LDL-c at 12 months.<sup>152</sup> There was a statistically significant difference between the groups (p<0.001) in favour of ezetimibe plus fenofibrate (*Table 32*).

Table 32 Ezetimibe plus fenofibrate compared to fenofibrate: percentage change in LDL-c at 12 months

Study	Follow-up	Ezetimibe plus fenofibrate mean ± SD, n	Fenofibrate mean ± SD, n	p value
McKenney	Baseline	159.7 ± 27.7mg/dL	164.1 ± 27.9mg/dL	NR
2006 <sup>152</sup>	12 months	-22.0 ± 15.9%, n=337	-8.6 ± 16.0%, n=234	<0.001

**Abbreviations** 

mg/dL = milligrams per decilitre, n = number of patients, NR = not reported, SD = standard deviation.

#### Ezetimibe plus fenofibrate vs fenofibrate, number of patients achieving LDL-c goals, 3 months

Two studies provided evidence on the number of patients achieving LDL-c goals at 3 months. Both studies were included in the meta-analysis.<sup>165</sup> <sup>166</sup> Overall, there was a statistically significant difference between ezetimibe plus fenofibrate and fenofibrate groups at 3 months (RR 2.48; 95% CI 1.92, 3.19, p<0.00001) (*Figure 46*). Further, Chi<sup>2</sup> and I<sup>2</sup> statistic indicated low levels of heterogeneity and inconsistency (P=0.93, I<sup>2</sup>=0%).

#### Both studies defined goal achievement in accordance with NCEP-ATP III goals.<sup>165 166</sup>



#### Figure 46 Forest plot indicating risk ratio of patients achieving LDL-c goals for ezetimibe plus

#### fenofibrate compared to fenofibrate (3 months)

#### Abbreviations

CI = confidence interval, LDL-c = low density lipoprotein-cholesterol, SD = standard deviation.

### HDL-c

## Ezetimibe plus fenofibrate vs fenofibrate, percentage change in HDL-c, 3-12 months

Two studies provided evidence on the percentage change in HDL-c at 3 months.<sup>165 166</sup> Both studies were included in the meta-analysis. Overall, there was no statistically significant difference between ezetimibe plus fenofibrate and fenofibrate groups at 3 months (MD 0.92%; 95% CI -2.06, 3.91%; p=0.54) (*Figure* **47**). Chi<sup>2</sup> and I<sup>2</sup> statistics indicated low levels of heterogeneity and inconsistency (P=0.36, I<sup>2</sup>=0%).



# Figure 47 Forest plot indicating the mean difference in HDL-c (percentage change) for ezetimibe

# plus fenofibrate compared to fenofibrate (3 months)

#### Abbreviations

CI = confidence interval, HDL-c = high density lipoprotein-cholesterol, SD = standard deviation.

One study provided evidence on the percentage change in HDL-c at 12 months.<sup>152</sup> There was a statistically significant difference between the groups (p=0.02) in favour of ezetimibe plus fenofibrate (*Table 33*).

# Table 33 Ezetimibe plus fenofibrate compared to fenofibrate: percentage change in HDL-c at 12 months

Study	Follow-up	Ezetimibe plus fenofibrate mean ± SD, n	Fenofibrate mean ± SD, n	p value
McKenney	Baseline	41.7 ± 8.8mg/dL	41.9 ± 9.5mg/dL	NR
2006 <sup>152</sup>	12 months	20.9 ± 14.4%, n=337	17.8 ± 15.3%, n=234	0.02

Abbreviations

mg/dL = milligrams per decilitre, n = number of patients, NR = not reported, SD = standard deviation.

#### Ezetimibe plus fenofibrate vs fenofibrate, percentage change in total cholesterol, 3-12 months

Two studies provided evidence on the percentage change in total cholesterol at 3 months.<sup>165 166</sup> Both studies were included in the meta-analysis. Overall, there was a statistically significant difference between ezetimibe plus fenofibrate and fenofibrate groups at 3 months (MD -10.40%; 95% CI -12.94, -7.86%; p<0.00001) (*Figure 48*). Chi<sup>2</sup> and I<sup>2</sup> statistics indicated low levels of heterogeneity and inconsistency (P=0.30, I<sup>2</sup>=7%).

	Ezetimibe + Fenofibrate Fenofibrate				Mean Difference	Mean Difference			
Study or Subgroup	Mean	SD	Total	Mean	<b>SD</b>	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Ansquer 2009	-27.9	10	59	-18.9	9.9	58	46.3%	-9.00 [-12.61, -5.39]	<b>_</b>
Farnier 2005b	-22.4	10.8	175	-10.8	19.9	179	53.7%	-11.60 [-14.93, -8.27]	
Total (95% CI)			234			237	100.0%	-10.40 [-12.94, -7.86]	· • · · ·
Heterogeneity: Tau² = 0.25; Chi² = 1.08, df = 1 (P = 0.30); l² = 7% Test for overall effect: Z = 8.02 (P < 0.00001)								-20 -10 0 10 20 Favours Ezetimibe + Feno Favours Fenofibrate	

# Figure 48 Forest plot indicating mean difference in total cholesterol (percentage change) for ezetimibe plus fenofibrate compared to fenofibrate (3 months)

#### **Abbreviations**

CI = confidence interval, SD = standard deviation.

One study provided evidence on percentage change in total cholesterol at 12 months.<sup>152</sup> There was a statistically significant difference between groups (p<0.001) in favour of ezetimibe plus fenofibrate (*Table 34*).

# Table 34 Ezetimibe plus fenofibrate compared to fenofibrate: percentage change in total cholesterol at 12 months

Study	Follow-up	Ezetimibe plus fenofibrate mean ± SD, n	Fenofibrate mean ± SD, n	p value
McKenney	Baseline	275.0 ± 101.6mg/dL	277.0 ± 86.5mg/dL	NR
2000132	12 months	-46.0 ± 23.4%, n=337	-41.8 ± 24.2%, n=234	0.02

**Abbreviations** 

mg/dL = milligrams per decilitre, n = number of patients, NR = not reported, SD = standard deviation.

# Ezetimibe plus fenofibrate vs fenofibrate, percentage change in triglycerides, 3–12 months

Two studies provided evidence on the percentage change in triglycerides at 3 months<sup>165 166</sup> and 1 study provided evidence at 12 months.<sup>152</sup> The results were described narratively rather than meta-analysed because it was unclear whether the results from each study were normally distributed.

Two studies reported statistically significant differences between the groups at 3<sup>165</sup> and 12 months<sup>152</sup> in favour of ezetimibe plus fenofibrate (*Table 35*). Another study found no difference between the groups at 3 months.<sup>166</sup>

# Table 35 Ezetimibe plus fenofibrate compared to fenofibrate: percentage change in triglycerides at 3 and 12 months

Study	Follow-up	Ezetimibe plus fenofibrate median ± SD, n	Fenofibrate median ± SD, n	p value
Ansquer 2009 <sup>166</sup>	Baseline	199.0 ± NR mg/dL	223.0 ± NR mg/dL	NR
	3 months	-38.3 ± 24.9%, n=56	-38.3 ± 24.7%, n=58	NS
Farnier 2005 <sup>165</sup>	Baseline	274.6 ± 97.4mg/dL	283.4 ± 88.6mg/dL	NR
	3 months	-44.0 ± 25.3%, n=175	-43.2 ± 27.0%, n=160	0.021
McKenney	Baseline	259.9 ± 32.2mg/dL	264.4 ± 33.5mg/dL	NR
2006 <sup>152</sup>	12 months	-23.2 ± 11.2%, n=337	-13.6 ± 23.8%, n=234	<0.001

Abbreviations

**mg/dL** = milligrams per decilitre, **n** = number of patients, **NR** = not reported, **NS** = not significant.

# 7.3.6 Results: Safety

Studies either reported the specific adverse event or stratified events based on relevant physiology. (*Table 36*). To ensure readability of the report, specific events were reported if there were four or fewer studies describing the adverse events, or there were low event numbers. Adverse events were stratified by body system or organs involved (e.g. gastrointestinal-related) if five or more studies reported events associated with the safety outcome.

Body system	Common adverse events
Gastrointestinal	Constipation, nausea and diarrhea
Hepatobiliary	Elevated liver enzymes (aspartate or alanine aminotransferase)
Musculoskeletal	Myalgia, myopathy, elevated creatine kinase with/without pain
Nervous system	Headache, dizziness
Respiratory	Nasopharyngitis, upper respiratory tract infection

#### Table 36 Common adverse events by body system

#### Hypercholesterolaemia without ASCVD

*Table 37* provides a summary of the main pooled safety outcomes comparing ezetimibe to placebo and statins and ezetimibe plus statin to statins. At 3 months, ezetimibe and placebo groups had similar incidences of adverse events (serious, treatment-related, any, or withdrawal due to). Similarly, there were no significant differences between ezetimibe and statin groups for any safety-related outcome. There was a significantly higher incidence of treatment-related adverse events in the ezetimibe plus statin group compared to the statin group, however, the groups did not differ in any other safety outcome. Common adverse events included gastrointestinal-, musculoskeletal- and nervous system-related adverse events.

Generally, mortality and serious treatment-related adverse events could not be pooled owing to low event rates.

Outcomes	Risk ratio (95% CI)							
	Ezetimibe vs placebo	Ezetimibe vs statins	Ezetimibe plus statins vs statins					
All-cause mortality	NA	NA	NA					
Withdrawal due to adverse	1.18 (0.79, 1.76)	0.95 (0.49, 1.82)	1.18 (0.95, 1.45)					
events	p=0.41	p=0.87	p=0.13					
Serious adverse events	0.98 (0.27, 3.57)	0.70 (0.21, 2.36)	1.08 (0.66, 1.77)					
	p=0.98	p=0.56	p=0.75					
Serious treatment-related	NA	NA	0.52 (0.11, 2.42)					
adverse events			p=0.41					
Any adverse events	0.98 (0.93, 1.04)	1.01 (0.93, 1.10)	1.02 (0.99, 1.05)					
	p=0.51	p=0.77	p=0.15					
Treatment-related adverse	0.91 (0.68, 1.22)	0.85 (0.65, 1.11)	1.12 (1.01, 1.25)					
events	p=0.52	p=0.23	p=0.04					

# Table 37 Summary of safety-related meta-analyses for hypercholesterolaemia without ASCVD

#### **Abbreviations**

**ASCVD** = atherosclerotic cardiovascular disease, **CI** = confidence interval.

## <u>Notes</u>

Risk ratio indicates direction of effect. Numbers >1 indicate risks were lower in placebo or statin groups (higher event rate in ezetimibe or ezetimibe plus statins), numbers <1 indicate risks were lower in ezetimibe or ezetimibe plus statin groups (higher event rate in placebo or statins).

#### Ezetimibe vs placebo

#### Ezetimibe vs placebo, all-cause mortality, 2 weeks-3 months

Ten studies reported all-cause mortality.<sup>104 108 126-128 130-133 167</sup> The results were not meta-analysed owing to the low event rate. There was one death in the ezetimibe group that was deemed unrelated to the intervention (*Table 38*). There were no deaths in the placebo group.

Study	Follow-up	Ezetimibe n/N (%)	Placebo n/N (%)
Ballantyne 2003 <sup>126</sup>	3 months	0/65 (0.0%)	0/60 (0.0%)
Bays 2004 <sup>127</sup>	3 months	0/149 (0.0%)	0/148 (0.0%)
Davidson 2002128	3 months	0/61 (0.0%)	0/70 (0.0%)
Kerzner 2003 <sup>130</sup>	3 months	0/72 (0.0%)	0/64 (0.0%)
Knopp 2003 <sup>131</sup>	3 months	1/622 (0.2%) *	0/205 (0.0%)
Koren 2012 <sup>104</sup>	3 months	0/45 (0.0%)	0/90 (0.0%)
Koren 2014 <sup>132</sup>	3 months	0/77 (0.0%)	0/78 (0.0%)
Kosoglou 2004167	2 weeks	0/9 (0.0%)	0/8 (0.0%)
Melani 2003 <sup>133</sup>	3 months	0/64 (0.0%)	0/65 (0.0%)
Sudhop 2009 <sup>108</sup>	7 weeks	0/41 (0.0%)	0/41 (0.0%)
Absolute rate	2 weeks-3 months	1/1,205 (0.1%)	0/829 (0.0%)

Table 38 Ezetimibe vs p	placebo: all-cause mortalit	у (	2 weeks–3 months)
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### Abbreviations

n = number of patients with event, N = total number of patients.

**Notes** 

\* One death, deemed unrelated to the intervention.

#### Ezetimibe vs placebo, withdrawal due to adverse events, 2 weeks–3 months

Sixteen studies provided evidence on withdrawal due to adverse events and all were included in the meta-analysis.<sup>104 107 108 121 126-135 167 168</sup> Overall, there was no statistically significant difference between the ezetimibe and placebo groups (RR 1.18; 95% CI 0.79, 1.76; p=0.41) (*Figure 49*). The absolute risk for ezetimibe was 3.7% (n=82/2,216) and for the placebo group, 3.0% (n=41/1,353). Chi<sup>2</sup> test and I<sup>2</sup> statistics indicated low levels of heterogeneity and inconsistency (P=0.82, I<sup>2</sup>=0%).

Four studies reported patient withdrawal due to increased aspartate aminotransferases or alanine aminotransferases, prurigo or epileptic events in the ezetimibe group.<sup>121 131 134 135</sup> The events leading to withdrawal were not reported for the placebo group. The remaining studies either had no withdrawals<sup>108</sup> <sup>167 168</sup> or did not report the adverse event leading to withdrawal.<sup>104 107 126-130 132 133</sup>

	Ezetim	ibe	Place	bo		Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI		M-H, Random, 95% Cl
Ballantyne 2003	3	65	3	60	6.6%	0.92 [0.19, 4.40]		
Bays 2004	3	149	4	148	7.3%	0.74 [0.17, 3.27]		
Davidson 2002	5	61	3	71	8.3%	1.94 [0.48, 7.79]		
Dujovne 2002	29	666	6	226	21.3%	1.64 [0.69, 3.90]		- <b>+</b>
Goldberg 2004	5	92	2	93	6.1%	2.53 [0.50, 12.70]		
Kerzner 2003	3	72	5	64	8.3%	0.53 [0.13, 2.14]		
Knopp 2003	22	622	5	205	17.4%	1.45 [0.56, 3.78]		
Koren 2012	0	45	2	90	1.8%	0.40 [0.02, 8.07]		
Koren 2014	5	154	6	154	11.8%	0.83 [0.26, 2.67]		
Kosoglou 2004	0	8	0	8		Not estimable		
Krysiak 2011a	1	43	0	41	1.6%	2.86 [0.12, 68.35]		
Krysiak 2011b	1	24	0	24	1.6%	3.00 [0.13, 70.16]		
Kusters 2015	3	92	0	45	1.8%	3.46 [0.18, 65.63]		
Melani 2003	2	64	5	65	6.2%	0.41 [0.08, 2.02]		
Sudhop 2002	0	18	0	18		Not estimable		
Sudhop 2009	0	41	0	41		Not estimable		
Total (95% CI)		2216		1353	100.0%	1.18 [0.79, 1.76]		<b>◆</b>
Total events	82		41					
Heterogeneity: Tau <sup>2</sup> = Test for overall effect:	0.00; Ch Z = 0.82	i² = 7.50 (P = 0.4	D, df = 12 (1)	(P = 0.	82); I <sup>z</sup> = 0'	%	0.01	0.1 1 10 100 Eavours Placebo Eavours Ezetimibe

#### Figure 49 Forest plot indicating risk ratio of withdrawal due to adverse events for ezetimibe

#### compared to placebo (2 weeks-3 months)

#### Abbreviations

**CI** = confidence interval.

#### Ezetimibe vs placebo, serious adverse events, 2 weeks–3 months

Nine studies provided evidence on serious adverse events and all were included in the meta-analysis.<sup>104</sup>  $^{107 \ 121 \ 127 \ 128 \ 132 \ 167-169}$  Overall, there was no statistically significant difference between the ezetimibe and placebo groups (RR 0.98; 95% CI 0.27, 3.57; p=0.77) (*Figure 50*). The absolute risk for ezetimibe was 0.8% (n=5/645) and for the placebo group, 0.6% (n=4/652). Chi<sup>2</sup> and I<sup>2</sup> statistics indicated low levels of heterogeneity and inconsistency (P=0.85, I<sup>2</sup>=0%).

No study reported the types of serious adverse events, or provided a definition of what constituted a serious adverse event. Five studies reported no serious adverse events.<sup>104 128 167-169</sup> All studies reported the number of events per patient.

	Ezetim	ibe	Place	bo		Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl		M-H, Random, 95% Cl
Bays 2004	2	149	2	148	43.7%	0.99 [0.14, 6.96]		<b>-</b>
Davidson 2002	0	61	0	70		Not estimable		
Davidson 2013	0	26	0	26		Not estimable		
Goldberg 2004	0	92	1	93	16.3%	0.34 [0.01, 8.16]		
Koren 2012	0	45	0	90		Not estimable		
Koren 2014	1	154	1	154	21.7%	1.00 [0.06, 15.84]		
Kosoglou 2004	0	8	0	8		Not estimable		
Kusters 2015	2	92	0	45	18.2%	2.47 [0.12, 50.46]		
Sudhop 2002	0	18	0	18		Not estimable		
Total (95% CI)		645		652	100.0%	0.98 [0.27, 3.57]		
Total events	5		4					
Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 0.79, df = 3 (P = 0.85); I <sup>2</sup> = 0%					5); I² = 09	6		
Test for overall effect: Z = 0.02 (P = 0.98)							0.01	Favours Placebo Favours Ezetimibe

# Figure 50 Forest plot indicating risk ratio of serious adverse events for ezetimibe compared to

#### placebo (2 weeks-3 months)

#### Abbreviations

**CI** = confidence interval.

### Ezetimibe vs placebo, serious treatment-related adverse events, 7 weeks–3 months

Five studies reported serious treatment-related adverse events.<sup>104 107 108 127 132</sup> The results were not meta-analysed because there were no events in the ezetimibe or placebo group (*Table 39*).

No study provided a definition of what constituted a serious adverse event.

Table 39 Ezetimibe vs	placebo: serious	treatment-related	adverse events	(7 weeks–3 months)
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Study	Follow-up	Ezetimibe	Placebo
		n/N (%)	n/N (%)
Bays 2004 <sup>127</sup>	3 months	0/149 (0.0%)	0/148 (0.0%)
Goldberg 2004 <sup>107</sup>	3 months	0/92 (0.0%)	0/93 (0.0%)
Koren 2012 <sup>104</sup>	3 months	0/45 (0.0%)	0/90 (0.0%)
Koren 2014 <sup>132</sup>	3 months	0/154 (0.0%)	0/154 (0.0%)
Sudhop 2009 <sup>108</sup>	7 weeks	0/41 (0.0%)	0/41 (0.0%)
Absolute rate	7 weeks-3 months	0/668 (0.0%)	0/590 (0.0%)

#### **Abbreviations**

n = number of patients with events, N = total number of patients.

# <u>Notes</u>

No serious treatment-related adverse events reported.

#### Ezetimibe vs placebo, any adverse events, 2 weeks-3 months

Fourteen studies provided evidence on adverse events and all were included in the meta-analysis.<sup>104 107</sup>  $^{121 \ 126 \ 135 \ 167}$  Overall, there was no statistically significant difference between the ezetimibe and placebo groups (RR 0.98; 95% Cl 0.93, 1.04; p=0.51) (*Figure 51*). The absolute risk for ezetimibe was 58.6% (n=1,263/2,157) and for the placebo group, 56.4% (n=729/1,293). Chi<sup>2</sup> and I<sup>2</sup> statistics indicated low levels of heterogeneity and inconsistency (P=0.58, I<sup>2</sup>=0%).

In six studies, common adverse events in both treatment arms included gastrointestinal-, musculoskeletal-, nervous system- and respiratory-related adverse events.<sup>104</sup> <sup>121</sup> <sup>129</sup> <sup>131</sup> <sup>132</sup> <sup>167</sup> The remaining studies did not report the type of adverse events.<sup>107</sup> <sup>126-128</sup> <sup>130</sup> <sup>133-135</sup>

No study provided a definition of what constituted an adverse event. Three studies delineated the types of adverse events in accordance with the Medical Dictionary for Regulatory Activities or the National Cancer Institute's Common Toxicity Criteria grading system.<sup>104 132 167</sup> All studies reported the number of events per patient.

	Ezetim	ibe	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% CI
Ballantyne 2003	41	65	34	60	4.0%	1.11 [0.83, 1.49]	
Bays 2004	79	149	80	148	7.4%	0.98 [0.79, 1.21]	+
Davidson 2002	45	61	49	70	7.3%	1.05 [0.85, 1.31]	+
Dujovne 2002	417	666	150	226	27.7%	0.94 [0.85, 1.05]	•
Goldberg 2004	52	92	61	93	6.2%	0.86 [0.68, 1.09]	
Kerzner 2003	46	72	46	64	6.2%	0.89 [0.71, 1.12]	
Knopp 2003	379	622	134	205	24.0%	0.93 [0.83, 1.05]	-
Koren 2012	26	45	41	90	2.9%	1.27 [0.91, 1.78]	
Koren 2014	70	154	68	154	5.4%	1.03 [0.80, 1.32]	+
Kosoglou 2004	5	8	4	8	0.4%	1.25 [0.52, 3.00]	
Krysiak 2011a	1	43	0	41	0.0%	2.86 [0.12, 68.35]	
Krysiak 2011b	1	24	0	24	0.0%	3.00 [0.13, 70.16]	
Kusters 2015	56	92	25	45	3.5%	1.10 [0.80, 1.49]	+-
Melani 2003	45	64	37	65	4.8%	1.24 [0.95, 1.61]	-
Total (95% CI)		2157		1293	100.0%	0.98 [0.93, 1.04]	
Total events	1263		729				
Heterogeneity: Tau <sup>2</sup> = Test for overall effect:	0.00; Chi Z = 0.66 (	i² = 11.3 (P = 0.6	32, df = 1 51)	3 (P = (	).58); I² =	0%	0.005 0.1 1 10 200 Favours Placebo Favours Ezetimibe

#### Figure 51 Forest plot indicating risk ratio of any adverse events for ezetimibe compared to

#### placebo (2 weeks-3 months)

<u>Abbreviations</u> CI = confidence interval.

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#### Ezetimibe vs placebo, any treatment-related adverse events, 7 weeks-3 months

Nine studies provided evidence on treatment-related adverse events and all were included in the metaanalysis.<sup>104</sup> <sup>107</sup> <sup>108</sup> <sup>121</sup> <sup>126-128</sup> <sup>130</sup> <sup>133</sup> Overall, there was no statistically significant difference between the ezetimibe and placebo groups (RR 0.91 95% CI 0.68, 1.22; p=0.52) (*Figure 52*). The absolute risk for ezetimibe was 11.3% (n=77/681) and for the placebo group, 12.4% (n=84/676). Chi<sup>2</sup> and I<sup>2</sup> statistics indicated low levels of heterogeneity and inconsistency (P=0.52, I<sup>2</sup>=0%).

In three studies, common treatment-related adverse events included gastrointestinal-, musculoskeletaland nervous system-related adverse events.<sup>121 126 130</sup> Specific events were not reported. The remaining studies did not report the type of treatment-related adverse events.<sup>104 107 108 127 128 133</sup>

No study provided a definition of what constituted an adverse event. All studies reported the number of events per patient.

	Ezetim	ibe	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
Ballantyne 2003	12	65	12	60	16.5%	0.92 [0.45, 1.89]	<b>e</b>
Bays 2004	19	149	12	148	18.1%	1.57 [0.79, 3.12]	+
Davidson 2002	11	61	17	70	18.7%	0.74 [0.38, 1.46]	
Goldberg 2004	8	92	8	93	9.7%	1.01 [0.40, 2.58]	<b>_</b>
Kerzner 2003	12	72	11	64	15.4%	0.97 [0.46, 2.04]	
Koren 2012	3	45	8	90	5.2%	0.75 [0.21, 2.69]	
Kusters 2015	5	92	6	45	6.7%	0.41 [0.13, 1.26]	
Melani 2003	6	64	7	65	8.0%	0.87 [0.31, 2.45]	
Sudhop 2009	1	41	3	41	1.7%	0.33 [0.04, 3.07]	
Total (95% CI)		681		676	100.0%	0.91 [0.68, 1.22]	•
Total events	77		84				
Heterogeneity: Tau <sup>2</sup> =	0.00; Ch	<sup>2</sup> = 5.6	8, df = 8 (	6			
Test for overall effect:	Z=0.64	(P = 0.5	52)		Favours Placebo Favours Ezetimibe		

#### Figure 52 Forest plot indicating risk ratio of treatment-related adverse events for ezetimibe

#### compared to placebo (7 weeks-3 months)

#### **Abbreviations**

#### Ezetimibe vs statin

#### Ezetimibe vs statin, all-cause mortality, 7 weeks-3 months

Six studies reported all-cause mortality.<sup>108 126-128 130 133</sup> The results were not meta-analysed because there were no events in the ezetimibe or statin group (*Table 40*).

Study	Follow-up	Ezetimibe	Statin
		n/N (%)	n/N (%)
Ballantyne 2003 <sup>126</sup>	3 months	0/65	0/248
Bays 2004 <sup>127</sup>	3 months	0/149	0/622
Davidson 2002 <sup>128</sup>	3 months	0/61	0/263
Kerzner 2003 <sup>130</sup>	3 months	0/72	0/220
Melani 2003 <sup>133</sup>	3 months	0/64	0/205
Sudhop 2009 <sup>108</sup>	7 weeks	0/41	0/41
Absolute rate	7 weeks-3 months	0/452 (0.0%)	0/1,599 (0.0%)

Table 40 Ezetimibe vs statin: all-cause mortality (7 weeks-3 months)

**Abbreviations** 

**n** = number of patients with event, **N** = total number of patients.

#### Ezetimibe vs statin, withdrawal due to adverse events, 2 weeks-3 months

Nine studies provided evidence on withdrawal due to adverse events and all were included in the metaanalysis.<sup>107</sup> <sup>108</sup> <sup>126-128</sup> <sup>133-135</sup> <sup>167</sup> Overall, there was no statistically significant difference between the ezetimibe and statin groups (RR 0.95; 95% CI 0.49, 1.82; p=0.87) (*Figure 53*). The absolute risk for ezetimibe was 3.7% (n=20/547) and for the statin group, 5.4% (n=97/1,809). Chi<sup>2</sup> test and I<sup>2</sup> statistics indicated moderate levels of heterogeneity and inconsistency (P=0.16, I<sup>2</sup>=35%).

Patient withdrawal occurred due to increased aminotransferases in the ezetimibe group,<sup>134 135</sup> and myalgia, hepatomegaly and serious cholelithiasis-cholecystectomy in the statin group.<sup>128 134 135</sup> The remaining studies either had no withdrawals<sup>108 167</sup> or did not report the adverse event leading to withdrawal.<sup>107 126 133</sup>

	Ezetim	ibe	Stati	n		Risk Ratio		Risk	Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl		M-H, Rand	om, 95% Cl	
Ballantyne 2003	3	65	13	248	17.1%	0.88 [0.26, 3.00]				
Bays 2004	3	149	52	622	18.4%	0.24 [0.08, 0.76]	-			
Davidson 2002	5	61	14	263	21.7%	1.54 [0.58, 4.11]				
Goldberg 2004	5	92	12	349	20.9%	1.58 [0.57, 4.37]				
Kosoglou 2004	0	8	0	12		Not estimable				
Krysiak 2011a	1	43	2	44	6.5%	0.51 [0.05, 5.44]		•		
Krysiak 2011b	1	24	1	25	5.1%	1.04 [0.07, 15.73]	-			
Melani 2003	2	64	3	205	10.4%	2.14 [0.36, 12.50]				
Sudhop 2009	0	41	0	41		Not estimable				
Total (95% CI)		547		1809	100.0%	0.95 [0.49, 1.82]		-		
Total events	20		97							
Heterogeneity: Tau <sup>2</sup> =	0.26; Ch	i <sup>z</sup> = 9.2	9, df = 6 (	P = 0.1	6); <b>I<sup>2</sup> =</b> 35	%	L	+		400
Test for overall effect: 2	(P = 0.8	)7)				0.01 Fa	vours Statins	Favours Ezetimibe	100	

#### Figure 53 Forest plot indicating risk ratio of withdrawal due to adverse events for ezetimibe

#### compared to statin (2 weeks-3 months)

#### Abbreviations

**CI** = confidence interval.

#### Ezetimibe vs statin, serious adverse events, 2 weeks–3 months

Four studies provided evidence on serious adverse events and all were included in the meta-analysis.<sup>107</sup>  $^{127 \, 128 \, 167}$  Overall, there was no statistically significant difference between the ezetimibe and statin groups (RR 0.70; 95% CI 0.21 2.36; p=0.56) (*Figure 54*). The absolute risk for ezetimibe was 0.6% (n=2/310) and for the statin group, 1.4% (n=17/1,246). Chi<sup>2</sup> and I<sup>2</sup> statistics indicated low levels of heterogeneity and inconsistency (P=0.93, I<sup>2</sup>=0.0%).

Serious adverse events included cholelithiasis/cholecystectomy and hepatomegaly in the statin group.<sup>128</sup> The remaining studies had no serious adverse events<sup>167</sup> or did not report the type of serious adverse event.<sup>107 127</sup>

No study provided a definition of what constituted a serious adverse event. All studies reported the number of events per patient.

	Ezetim	ibe	Stati	n		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
Bays 2004	2	149	11	622	66.3%	0.76 [0.17, 3.39]	
Davidson 2002	0	61	2	263	16.2%	0.85 [0.04, 17.52]	
Goldberg 2004	0	92	4	349	17.5%	0.42 [0.02, 7.70]	
Kosoglou 2004	0	8	0	12		Not estimable	
Total (95% CI)		310		1246	100.0%	0.70 [0.21, 2.36]	
Total events	2		17				
Heterogeneity: Tau <sup>2</sup> =	0.00; Ch	i <sup>2</sup> = 0.1:	5, df = 2 (	P = 0.9	3); <b>I<sup>2</sup> = 0%</b>	6	
Test for overall effect:	Z = 0.58	(P = 0.5	i6)				Favours Statins Favours Ezetimibe

#### Figure 54 Forest plot indicating risk ratio of serious adverse events for ezetimibe compared to

statin (2 weeks-3 months)

#### Abbreviations

#### Ezetimibe vs statin, serious treatment-related adverse events, 7 weeks-3 months

Three studies reported serious treatment-related adverse events.<sup>107 108 127</sup> The results were not metaanalysed owing to low event numbers. The absolute risk for ezetimibe was 0.0% (0/348) and for the statin group, 0.1% (1/1,081) (*Table 41*).

The serious treatment-related adverse event in the statin group was myopathy.<sup>127</sup> No study provided a definition of what constitutes a serious adverse event. All studies reported the number of events per patient.

Author, year	Follow-up	Ezetimibe	Statin
		n/N (%)	n/N (%)
Bays 2004 <sup>127</sup>	3 months	0/149	1/622
Goldberg 2004 <sup>107</sup>	3 months	0/92	0/349
Sudhop 2009 <sup>108</sup>	7 weeks	0/41	0/41
Absolute rate	7 weeks-3 months	0/348 (0.0%)	1/1,081 (0.1%)

Table 41 Ezetimibe vs statin: serious treatment-related adverse events (7 weeks-3 months)

#### Abbreviations

n = number of patients with events, N = total number of patients.

#### Ezetimibe vs statin, any adverse events, 2 weeks-3 months

Eight studies provided evidence on adverse events and all were included in the meta-analysis.<sup>107 126-128</sup>  $^{133-135\ 167}$  Overall, there was no statistically significant difference between the ezetimibe and statin groups (RR 1.01; 95% CI 0.93, 1.10; p=0.77) (*Figure 55*). The absolute risk for ezetimibe was 53.2% (n=269/506) and 58.1% (n=1,028/1,768) for the statin group. Chi<sup>2</sup> and I<sup>2</sup> statistics indicated low levels of heterogeneity and inconsistency (P=0.84, I<sup>2</sup>=0%).

In five studies, common adverse events in both treatment groups included gastrointestinal-, musculoskeletal-, nervous system- and respiratory-related adverse events. Five studies reported the type of adverse event, <sup>128</sup> <sup>133-135</sup> <sup>167</sup> while the remaining studies did not. <sup>107</sup> <sup>126</sup> <sup>127</sup>

No study provided a definition of what constituted an adverse event. Kosoglou (2004) graded adverse events in accordance with the National Cancer Institute's Common Toxicity Criteria.<sup>167</sup> All studies reported the number of events per patient.

	Ezetim	ibe	Stati	in	Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
Ballantyne 2003	41	65	146	248	14.7%	1.07 [0.87, 1.33]	+
Bays 2004	79	149	332	622	23.7%	0.99 [0.84, 1.18]	+
Davidson 2002	45	61	190	263	23.9%	1.02 [0.86, 1.21]	+
Goldberg 2004	52	92	219	349	17.3%	0.90 [0.74, 1.10]	-
Kosoglou 2004	5	8	9	12	1.7%	0.83 [0.44, 1.56]	
Krysiak 2011a	1	43	2	44	0.1%	0.51 [0.05, 5.44]	
Krysiak 2011b	1	24	1	25	0.1%	1.04 [0.07, 15.73]	
Melani 2003	45	64	129	205	18.4%	1.12 [0.92, 1.35]	+
Total (95% CI)		506		1768	100.0%	1.01 [0.93, 1.10]	•
Total events	269		1028				
Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 3.46, df = 7 (P = 0.84); l <sup>2</sup> = 0%						, 0	
Test for overall effect:	Z = 0.29 (	(P = 0.7	'7)				Favours Statins Favours Ezetimibe

#### Figure 55 Forest plot indicating risk ratio of any adverse events for ezetimibe compared to

#### statin (2 weeks-3 months)

#### <u>Abbreviations</u> CI = confidence interval.

### Ezetimibe vs statin, treatment-related adverse events, 7 weeks–3 months

Six studies provided evidence on treatment-related adverse events and all were included in the metaanalysis.<sup>107 108 126-128 133</sup> Overall, there was no statistically significant difference between the ezetimibe and statin groups (RR 0.85; 95% CI 0.65, 1.11; p=0.23) (*Figure 56*). The absolute risk for ezetimibe was 12.1% (n=57/472) and for the statin group, 15.3% (n=264/1,728). Chi<sup>2</sup> and I<sup>2</sup> statistics indicated low levels of heterogeneity and inconsistency (P=0.76, I<sup>2</sup>=0%).

The types of treatment-related adverse events were reported in one study and included gastrointestinaland musculoskeletal-related adverse events.<sup>126</sup> Specific events were not reported. The remaining studies did not report the type of treatment-related adverse events.<sup>107 108 127 128 133</sup>

No study provided a definition of what constituted a treatment-related adverse event. All studies reported the number of events per patient.

	Ezetim	ibe	Stati	in		Risk Ratio	Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl	
Ballantyne 2003	12	65	42	248	20.9%	1.09 [0.61, 1.95]	│	
Bays 2004	19	149	92	622	33.3%	0.86 [0.54, 1.37]	-∎-	
Davidson 2002	11	61	50	263	20.2%	0.95 [0.53, 1.71]	│	
Goldberg 2004	8	92	46	349	13.8%	0.66 [0.32, 1.35]	I —■+	
Melani 2003	6	64	31	205	10.3%	0.62 [0.27, 1.42]	I —●+	
Sudhop 2009	1	41	3	41	1.4%	0.33 [0.04, 3.07]		
Total (95% CI)		472		1728	100.0%	0.85 [0.65, 1.11]	↓ ◆	
Total events	57		264					
Heterogeneity: Tau <sup>2</sup> =	0.00; Ch	i <sup>2</sup> = 2.5	9, df = 5 (	P = 0.7	6); I <sup>z</sup> = 09	6		4
Test for overall effect:	Z=1.21 (	(P = 0.2	:3)				Favours Statins Favour Ezetimibe	1

#### Figure 56 Forest plot indicating risk ratio of treatment-related adverse events for ezetimibe

#### compared to statin (7 weeks-3 months)

#### Abbreviations

#### Ezetimibe plus statin vs statin, all-cause mortality, 7 weeks-24 months

Twelve studies provided evidence on all-cause mortality.<sup>106 108 109 120 122 126-128 133 137 138 140</sup> The results were not meta-analysed due to low event numbers. The absolute risk for ezetimibe plus statins was 0.2% (5/2,802) and in the statin group, 0.1% (1/1,984) (*Table 42*). All deaths were deemed unrelated to the intervention.

Study	Follow-up	Ezetimibe plus statin n/N (%)	Statin n/N (%)
Ballantyne 2003126	3 months	0/255	0/248
Ballantyne 2004b <sup>137</sup>	12 months	0/201	0/45
Bays 2004 <sup>127</sup>	3 months	1/609	0/622
Bays 2008 <sup>106</sup>	15 months	0/539	0/229
Davidson 2002 <sup>128</sup>	3 months	1/274	0/263
Kastelein 2008120	24 months	2/357 (0.6%)	1/363 (0.3%)
Masana 2005 <sup>138</sup>	12 months	1/355	0/78
Melani 2003 <sup>133</sup>	3 months	0/204	0/205
Robinson 2014 <sup>109</sup>	3 months	0/111	0/111
Strony 2008 <sup>140</sup>	12 months	0/87	0/22
Sudhop 2009 <sup>108</sup>	7 weeks	0/41	0/41
Van der Graff 2008 <sup>122</sup>	12 months	0/126	0/120
Absolute rate	7 weeks-24 months	5/2,802 (0.2%)	1/1,984 (0.1%)

Table 42 Ezetimibe plus statin vs statin: all-cause mortality (7 weeks-24 months)

#### **Abbreviations**

n = number of patients with events, N = total number of patients.

#### <u>Notes</u>

All deaths were deemed unrelated to interventions.

#### Ezetimibe plus statin vs statin, withdrawal due to adverse events, 2 weeks-24 months

Twenty-one studies provided evidence on withdrawal due to adverse events and all were included in the meta-analysis.<sup>106-109 120 122 126-128 133-142 167 170</sup> Overall, there was no statistically significant difference between the ezetimibe plus statin and statin groups (RR 1.18; 95% CI 0.95, 1.45; p=0.13) (*Figure 57*). The absolute risk for ezetimibe plus statin was 5.8% (n=248/4,271) and for the statin group, 4.1% (n=143/3,484). Chi<sup>2</sup> test and l<sup>2</sup> statistics indicated low levels of heterogeneity and inconsistency (P=0.46,  $l^2=0\%$ ).

In six studies, common reasons for patient withdrawal in both groups included musculoskeletal-related adverse events (myalgia and elevated levels of creatine kinase) and hepatobiliary-related adverse events (elevated liver enzymes).<sup>107 120 122 128 134 135</sup> The remaining studies either had no withdrawals<sup>108</sup> <sup>141 142</sup> or did not report the adverse event leading to withdrawal.<sup>106 109 126 127 133 136-140 167 170</sup>

	Ezetimibe +	Statin	Stati	in		Risk Ratio		Risk Rat	lio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl		M-H, Random,	, 95% CI
Alvarez-Sala 2008	2	38	0	44	0.5%	5.77 [0.29, 116.57]			· · · · · · · · · · · · · · · · · · ·
Ballantyne 2003	15	255	13	248	8.5%	1.12 [0.55, 2.31]			_
Ballantyne 2004b	32	201	6	45	6.7%	1.19 [0.53, 2.68]			
Bays 2004	31	609	31	622	18.8%	1.02 [0.63, 1.66]			
Bays 2008	40	539	8	229	8.0%	2.12 [1.01, 4.47]			
Chirinos 2010	1	28	0	30	0.4%	3.21 [0.14, 75.61]			
Davidson 2002	20	274	14	263	10.1%	1.37 [0.71, 2.66]			
Florentin 2011	0	50	0	50		Not estimable			
Goldberg 2004	16	353	7	349	5.8%	2.26 [0.94, 5.43]		-	
Kastelein 2008	29	357	34	363	19.7%	0.87 [0.54, 1.39]			
Kosoglou 2004	0	12	0	12		Not estimable			
Krysiak 2011a	2	42	2	44	1.2%	1.05 [0.15, 7.10]			
Krysiak 2011b	1	24	1	25	0.6%	1.04 [0.07, 15.73]			
Liberopoulos 2013	0	25	0	25		Not estimable			
Masana 2005	26	355	8	78	7.8%	0.71 [0.34, 1.52]			
Melani 2003	9	204	3	205	2.6%	3.01 [0.83, 10.98]		+	
Ose 2007	11	544	12	560	6.8%	0.94 [0.42, 2.12]			-
Robinson 2014	1	111	3	111	0.9%	0.33 [0.04, 3.16]			
Strony 2008	7	87	0	22	0.6%	3.92 [0.23, 66.15]			
Sudhop 2009	0	41	0	41		Not estimable			
van der Graff 2008	5	122	1	118	1.0%	4.84 [0.57, 40.78]			
Total (95% CI)		4271		3484	100.0%	1.18 [0.95, 1.45]		•	
Total events	248		143					-	
Heterogeneity: Tau <sup>2</sup> =	0.00; Chi <sup>2</sup> = 1	5.94, df=	= 16 (P =	0.46): f	²=0%		L		
Test for overall effect:	Z = 1.53 (P = (	0.13)					0.005	U.1 1	10 200
		-,						Favours Statins Fa	wours Ezetimide+Statins

#### Figure 57 Forest plot indicating risk ratio of withdrawal due to adverse events for ezetimibe

#### plus statin compared to statin (2 weeks-24 months)

<u>Abbreviations</u> CI = confidence interval.

#### Ezetimibe plus statin vs statin, serious adverse events, 2 weeks–12 months

Twelve studies provided evidence on serious adverse events and all were included in the metaanalysis.<sup>106 107 109 127 128 136-140 167 170</sup> Overall, there was no statistically significant difference between the ezetimibe plus statin and statin groups (RR 1.08; 95% CI 0.66, 1.77; p=0.75) (*Figure 58*). The absolute risk for ezetimibe plus statin was 4.2% (n=132/3,151) and for the statin group, 2.1% (n=49/2,365). Chi<sup>2</sup> and I<sup>2</sup> statistics indicated moderate levels of heterogeneity and inconsistency (P=0.12, I<sup>2</sup>=36%).

Serious adverse events were reported in three studies and included generalised convulsive crisis in the ezetimibe plus statin group,<sup>136</sup> and hepatomegaly and cholelithiasis in the statin group.<sup>128</sup> <sup>139</sup> The remaining studies had no serious adverse events<sup>170</sup> or did not report the type of events.<sup>106</sup> <sup>107</sup> <sup>109</sup> <sup>127</sup> <sup>137-</sup>

No study provided a definition of what constitutes an adverse event. All studies reported the number of events per patient.

	Ezetimibe +	timibe + Statin		Statin		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
Alvarez-Sala 2008	1	38	0	44	2.2%	3.46 [0.15, 82.56]	· · · · · · · · · · · · · · · · · · ·
Ballantyne 2004b	17	201	5	45	14.7%	0.76 [0.30, 1.96]	<b>-</b>
Bays 2004	9	609	1	622	4.8%	9.19 [1.17, 72.33]	
Bays 2008	28	539	6	229	16.1%	1.98 [0.83, 4.72]	↓ <b>-</b>
Chirinos 2010	0	28	0	30		Not estimable	
Davidson 2002	0	274	2	263	2.4%	0.19 [0.01, 3.98]	
Goldberg 2004	3	353	4	349	8.1%	0.74 [0.17, 3.29]	
Kosoglou 2004	0	12	0	12		Not estimable	
Masana 2005	43	355	13	78	22.5%	0.73 [0.41, 1.28]	
Ose 2007	11	544	13	560	17.5%	0.87 [0.39, 1.93]	
Robinson 2014	0	111	3	111	2.5%	0.14 [0.01, 2.73]	· · · · · · · · · · · · · · · · · · ·
Strony 2008	20	87	2	22	9.1%	2.53 [0.64, 10.01]	
Total (95% CI)		3151		2365	100.0%	1.08 [0.66, 1.77]	↓ <b>◆</b>
Total events	132		49				
Heterogeneity: Tau <sup>2</sup> = Test for overall effect:	0.19; Chi² = 1 Z = 0.32 (P = 1	4.10, df= 0.75)	= 9 (P = 0	.12); I²	= 36%		0.005 0.1 1 10 200 Favours Statins Favours Ezetimibe+Statins

# Figure 58 Forest plot indicating risk ratio of serious adverse events for ezetimibe plus statin compared to statin (2 weeks–12 months)

#### Abbreviations

**CI** = confidence interval.

#### Ezetimibe plus statin vs statin, serious treatment-related adverse events, 7 weeks-12 months

Six studies provided evidence on serious treatment-related adverse events and all were included in the meta-analysis.<sup>106-108</sup> <sup>127</sup> <sup>137</sup> <sup>140</sup> Overall, there was no statistically significant difference between the ezetimibe plus statin and statin groups (RR 0.52; 95% Cl 0.11, 2.42; p=0.41) (*Figure 59*). The absolute risk for ezetimibe plus statin was 0.4% (n=7/1,830) and for the statin group, 0.2% (n=3/1,308). Chi<sup>2</sup> and I<sup>2</sup> statistics indicated low levels of heterogeneity and inconsistency (P=0.33, I<sup>2</sup>=13%).

Serious adverse events were reported in four studies and included cholestatic hepatits,<sup>137</sup> myalgia, gastroesophageal reflux, alanine aminotransferase greater than three times upper limit, elevated CK with back pain<sup>140</sup> and cholecystitis<sup>106</sup> in the ezetimibe plus statin group; and duodenitis, myalgia, nausea<sup>137</sup> and myopathy in the statin group.<sup>127</sup> Symptoms resolved in two studies.<sup>106 137</sup> It was not reported whether symptoms resolved in the other studies.<sup>127 140</sup> The remaining studies had no serious treatment-related adverse events.<sup>107 108</sup>

No study provided a definition of what constituted a serious adverse event. All studies reported the number of events per patient.



## Figure 59 Forest plot indicating risk ratio of serious treatment-related adverse events for ezetimibe plus statin compared to statin (7 weeks–12 months)

Abbreviations

**CI** = confidence interval.

#### Ezetimibe plus statin vs statin, any adverse events, 2 weeks-24 months

Seventeen studies provided evidence on any adverse events and all were included in the metaanalysis.<sup>106 107 109 120 122 126-128 133-140 167</sup> Overall, there was no statistically significant difference between the ezetimibe plus statin and statin groups (RR 1.02; 95% CI 0.99, 1.05; p=0.15) (*Figure 60*). The absolute risk for ezetimibe plus statin was 63.6% (n=2,626/4,131) and for the statin group, 59.4% (n=1,985/3,342). Chi<sup>2</sup> and I<sup>2</sup> statistics indicated low levels of heterogeneity and inconsistency (P=0.94, I<sup>2</sup>=0%).

In ten studies, common adverse events in both treatment groups included gastrointestinal-, hepatobiliary-, musculoskeletal-, nervous system- and respiratory-related adverse events.<sup>106 109 122 126 128</sup> <sup>134-136 140 167</sup> The remaining studies did not report the type of adverse events.<sup>107 120 127 133 137-139</sup>

No study provided a definition of what constituted an adverse event. Kosoglou (2004) graded adverse events in accordance with the National Cancer Institute's Common Toxicity Criteria.<sup>167</sup> All studies reported the number of events per patient.



#### Figure 60 Forest plot indicating risk ratio of any adverse events for ezetimibe plus statin

#### compared to statin (2 weeks-24 months)

#### Abbreviations

CI = confidence interval.

#### Ezetimibe plus statin vs statin, treatment-related adverse events, 3–24 months

Twelve studies provided evidence on treatment-related adverse events and all were included in the meta-analysis.<sup>106-108 120 126-128 133 137-140</sup> Overall, there was a statistically significant difference between the ezetimibe plus statin and statin groups (RR 1.12; 95% CI 1.01, 1.35; p=0.04) (*Figure 61*). The absolute risk for ezetimibe plus statin was 17.2% (n=657/3,819) and for the statin group, 15.1% (n=456/3,025). Chi<sup>2</sup> and I<sup>2</sup> statistics indicated low levels of heterogeneity and inconsistency (P=0.86, I<sup>2</sup>=0%).

In three studies, common treatment-related adverse events in both groups included gastrointestinaland musculoskeletal-related adverse events.<sup>126</sup> <sup>128</sup> <sup>139</sup> The remaining studies did not report the type of adverse events.<sup>106-108</sup> <sup>120</sup> <sup>127</sup> <sup>133</sup> <sup>137</sup> <sup>138</sup> <sup>140</sup>

No study provided a definition of what constituted a treatment-related adverse event. All studies reported the number of events per patient.

	Ezetimibe +	Statin	Stati	atin Risk Ratio		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% CI
Ballantyne 2003	58	255	42	248	9.5%	1.34 [0.94, 1.92]	
Ballantyne 2004b	45	201	12	45	4.0%	0.84 [0.49, 1.45]	
Bays 2004	92	609	92	622	17.1%	1.02 [0.78, 1.33]	+
Bays 2008	73	539	26	229	6.9%	1.19 [0.78, 1.82]	
Davidson 2002	54	274	50	263	10.2%	1.04 [0.73, 1.46]	+
Goldberg 2004	48	353	46	349	8.6%	1.03 [0.71, 1.50]	+
Kastelein 2008	122	357	107	363	26.4%	1.16 [0.94, 1.44]	
Masana 2005	69	355	13	78	4.2%	1.17 [0.68, 2.00]	<del></del>
Melani 2003	35	204	31	205	6.2%	1.13 [0.73, 1.77]	
Ose 2007	40	544	31	560	5.9%	1.33 [0.84, 2.09]	+
Strony 2008	21	87	3	22	1.0%	1.77 [0.58, 5.40]	
Sudhop 2009	0	41	3	41	0.1%	0.14 [0.01, 2.68]	
Total (95% CI)		3819		3025	100.0%	1.12 [1.01, 1.25]	•
Total events	657		456				
Heterogeneity: Tau <sup>z</sup> = 0.00; Chi <sup>z</sup> = 6.18, df = 11 (P = 0.86); I <sup>z</sup> = 0% Test for overall effect: Z = 2.06 (P = 0.04)							0.005 0.1 1 10 200 Favours Statins Favours Ezetimibe+Statins

#### Figure 61 Forest plot indicating risk ratio of treatment-related adverse events for ezetimibe

#### plus statin compared to statin (3-24 months)

#### **Abbreviations**

CI = confidence interval.

#### Sub-groups

#### Ezetimibe vs statins

Meta-analyses determined there was no difference between ezetimibe and simvastatin for any safetyrelated outcomes.

The remaining statins could not be meta-analysed owing to insufficient study numbers. In one study, there was a similar incidence of adverse events (serious, treatment-related, any, or withdrawal due to) between ezetimibe and atorvastatin, pravastatin or rosuvastatin. The statistical significance was not reported so it is unclear whether the groups differed. For further information, refer to **Table 104**, **Appendix D**.

#### Ezetimibe plus statins vs statins

Meta-analyses determined there was no difference between ezetimibe plus atorvastatin and atorvastatin or ezetimibe plus simvastatin and simvastatin for any safety-related outcomes.

The remaining statins could not be meta-analysed owing to insufficient study numbers. There was a similar incidence of adverse events (serious, treatment-related, any, or withdrawal due to) between ezetimibe and pravastatin or rosuvastatin. The statistical significance was not reported so it is unclear whether the groups differed. For further information, refer to *Table 105, Appendix D*.

#### Hypercholesterolaemia with ASCVD

*Table 43* provides a summary of the main pooled safety outcomes comparing ezetimibe plus statin to statins. There was no statistically significant difference between ezetimibe plus statins and statins for mortality or adverse events (serious, treatment-related or withdrawal due to). Musculoskeletal-related adverse events (myopathy and myalgia) and gastrointestinal-related adverse events (diarrhoea or nausea) were common to both treatment groups.

Table 43 Summar	y of safet	y-related n	neta-analyse	es for hype	rcholesterola	aemia and	ASCVD

Outcomes	Ezetimibe plus statins vs statins Risk ratio (95% CI)
All-cause mortality	0.99 (0.92, 1.07); p=0.80
Withdrawal due to adverse events	1.05 (0.97, 1.13); p=0.23
Serious adverse events	1.20 (1.00, 1.44); p=0.06
Serious treatment-related adverse events	1.26 (0.51, 3.15); p=0.61
Any adverse events	0.98 (0.93, 1.03); p=0.48
Treatment-related adverse events	1.08 (0.94, 1.23); p=0.29

#### **Abbreviations**

**ASCVD** = atherosclerotic cardiovascular disease, **CI** = confidence interval.

#### Notes

Risk ratio indicates direction of effect i.e. numbers >1 indicate risks were lower in statin groups (higher event rate in ezetimibe plus statins), numbers <1 indicate risks were lower in ezetimibe plus statin groups (higher event rate in statins).

#### Ezetimibe plus statin vs statin

#### Ezetimibe plus statin vs statin, all-cause mortality, 6 weeks-7 years

A total of 29 studies provided evidence on all-cause mortality and all were included in the metaanalysis.<sup>52 110</sup> 111 124 144 145 148 149 154-157 159 161 171-185 Overall, there was no statistically significant difference between the ezetimibe plus statin and statin groups (RR 0.99; 95% CI 0.92, 1.07; p=0.80) (*Figure 62*). The absolute risk for ezetimibe plus statin was 7.9% (n=1,232/15,578) and for the statin group, 7.8% (n=1,243/15,905). Chi<sup>2</sup> test and I<sup>2</sup> statistics indicated low levels of heterogeneity and inconsistency (P=0.91, I<sup>2</sup>=0%). Any reported deaths were deemed unrelated to the intervention.

	Ezetimibe +	+ Statin	Stat	in		Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI		M-H, Random, 95% Cl
Ballantyne 2007	1	239	0	230	0.1%	2.89 [0.12, 70.52]		
Bardini 2010	0	42	0	51		Not estimable		
Bays 2011	0	221	0	219		Not estimable		
Bays 2013	0	124	0	124		Not estimable		
Bays 2015	2	101	0	149	0.1%	7.35 [0.36, 151.57]		
Blagden 2007	0	72	0	76		Not estimable		
Brohet 2005	0	208	0	210		Not estimable		
Cannon 2015	1215	9067	1231	9077	98.9%	0.99 [0.92, 1.06]		
Catapano 2006	0	1478	0	1481		Not estimable		
Conard 2008	0	96	0	98		Not estimable		
Cruz-Fernandez 2005	0	220	1	230	0.1%	0.35 [0.01, 8.51]		
Farnier 2005a	0	181	0	191		Not estimable		
Farnier 2009	1	314	0	304	0.1%	2.90 [0.12, 71.03]		
Farnier 2016	1	101	0	101	0.1%	3.00 [0.12, 72.78]		
Foody 2010	1	257	2	257	0.1%	0.50 [0.05, 5.48]		
Gagne 2002	0	379	0	390		Not estimable		
Hing Ling 2012	0	120	0	130		Not estimable		
Kouvelos 2013	0	126	1	136	0.1%	0.36 [0.01, 8.75]		
Landray 2006	3	101	0	102	0.1%	7.07 [0.37, 135.12]		
Leiter 2004	0	286	0	289		Not estimable		
Ostad 2009	1	29	0	29	0.1%	3.00 [0.13, 70.74]		
Patel 2008	0	78	1	75	0.1%	0.32 [0.01, 7.75]		
Reckless 2008	4	213	4	211	0.3%	0.99 [0.25, 3.91]		
Robinson 2009	0	450	0	678		Not estimable		
Roeters Van Lennep 2008	0	178	0	189		Not estimable		
Stein 2004	0	293	1	303	0.1%	0.34 [0.01, 8.43]		
Stojakovic 2010	0	56	0	28		Not estimable		
West 2011	1	22	1	22	0.1%	1.00 [0.07, 15.00]		
Zieve 2010	2	526	1	525	0.1%	2.00 [0.18, 21.95]		
Total (95% CI)		15578		15905	100.0%	0.99 [0.92, 1.07]		
Total events	1232		1243					
Heterogeneity: Tau <sup>2</sup> = 0.00; 0	Chi² = 7.54, df	= 14 (P =	0.91); I <sup>2</sup> :	= 0%			L	
Test for overall effect: Z = 0.2	.5 (P = 0.80)						0.005	U.1 1 1U 200 Eavours Stating Eavours Exetimibe+Stating
								r avours statins in avours Ezetimine*Statins

#### Figure 62 Forest plot indicating risk ratio of all-cause mortality for ezetimibe plus statin

#### compared to statin (6 weeks-7 years)

#### Abbreviations

#### Ezetimibe plus statin vs statin, withdrawal due to adverse events, 1–30 months

A total of 39 studies provided evidence on withdrawal due to adverse events and all were included in the meta-analysis.<sup>52 110</sup> <sup>111</sup> <sup>124</sup> <sup>144-151</sup> <sup>153-157</sup> <sup>161</sup> <sup>171-191</sup> Overall, there was no statistically significant difference between the ezetimibe plus statin and statin groups (RR 1.05; 95% CI 0.97, 1.13; p=0.23) (*Figure 63*). The absolute risk for ezetimibe plus statin was 7.1% (n=1,199/16,828) and for the statin group, 6.7% (n=1,151/17,199). Chi<sup>2</sup> test and I<sup>2</sup> statistics indicated low levels of heterogeneity and inconsistency (P=0.52, I<sup>2</sup>=0%).

In twelve studies, common adverse events leading to withdrawals in both groups included musculoskeletal-,<sup>110 145 147 173</sup> gastrointestinal-,<sup>173 180 183</sup> nervous system-,<sup>148 174</sup> hepatobiliary-,<sup>172 173 175 180</sup> <sup>188</sup> and skin-related adverse events.<sup>173 191</sup> The remaining studies either had no withdrawals or did not specify the type of adverse events.<sup>52 111 124 144 146 149-151 153-157 161 171 176-179 181 182 184-187 189 190</sup>

	Ezetimibe +	Statin	Stati	n		Risk Ratio	Risk Ratio							
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl							
Averna 2010	0	60	1	60	0.1%	0.33 [0.01, 8.02]								
Ballantyne 2004a	24	263	14	262	1.5%	1.71 [0.90, 3.23]								
Ballantyne 2007	8	238	6	230	0.6%	1.29 [0.45, 3.66]								
Ballantyne 2019	10	109	2	55	0.3%	2.52 [0.57, 11.12]								
Bardini 2010	2	42	4	51	0.2%	0.61 [0.12, 3.15]								
Barrios 2005	10	221	16	214	1.0%	0.61 [0.28, 1.30]								
Bays 2011	5	221	0	219	0.1%	10.90 [0.61, 195.96]								
Bays 2013	1	124	1	124	0.1%	1.00 [0.06, 15.81]								
Bays 2015	4	101	8	149	0.4%	0.74 [0.23, 2.38]								
Blagden 2007	6	72	1	76	0.1%	6.33 [0.78, 51.32]								
Brohet 2005	4	208	0	210	0.1%	9.09 [0.49, 167.71]								
Cannon 2015	903	9067	877	9077	77.9%	1.03 [0.94, 1.13]								
Catapano 2006	33	1478	33	1481	2.7%	1.00 [0.62, 1.61]	+							
Chenot 2007	0	20	1	20	0.1%	0.33 [0.01, 7.72]								
Conard 2008	0	96	2	98	0.1%	0.20 [0.01, 4.20]								
Cruz-Fernandez 2005	4	220	1	230	0.1%	4.18 [0.47, 37.12]								
Deharo 2014	0	64	0	64		Not estimable								
Farnier 2005a	9	181	4	191	0.5%	2.37 [0.74, 7.57]	+							
Farnier 2009	17	314	11	304	1.1%	1.50 [0.71, 3.14]	<b></b>							
Farnier 2016	8	101	5	101	0.5%	1.60 [0.54, 4.72]								
Feldman 2004	10	109	16	253	1.1%	1.45 [0.68, 3.09]								
Foody 2010	14	257	11	257	1.0%	1.27 [0.59, 2.75]	- <del></del>							
Gagne 2002	14	379	14	390	1.1%	1.03 [0.50, 2.13]								
Hing Ling 2012	0	119	4	130	0.1%	0.12 [0.01, 2.23]								
Hougaard 2017	0	43	1	44	0.1%	0.34 [0.01, 8.14]								
Kouvelos 2013	2	126	2	136	0.2%	1.08 [0.15, 7.55]								
Landray 2006	0	101	1	102	0.1%	0.34 [0.01, 8.17]								
Leiter 2004	7	286	9	289	0.6%	0.79 [0.30, 2.08]								
McCormack 2010	7	259	9	261	0.6%	0.78 [0.30, 2.07]								
Nicholl 2017	3	127	2	54	0.2%	0.64 [0.11, 3.71]								
Ostad 2009	2	29	5	29	0.3%	0.40 [0.08, 1.90]								
Patel 2008	5	78	1	75	0.1%	4.81 [0.58, 40.19]								
Reckless 2008	28	213	31	211	2.7%	0.89 [0.56, 1.44]								
Robinson 2009	10	450	22	678	1.1%	0.68 [0.33, 1.43]								
Roeters Van Lennep 2008	10	178	7	189	0.7%	1.52 [0.59, 3.90]	_ <del></del>							
Settergren 2008	2	21	0	22	0.1%	5.23 [0.27, 102.87]								
Stein 2004	13	305	14	316	1.1%	0.96 [0.46, 2.01]	_ <del></del>							
West 2011	0	22	1	22	0.1%	0.33 [0.01, 7.76]								
Zieve 2010	24	526	14	525	1.4%	1.71 [0.90, 3.27]	<u>+</u>							
Total (95% CI)		16828		17199	100.0%	1.05 [0.97, 1.13]	•							
Total events	1199		1151											
Heterogeneity: Tau <sup>2</sup> = 0.00; C	hiZ-26.06 d	f - 27 /P	- 0.62\.18	- 0%										
	/m – JJ.UJ. u	n – Jr (r -	- 0.327.1	- 0.0										

#### Figure 63 Forest plot indicating risk ratio of withdrawal due to adverse events for ezetimibe

#### plus statin compared to statin (1-30 months)

#### Abbreviations

#### Ezetimibe plus statin vs statin, serious adverse events, 6 weeks-6 months

A total of 29 studies provided evidence on serious adverse events and all were included in the metaanalysis.<sup>110</sup> <sup>111</sup> <sup>124</sup> <sup>147-150</sup> <sup>154-157</sup> <sup>161</sup> <sup>171-182</sup> <sup>184-187</sup> <sup>190</sup> Overall, there was no statistically significant difference between the ezetimibe plus statin and statin groups (RR 1.20; 95% CI 1.00, 1.44; p=0.06) (*Figure 64*). The absolute risk for ezetimibe plus statin was 3.2% (n=228/7,047) and for the statin group, 2.7% (n=198/7,468). Chi<sup>2</sup> and I<sup>2</sup> statistics indicated low levels of heterogeneity and inconsistency (P=0.81, I<sup>2</sup>=0%).

In six studies, serious adverse events in the ezetimibe plus statin group included bone fracture,<sup>171</sup> overdose, chest pain,<sup>187</sup> angina, stent placement, stent occlusion, musculoskeletal chest pain,<sup>124</sup> stroke, initiation of dialysis, vascular access procedures, renal transplantation, surgical procedures, cancer, peritonitis, trauma and non-specified medical events.<sup>161</sup> Serious adverse events in the statin group included stroke,<sup>186</sup> ACS, pelvic fracture,<sup>187</sup> hip dislocation,<sup>174</sup> initiation of dialysis, vascular access procedures, trauma and non-specified medical procedures, trauma and non-specified medical procedures, trauma and non-specified medical event.<sup>161</sup> One study reported the type of serious adverse event but not the corresponding treatment group.<sup>187</sup> The remaining studies did not specify types of adverse events.<sup>110</sup> 111 147-150 154-157 161 172 173 175-182 184 185 190

Eight studies provided definitions of what constituted a serious adverse event.<sup>111 148 149 172 175 176 178 180</sup> All studies reported the number of events per patient.

	Ezetimibe +	Statin	Stati	n		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
Averna 2010	0	60	1	60	0.3%	0.33 [0.01, 8.02]	
Ballantyne 2007	5	238	4	230	2.0%	1.21 [0.33, 4.44]	
Ballantyne 2019	9	109	1	55	0.8%	4.54 [0.59, 34.94]	
Bardini 2010	1	42	0	51	0.3%	3.63 [0.15, 86.81]	
Barrios 2005	5	221	2	214	1.3%	2.42 [0.47, 12.34]	
Bays 2011	0	221	2	219	0.4%	0.20 [0.01, 4.10]	
Bays 2013	2	124	2	124	0.9%	1.00 [0.14, 6.99]	
Bays 2015	7	101	8	149	3.6%	1.29 [0.48, 3.45]	<del></del>
Blagden 2007	0	72	1	76	0.3%	0.35 [0.01, 8.49]	
Brohet 2005	5	208	0	210	0.4%	11.11 [0.62, 199.57]	
Catapano 2006	18	1478	16	1481	7.7%	1.13 [0.58, 2.20]	_ <b>-</b>
Conard 2008	0	96	0	98		Not estimable	
Cruz-Fernandez 2005	3	220	4	230	1.6%	0.78 [0.18, 3.46]	
Farnier 2005a	4	181	1	191	0.7%	4.22 [0.48, 37.41]	
Farnier 2009	3	314	5	304	1.7%	0.58 [0.14, 2.41]	
Farnier 2016	8	101	8	101	3.9%	1.00 [0.39, 2.56]	
Feldman 2004	3	109	12	253	2.2%	0.58 [0.17, 2.02]	
Foody 2010	3	257	4	257	1.6%	0.75 [0.17, 3.32]	
Gagne 2002	19	379	9	390	5.6%	2.17 [1.00, 4.74]	
Hing Ling 2012	1	119	1	130	0.5%	1.09 [0.07, 17.27]	
Landray 2006	36	102	25	101	18.6%	1.43 [0.93, 2.19]	+
Leiter 2004	9	286	5	289	2.9%	1.82 [0.62, 5.36]	
McCormack 2010	4	259	5	261	2.0%	0.81 [0.22, 2.97]	
Patel 2008	2	78	1	75	0.6%	1.92 [0.18, 20.77]	
Reckless 2008	44	213	42	211	24.1%	1.04 [0.71, 1.51]	+
Robinson 2009	1	450	9	678	0.8%	0.17 [0.02, 1.32]	
Roeters Van Lennep 2008	9	178	7	189	3.7%	1.37 [0.52, 3.59]	<b>-</b>
Stein 2004	12	305	9	316	4.8%	1.38 [0.59, 3.23]	_ <b>+•</b>
Zieve 2010	15	526	14	525	6.7%	1.07 [0.52, 2.19]	
Total (95% CI)		7047		7468	100.0%	1.20 [1.00, 1.44]	•
Total events	228		198				
Heterogeneity: Tau <sup>2</sup> = 0.00; C	hi <sup>2</sup> = 20.43, d	f = 27 (P	= 0.81); P	²= 0%			teen to teen ad
Test for overall effect: Z = 1.91	1 (P = 0.06)						U.UU5 U.1 1 10 200 Eavours Statins Eavours Ezetimibe+Statins

#### Figure 64 Forest plot indicating risk ratio of serious adverse events for ezetimibe plus statin

compared to statin (6 weeks-6 months)

#### Abbreviations

#### Ezetimibe plus statin vs statin, serious treatment-related adverse events, 6 weeks-6 months

Twenty-one studies provided evidence on serious treatment-related adverse events and all were included in the meta-analysis.<sup>110</sup> <sup>111</sup> <sup>124</sup> <sup>147</sup> <sup>150</sup> <sup>155-157</sup> <sup>161</sup> <sup>172-174</sup> <sup>176-180</sup> <sup>182</sup> <sup>185-187</sup> Overall, there was no statistically significant difference between the ezetimibe plus statin and statin groups (RR 1.26; 95% CI 0.51, 3.15; p=0.61) (*Figure 65*). The absolute risk for ezetimibe plus statin was 0.2% (n=10/4,691) and for the statin group, 0.2% (n=8/5,031). Chi<sup>2</sup> and I<sup>2</sup> statistics indicated low levels of heterogeneity and inconsistency (P=0.96, I<sup>2</sup>=0%).

In two studies, serious treatment-related adverse events included abdominal pain, diarrhoea, syncope, elevated liver enzymes,<sup>180</sup> seizure, pruritus, myalgia (without CK increases) and alanine aminotransferase levels three times above the upper limit<sup>155</sup> in the ezetimibe plus statin group; and chest heaviness and dyspepsia in the statin group.<sup>180</sup> The remaining studies had no serious treatment-related adverse events or did not specify the type of event.<sup>110</sup> 111 124 147 150 156 157 161 172-174 176-179 182 185-187

Five studies provided definitions of what constituted an adverse event.<sup>111 172 176 178 180</sup> All studies reported the number of events per patient.

	Ezetimibe +	Statin	Stat	in		Risk Ratio		Risk	Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl		M-H, Rand	om, 95% Cl
Averna 2010	0	60	0	60		Not estimable			
Ballantyne 2007	0	238	0	230		Not estimable			
Ballantyne 2019	0	109	0	55		Not estimable			
Barrios 2005	0	221	0	214		Not estimable			
Bays 2011	0	221	0	219		Not estimable			
Bays 2013	0	124	0	124		Not estimable			
Blagden 2007	0	72	0	76		Not estimable			
Brohet 2005	0	208	0	210		Not estimable			
Conard 2008	0	96	0	98		Not estimable			
Cruz-Fernandez 2005	0	220	0	230		Not estimable			
Farnier 2005a	0	181	0	191		Not estimable			
Farnier 2009	1	314	1	304	10.8%	0.97 [0.06, 15.41]			
Feldman 2004	0	109	0	253		Not estimable			
Foody 2010	0	257	0	257		Not estimable			
Gagne 2002	2	379	1	390	14.4%	2.06 [0.19, 22.60]			•
Landray 2006	0	102	0	101		Not estimable			
Leiter 2004	0	286	0	289		Not estimable			
Reckless 2008	4	213	4	211	44.0%	0.99 [0.25, 3.91]			
Robinson 2009	0	450	1	678	8.1%	0.50 [0.02, 12.29]	_	•	
Stein 2004	2	305	1	316	14.5%	2.07 [0.19, 22.73]			
Zieve 2010	1	526	0	525	8.1%	2.99 [0.12, 73.34]			
Total (95% CI)		4691		5031	100.0%	1.26 [0.51, 3.15]			
Total events	10		8						
Heterogeneity: Tau <sup>2</sup> = 0.	00; Chi <sup>2</sup> = 1.08	, df = 5 i	(P = 0.96)	; <b>I2</b> = 09	Х.		L		
Test for overall effect: Z =	= 0.51 (P = 0.6	i)		-			0.005	U.1 Equation Station	Foreuro Ezotimibe+Stating
								Favours Statins	Favours Ezetimine+Statins

#### Figure 65 Forest plot indicating risk ratio of serious treatment-related adverse events for

#### ezetimibe plus statin compared to statin (6 weeks-6 months)

#### **Abbreviations**

#### Ezetimibe plus statin vs statin, any adverse events, 1–30 months

A total of 31 studies provided evidence on any adverse events and all were included in the metaanalysis.<sup>52 110</sup> <sup>111</sup> <sup>124</sup> <sup>146-150</sup> <sup>154-157</sup> <sup>171-182</sup> <sup>184-187</sup> <sup>189</sup> <sup>190</sup> Overall, there was no statistically significant difference between the ezetimibe plus statin and statin groups (RR 0.98; 95% CI 0.93, 1.03; p=0.48) (*Figure 66*). The absolute risk for ezetimibe was 21.4% (n=3,026/14,140) and for the statin group, 22.2% (n=3,228/14,553). Chi<sup>2</sup> and I<sup>2</sup> statistics indicated low levels of heterogeneity and inconsistency (P=0.08, I<sup>2</sup>=27%).

In 22 studies, common adverse events in both treatment groups included hepatobiliary, gastrointestinaland musculoskeletal-related adverse events.<sup>52 110</sup> 111 124 147-149 154-157 172 174-176 178 181 182 184 185 189 190 The remaining studies did not specify the types of adverse events.<sup>146 150</sup> 171 173 177 179 180 186 187

Eight studies provided definitions of what constituted an adverse event.<sup>111 148 149 172 175 176 178 180</sup> All studies reported the number of events per patient.

	Ezetimibe +	Statin	Stat	in		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% Cl
Averna 2010	13	60	13	60	0.6%	1.00 [0.51, 1.97]	
Ballantyne 2004a	165	263	187	262	8.5%	0.88 [0.78, 0.99]	-
Ballantyne 2007	75	238	77	230	3.3%	0.94 [0.72, 1.22]	-
Ballantyne 2019	58	109	24	55	2.0%	1.22 [0.86, 1.73]	+
Bardini 2010	5	42	10	51	0.3%	0.61 [0.22, 1.64]	
Barrios 2005	44	221	51	214	2.0%	0.84 [0.58, 1.19]	-+
Bays 2011	33	221	31	219	1.3%	1.05 [0.67, 1.66]	_ <del></del>
Bays 2013	11	124	13	124	0.5%	0.85 [0.39, 1.82]	
Bays 2015	65	101	95	149	5.2%	1.01 [0.84, 1.22]	+
Blagden 2007	33	72	35	76	2.0%	1.00 [0.70, 1.41]	
Brohet 2005	40	208	27	210	1.3%	1.50 [0.95, 2.34]	<u>+</u>
Cannon 2015	903	6868	877	6860	10.7%	1.03 [0.94, 1.12]	+
Catapano 2006	432	1478	461	1481	9.2%	0.94 [0.84, 1.05]	+
Conard 2008	11	96	18	98	0.6%	0.62 [0.31, 1.25]	
Cruz-Fernandez 2005	34	220	31	230	1.3%	1.15 [0.73, 1.80]	
Deharo 2014	3	64	13	64	0.2%	0.23 [0.07, 0.77]	
Farnier 2005a	27	181	28	191	1.1%	1.02 [0.62, 1.66]	
Farnier 2009	22	314	34	304	1.0%	0.63 (0.38, 1.05)	
Farnier 2016	54	101	68	101	4.1%	0.79 [0.63, 1.00]	
Feldman 2004	74	109	168	253	6.6%	1.02 [0.87, 1.20]	+
Foody 2010	74	257	63	257	2.8%	1.17 [0.88, 1.57]	+
Gagne 2002	81	379	66	390	2.7%	1.26 [0.94, 1.69]	
Hing Ling 2012	11	119	18	130	0.6%	0.67 [0.33, 1.35]	
Leiter 2004	63	286	61	289	2.5%	1.04 [0.76, 1.43]	+
McCormack 2010	89	259	103	261	4.1%	0.87 [0.69, 1.09]	
Patel 2008	28	78	17	75	1.0%	1.58 [0.95, 2.64]	<u>–</u>
Reckless 2008	102	213	96	211	4.7%	1.05 [0.86, 1.29]	+
Robinson 2009	76	450	134	678	3.4%	0.85 [0.66, 1.10]	-+
Roeters Van Lennep 2008	64	178	66	189	3.0%	1.03 [0.78, 1.36]	+
Stein 2004	193	305	184	316	8.2%	1.09 [0.96, 1.23]	+
Zieve 2010	143	526	159	525	5.2%	0.90 [0.74, 1.09]	
Total (95% CI)		14140		14553	100.0%	0.98 [0.93, 1.03]	
Total events	3026		3228				
Heterogeneity: Tau <sup>2</sup> = 0.01; C	hi <sup>2</sup> = 41.24, d	lf = 30 (P =	= 0.08); l <sup>a</sup>	= 27%			
Test for overall effect: $Z = 0.7$	1 (P = 0.48)						Favours Statins Favours Ezetimibe+Statins

#### Figure 66 Forest plot indicating risk ratio of any adverse events for ezetimibe plus statin

#### compared to statin (1-30 months)

Abbreviations

#### Ezetimibe plus statin vs statin, treatment-related adverse events, 1 week–12 months

Twenty-nine studies provided evidence on treatment-related adverse events and 28 of these were included in the meta-analysis.<sup>110</sup> <sup>111</sup> <sup>124</sup> <sup>146-148</sup> <sup>150</sup> <sup>151</sup> <sup>154-157</sup> <sup>171-179</sup> <sup>181</sup> <sup>182</sup> <sup>184-188</sup> <sup>190</sup> Overall, there was no statistically significant difference between the ezetimibe plus statin and statin groups (RR 1.08; 95% CI 0.95, 1.23; p=0.27) (*Figure 67*). The absolute risk for ezetimibe plus statin was 6.7% (n=455/6,815) and for the statin group, 6.1% (n=444/7,189). Chi<sup>2</sup> and I<sup>2</sup> statistics indicated low levels of heterogeneity and inconsistency (P=0.44, I<sup>2</sup>=2%).

One study reported a similar incidence of treatment-related adverse events between the treatment groups.<sup>180</sup>

In six studies, treatment-related adverse events in the ezetimibe plus statin group included elevated liver enzymes, worsening of a pre-existing condition,<sup>151</sup> gastrointestinal events,<sup>124 180</sup> myalgia,<sup>110 124 173</sup> abdominal distension, abdominal pain, constipation, dry mouth, nausea, arthralgia, dermatitis and eczema.<sup>173</sup> Treatment-related adverse events in the statin group included transitory hepatitis,<sup>188</sup> gastrointestinal events,<sup>124 180</sup> myalgia,<sup>110 124</sup> constipation, asthenia, fatigue, myalgia and skin exfoliation.<sup>173</sup> The remaining studies did not specify the types of treatment-related adverse events.<sup>110 111</sup> 146-148 150 154-157 171-179 181 182 184-187 190

Eight studies provided definitions of what constituted an adverse event.<sup>111 148 172 175 176 178 180</sup> All studies reported the number of events per patient.

	Ezetimibe +	Statin	Stati	n		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
Averna 2010	7	60	4	60	1.3%	1.75 [0.54, 5.67]	
Ballantyne 2004a	36	263	42	262	9.5%	0.85 [0.57, 1.29]	
Ballantyne 2007	18	238	21	230	4.7%	0.83 [0.45, 1.51]	
Ballantyne 2019	9	109	4	55	1.4%	1.14 [0.37, 3.52]	
Bardini 2010	3	42	3	51	0.8%	1.21 [0.26, 5.71]	
Barrios 2005	17	221	23	214	4.8%	0.72 [0.39, 1.30]	
Bays 2011	10	221	6	219	1.8%	1.65 [0.61, 4.47]	
Bays 2013	2	124	3	124	0.6%	0.67 [0.11, 3.92]	
Blagden 2007	13	72	12	76	3.4%	1.14 [0.56, 2.34]	_ <del></del>
Brohet 2005	15	208	5	210	1.8%	3.03 [1.12, 8.18]	
Catapano 2006	120	1478	110	1481	20.9%	1.09 [0.85, 1.40]	-
Chenot 2007	0	20	1	20	0.2%	0.33 [0.01, 7.72]	
Conard 2008	1	96	6	98	0.4%	0.17 [0.02, 1.39]	
Cruz-Fernandez 2005	5	220	3	230	0.9%	1.74 [0.42, 7.20]	
Farnier 2005a	6	181	7	191	1.6%	0.90 [0.31, 2.64]	
Farnier 2009	8	314	10	304	2.1%	0.77 [0.31, 1.94]	
Feldman 2004	15	109	19	253	4.3%	1.83 [0.97, 3.47]	
Foody 2010	11	257	11	257	2.7%	1.00 [0.44, 2.27]	
Hing Ling 2012	2	119	3	130	0.6%	0.73 [0.12, 4.28]	
Hougaard 2017	2	43	0	44	0.2%	5.11 [0.25, 103.51]	
Leiter 2004	11	286	19	289	3.4%	0.59 [0.28, 1.21]	
McCormack 2010	23	259	27	261	6.0%	0.86 [0.51, 1.46]	
Patel 2008	30	77	14	75	5.6%	2.09 [1.21, 3.61]	_ <b></b>
Reckless 2008	18	213	17	211	4.3%	1.05 [0.56, 1.98]	
Robinson 2009	15	450	26	678	4.4%	0.87 [0.47, 1.62]	
Roeters Van Lennep 2008	24	178	19	189	5.3%	1.34 [0.76, 2.36]	-+
Stein 2004	2	305	1	316	0.3%	2.07 [0.19, 22.73]	
Zieve 2010	30	526	26	525	6.4%	1.15 [0.69, 1.92]	
Total (95% CI)		6689		7053	100.0%	1.08 [0.94, 1.23]	•
Total events	453		442				
Heterogeneity: Tau <sup>2</sup> = 0.01; C	hi² = 28.49, d	f= 27 (P	= 0.39); P	²= 5%			
Test for overall effect: Z = 1.00	6 (P = 0.29)						Favours Statins Favours Ezetimibe+Statins

#### Figure 67 Forest plot indicating risk ratio of treatment-related adverse events for ezetimibe

plus statin compared to statin (1 week-12 months)

Abbreviations

#### Sub-groups

#### Ezetimibe plus statins vs statins

Meta-analyses determined there was no difference between ezetimibe plus atorvastatin and atorvastatin or ezetimibe plus rosuvastatin and rosuvastatin for any safety-related outcomes. However, there was a significantly higher incidence of treatment-related adverse events in the ezetimibe plus simvastatin group compared to the simvastatin group. There were no significant differences for the remaining safety outcomes. For further information, refer to *Table 115, Appendix D*.

The remaining statins could not be meta-analysed owing to insufficient study numbers. There were no deaths in the only study to examine ezetimibe plus fluvastatin vs fluvastatin but adverse events (serious, any or withdrawal due to) were not reported.<sup>159</sup>

#### Hyperlipidaemia without ASCVD

**Table 44** provides a summary of the main pooled safety outcomes comparing ezetimibe to placebo or fenofibrate and ezetimibe plus fenofibrate to fenofibrate. Ezetimibe compared to statins and ezetimibe plus statins compared to statins were not included because the results were informed by only one study, noting all treatment groups had similar event rates.

There were no statistically significant differences between ezetimibe vs placebo and ezetimibe plus fenofibrate vs fenofibrate for any safety-related outcomes. There was a significantly lower incidence of treatment-related adverse events in the ezetimibe group compared to the fenofibrate group. The groups did not differ in any other safety-related outcomes. Mortality was not pooled for any comparisons owing to low event rates.

Outcomes	Risk ratio (95% CI)						
	Ezetimibe vs placebo	Ezetimibe vs fenofibrate	Ezetimibe plus fenofibrate vs fenofibrate				
All-cause mortality	NA	NA	NA				
Withdrawal due to adverse events	3.16 (0.17, 59.57) p=0.44	0.46 (0.16, 1.30) p=0.14	0.74 (0.43, 1.30) p=0.30				
Serious adverse events	NA	4.04 (0.46, 35.83) p=0.21	1.71 (0.64, 4.53) p=0.28				
Serious treatment- related adverse events	NA	NA	0.46 (0.08, 2.77) p=0.40				
Any adverse events	NA	0.92 (0.75, 1.13) p=0.41	1.08 (0.97, 1.20) p=0.18				
Treatment-related adverse events	NA	0.49 (0.28, 0.87) p=0.01	0.90 (0.66, 1.21) p=0.47				

Table 44 Summary of safety-related meta-analyses for hyperlipidaemia without ASCVD

#### **Abbreviations**

ASCVD = atherosclerotic cardiovascular disease, CI = confidence interval, NA = not applicable.

#### <u>Notes</u>

Risk ratio indicates direction of effect. Numbers >1 indicate risks were lower in placebo or statin groups (higher event rate in ezetimibe or ezetimibe plus fenofibrate), numbers <1 indicate risks were lower in ezetimibe or ezetimibe plus fenofibrate groups (higher event rate in placebo or fenofibrate).

#### Ezetimibe vs placebo

Two studies provided evidence for withdrawal due to adverse events.<sup>164 179</sup> The remaining outcomes were informed by one study only.<sup>179</sup> Overall, there was no statistically significant difference between the ezetimibe and placebo groups for withdrawal due to adverse events (RR 3.17; 95% CI 0.17, 57.01; p=0.44) (*Table 45*).<sup>164 179</sup> In one study, there was a similar incidence of mortality and adverse events (withdrawal, serious, serious treatment-related, any and treatment-related) between ezetimibe and placebo groups.<sup>179</sup> The statistical difference was not reported for these outcomes, so it was unclear whether the groups differed.

Outcome	Ezetimibe n/N (%)	Placebo n/N (%)	Risk ratio (95% CI)
All-cause mortality	0/187 (0.0%)	0/64 (0.0%)	NA
Withdrawal due to adverse	4/212 (1.9%)	0/89 (0.0%)	3.16 (0.17, 59.57)
event			p=0.44
Serious adverse events	4/187 (2.1%)	0/64 (0.0%)	NA
Serious treatment-related adverse events	0/187 (0.0%)	0/64 (0.0%)	NA
Any adverse events	84/187 (44.9%)	30/64 (46.9%)	NA
Treatment-related adverse events	12/187 (6.41)	5/64 (7.8%)	NA

Table 45 Ezetimibe vs placebo: summary of safety-related outcomes (3 months)

#### **Abbreviations**

CI = confidence interval, n = number of patients with event, N = total number of patients, NA = not applicable.

#### Notes

Only withdrawal due to adverse events had sufficient numbers to perform a meta-analysis. The remaining outcomes are informed by Farnier (2005b).<sup>179</sup>

#### Source

Drouin-Chartier (2016)<sup>164</sup> and Farnier (2005b).<sup>179</sup>

#### Ezetimibe vs statin

One study reported that the incidence of any adverse events, serious adverse events and withdrawal due to adverse events was similar between the ezetimibe and statin groups (*Table 46*).<sup>125</sup> The statistical difference was not reported for any outcome, so it was unclear whether ezetimibe and statin groups differed.

Outcome	Ezetimibe n/N (%)	Statin n/N (%)
All-cause mortality	NR	NR
Withdrawal due to adverse event	8/66 (12.1%)	8/69 (11.6%)
Serious adverse events	0/66 (0.0%)	0/69 (0.0%)
Serious treatment-related adverse events	NR	NR
Any adverse events	39/66 (59.1%)	34/69 (49.3%)
Treatment-related adverse events	NR	NR

#### **Abbreviations**

**CI** = confidence interval, **n** = number of patients with event, **N** = total number of patients, **NR** = not reported. Source

Stein (2008)125

#### Ezetimibe plus statin vs statin

One study reported that the incidence of any adverse events, serious adverse events and withdrawal due to adverse events was similar between the ezetimibe plus statin and statin groups (*Table 47*).<sup>125</sup> The statistical difference was not reported for any outcome, so it was unclear whether ezetimibe plus statin and statin groups differed.

Table 47 Ezetimibe plus statin vs statin: summa	ry of safety-related outcomes (3 months)
-------------------------------------------------	------------------------------------------

Outcome	Ezetimibe plus statin n/N (%)	Statin n/N (%)
All-cause mortality	NR	NR
Withdrawal due to adverse event	5/64 (7.8%)	8/69 (11.6%)
Serious adverse events	0/64 (0.0%)	0/69 (0.0%)
Serious treatment-related adverse events	NR	NR
Any adverse events	34/64 (53.1%)	34/69 (49.3%)
Treatment-related adverse events	NR	NR

#### Abbreviations

**CI** = confidence interval, **n** = number of patients with event, **N** = total number of patients, **NR** = not reported. <u>Source</u> Stein (2008)<sup>125</sup>

#### Ezetimibe vs fenofibrate

#### Ezetimibe vs fenofibrate, all-cause mortality

No study provided evidence on all-cause mortality.

#### Ezetimibe vs fenofibrate, withdrawal due to adverse events, 3 months

Two studies provided evidence on withdrawal due to adverse events and both were included in the meta-analysis.<sup>166 179</sup> Overall, there was no statistically significant difference between the ezetimibe and fenofibrate groups at 3 months (RR 0.46; 95% CI 0.16, 1.30; p=0.14) (*Figure 68*). The absolute risk for ezetimibe was 2.0% (n=5/247) and for the fenofibrate group, 4.4% (n=11/249). Chi<sup>2</sup> test and I<sup>2</sup> statistic indicated low levels of heterogeneity and inconsistency (P=0.94, I<sup>2</sup>=0%).

In Ansquer (2009) patient withdrawal was due to nausea and headache in the ezetimibe group and to urticaria and gastroenteritis in the fenofibrate group.<sup>166</sup> In Farnier (2005b) one patient in the fenofibrate group withdrew due to angio-oedema.<sup>179</sup> The adverse events leading to the remaining withdrawals were not reported.



#### Figure 68 Forest plot indicating risk ratio of withdrawal due to adverse events for ezetimibe

#### compared to fenofibrate (3 months)

#### Abbreviations

**CI** = confidence interval.

#### Ezetimibe vs fenofibrate, serious adverse events, 3 months

Two studies provided evidence on serious adverse events and both were included in the metaanalysis.<sup>166 179</sup> Overall, there was no statistically significant difference between the ezetimibe and fenofibrate groups (RR 4.04; 95% CI 0.46, 35.83; p=0.21) (*Figure 69*). The absolute risk for ezetimibe was 1.6% (n=4/247) and for the fenofibrate group, 0.4% (n=1/249). Chi<sup>2</sup> and I<sup>2</sup> statistics could not be calculated. Both studies did not specify the types of serious adverse events.

	Ezetim	ibe	Fenofib	rate	Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
Ansquer 2009	0	60	0	60		Not estimable	
Farnier 2005b	4	187	1	189	100.0%	4.04 [0.46, 35.83]	
Total (95% CI)		247		249	100.0%	4.04 [0.46, 35.83]	
Total events	4		1				
Heterogeneity: Not ap Test for overall effect:	plicable Z = 1.25 (	(P = 0.2	?1)				0.01 0.1 1 10 100 Favours Fenofibrate Favours Ezetimibe

#### Figure 69 Forest plot indicating risk ratio of serious adverse events for ezetimibe compared to

#### fenofibrate (3 months)

Abbreviations

CI = confidence interval.

#### Ezetimibe vs fenofibrate, serious treatment-related adverse events, 3 months

One study reported no serious treatment-related adverse events (Table 48).179

Table 48 Ezetimibe vs	s fenofibrate: serious	treatment-related	adverse events,	3 months
-----------------------	------------------------	-------------------	-----------------	----------

Study	Length of follow-up	Ezetimibe n/N	Fenofibrate n/N
Farnier 2005b 179	3 months	0/187 (0.0%)	0/189 (0.0%)

#### **Abbreviations**

**n** = number of patients with events, **N** = total number of patients.

#### Ezetimibe vs fenofibrate, any adverse events, 3 months

Two studies provided evidence on any adverse events and both were included in the meta-analysis.<sup>166</sup> <sup>179</sup> Overall, there was no statistically significant difference between the ezetimibe and fenofibrate groups (RR 0.92; 95% CI 0.75, 1.13; p=0.41) (*Figure 70*). The absolute risk for ezetimibe was 39.3% (n=97/247) and for the fenofibrate group, 43.0% (n=107/249). Chi<sup>2</sup> and I<sup>2</sup> statistics indicated low levels of heterogeneity and inconsistency (P=0.86, I<sup>2</sup>=0%). Both studies did not specify the types of adverse events.

	Ezetim	ibe	Fenofib	rate	Risk Ratio			Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl		M-H, Random, 95% Cl	
Ansquer 2009	13	60	15	60	9.9%	0.87 [0.45, 1.66]			
Farnier 2005b	84	187	92	189	90.1%	0.92 [0.74, 1.15]			
Total (95% CI)		247		249	100.0%	0.92 [0.75, 1.13]		•	
Total events	97		107						
Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 0.03, df = 1 (P = 0.86); i <sup>2</sup> = 0% Test for overall effect: Z = 0.83 (P = 0.41)				6); I² = 0%		0.01	0.1 1 10 Favours Fenofibrate Favours Ezetimibe	100	

#### Figure 70 Forest plot indicating risk ratio of any adverse events for ezetimibe compared to

#### fenofibrate (3 months)

#### **Abbreviations**

#### Ezetimibe vs fenofibrate, treatment-related adverse events, 3 months

Two studies provided evidence on treatment-related adverse events and both were included in the metaanalysis.<sup>166</sup> <sup>179</sup> Overall, there was a statistically significant difference between the ezetimibe and fenofibrate groups at 3 months (RR 0.49; 95% CI 0.28, 0.87; p=0.01) (*Figure 71*). The absolute risk for ezetimibe was 6.5% (n=16/247) and for the fenofibrate group, 13.3% (n=33/249). Chi<sup>2</sup> and I<sup>2</sup> statistics indicated low levels of heterogeneity and inconsistency (P=0.57, I<sup>2</sup>=0%).

Treatment-related adverse events included abnormal liver enzyme changes in the ezetimibe and fenofibrate groups.<sup>166</sup> Farnier (2005b) did not report the type of treatment-related adverse events.<sup>179</sup>



#### Figure 71 Forest plot indicating risk ratio of treatment-related adverse events for ezetimibe

#### compared to fenofibrate (3 months)

<u>Abbreviations</u> CI = confidence interval.

#### Ezetimibe plus fenofibrate vs to fenofibrate

#### Ezetimibe plus fenofibrate vs fenofibrate, all-cause mortality, 12 months

One study reported all-cause mortality.<sup>152</sup> There was one death in the ezetimibe plus fenofibrate group,

which was deemed unrelated to the intervention. There were no deaths in the fenofibrate group (Table

**49**).

#### Table 49 Ezetimibe plus fenofibrate vs fenofibrate: all-cause mortality 12 months

Study	Follow-up	Ezetimibe plus fenofibrate n/N (%)	Fenofibrate n/N (%)
McKenney 2006 <sup>152</sup>	12 months	1/340 (0.3%)	0/236 (0.0%)

#### **Abbreviations**

**n** = number of patients with events, **N** = total number of patients. Notes

One death, unrelated to the intervention.

#### Ezetimibe plus fenofibrate vs fenofibrate, withdrawal due to adverse events, 3–12 months

Three studies provided evidence on withdrawal due to adverse events and all three were included in the meta-analysis.<sup>152</sup> <sup>166</sup> <sup>179</sup> Overall, there was no statistically significant difference between the ezetimibe plus fenofibrate and fenofibrate groups (RR 0.74; 95% CI 0.43, 1.30; p=0.30) (*Figure 72*). The absolute risk for ezetimibe plus fenofibrate was 3.9% (n=23/587) and for the fenofibrate group 5.2% (n=25/485). Chi<sup>2</sup> test and I<sup>2</sup> statistic indicated low levels of heterogeneity and inconsistency (P=0.94, I<sup>2</sup>=0%).

In Ansquer (2009), patient withdrawal was due to urticaria and gastroenteritis in the fenofibrate group, and to pruritus in the ezetimibe plus fenofibrate group.<sup>166</sup> Farnier (2005b) provided information on two of the withdrawals, which included cholecystitis and cholelithiasis in the ezetimibe plus fenofibrate group and angio-oedema in the fenofibrate group.<sup>179</sup> McKenney (2006) did not report the adverse events leading to withdrawal.<sup>152</sup>



#### Figure 72 Forest plot indicating risk ratio of withdrawal due to adverse events for ezetimibe

#### plus fenofibrate compared to fenofibrate (3–12 months)

<u>Abbreviations</u> CI = confidence interval.

#### Ezetimibe plus fenofibrate vs fenofibrate, serious adverse events, 3–12 months

Three studies provided evidence on serious adverse events and all were included in the metaanalysis.<sup>152</sup> <sup>166</sup> <sup>179</sup> Overall, there was no statistically significant difference between the ezetimibe plus fenofibrate and fenofibrate groups (RR 1.71; 95% CI 0.64, 4.53; p=0.28) (*Figure 73*). The absolute risk for ezetimibe plus fenofibrate was 5.1% (n=30/585) and for the fenofibrate group, 3.1% (n=15/485). Chi<sup>2</sup> test and l<sup>2</sup> statistic indicated low levels of heterogeneity and inconsistency (P=0.28, l<sup>2</sup>=21%).

The serious adverse events included multinodular goitre, diagnosis of prostate cancer and prostatectomy in the ezetimibe plus fenofibrate group. There were no events in the fenofibrate group.<sup>166</sup> Farnier (2005b) and McKenney (2006) did not report the type of serious adverse events.<sup>179</sup>

	Ezetimibe + Fenof	ibrate	Fenofib	rate	e Risk Ratio			Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl		M-H, Random, 95% Cl
Ansquer 2009	2	60	0	60	9.5%	5.00 [0.25, 102.00]		
Farnier 2005b	5	185	1	189	17.4%	5.11 [0.60, 43.31]		
McKenney 2006	23	340	14	236	73.0%	1.14 [0.60, 2.17]		
Total (95% CI)		585		485	100.0%	1.71 [0.64, 4.53]		
Total events	30		15					
Heterogeneity: Tau <sup>2</sup> = Test for overall effect: .	0.23; Chi² = 2.53, d Z = 1.07 (P = 0.28)	f= 2 (P =	0.28); l² =	= 21%			0.005	0.1 1 10 200 Favours Fenofibrate Favours Ezetimibe + Feno

#### Figure 73 Forest plot indicating risk ratio of serious adverse events for ezetimibe plus

#### fenofibrate compared to fenofibrate (3-12 months)

#### Abbreviations

CI = confidence interval.

#### Ezetimibe plus fenofibrate vs fenofibrate, serious treatment-related adverse events, 3–12 months

Two studies provided evidence on serious treatment-related adverse events and both were included in the meta-analysis.<sup>152 179</sup> Overall, there was no statistically significant difference between the ezetimibe plus fenofibrate and fenofibrate groups (RR 0.46; 95% CI 0.08, 2.75; p=0.40) (*Figure 74*). The absolute risk for ezetimibe plus fenofibrate was 0.4% (n=2/525) and for the fenofibrate group, 0.7% (n=3/425). Chi<sup>2</sup> and I<sup>2</sup> statistics could not be calculated.

Serious treatment-related adverse events included cholangitis and cholecystitis in the ezetimibe plus fenofibrate group, and angioneurotic oedema, pancreatitis and polyarthropathy in the fenofibrate group.<sup>152</sup> There were no treatment-related adverse events in the study by Farnier (2005b).<sup>179</sup>



# Figure 74 Forest plot indicating risk ratio of serious treatment-related adverse events for ezetimibe plus fenofibrate compared to fenofibrate (3–12 months)

#### Abbreviations

CI = confidence interval.

#### Ezetimibe plus fenofibrate vs fenofibrate, any adverse events, 3–12 months

Three studies provided evidence on any adverse events and all were included in the meta-analysis.<sup>152</sup> <sup>166 179</sup> Overall, there was no statistically significant difference between the ezetimibe plus fenofibrate and fenofibrate groups (RR 1.08; 95% CI 0.97, 1.20; p=0.18) (*Figure 75*). The absolute risk for ezetimibe plus fenofibrate was 57.8% (n=338/585) and for the fenofibrate group, 52.0% (n=252/485). Chi<sup>2</sup> test and I<sup>2</sup> statistic indicated low levels of heterogeneity and inconsistency (P=0.64, I<sup>2</sup>=0%). None of the

studies specified the types of adverse events.



#### Figure 75 Forest plot indicating risk ratio of any adverse events for ezetimibe plus fenofibrate

compared to fenofibrate (3-12 months)

#### Abbreviations

CI = confidence interval.

#### Ezetimibe plus fenofibrate vs fenofibrate, treatment-related adverse events, 3–12 months

Three studies provided evidence on treatment-related adverse events and all three were included in the meta-analysis.<sup>152</sup> <sup>166</sup> <sup>179</sup> Overall, there was no statistically significant difference between the ezetimibe plus fenofibrate and fenofibrate groups (RR 0.90; 95% CI 0.66, 1.21; p=0.47) (*Figure 76*). The absolute risk for ezetimibe plus fenofibrate was 13.3% (n=78/585) and for the fenofibrate group, 14.6% (n=71/485). Chi<sup>2</sup> test and I<sup>2</sup> statistic indicated low levels of heterogeneity and inconsistency (P=0.39, I<sup>2</sup>=0%). None of the studies specified the types of treatment-related adverse events.

	Ezetimibe + Feno	fibrate	Fenofib	rate	Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
Ansquer 2009	10	60	6	60	10.1%	1.67 [0.65, 4.30]	
Farnier 2005b	21	185	27	189	31.8%	0.79 [0.47, 1.35]	
McKenney 2006	47	340	38	236	58.2%	0.86 [0.58, 1.27]	
Total (95% CI)		585		485	100.0%	0.90 [0.66, 1.21]	•
Total events	78		71				
Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 1.89, df = 2 (P = 0.39); l <sup>2</sup> = 0%							
Test for overall effect:	Z = 0.72 (P = 0.47)						Favours Fenofibrate Favours Ezetimibe + Feno

#### Figure 76 Forest plot indicating risk ratio of treatment-related adverse events for ezetimibe

#### plus fenofibrate compared to fenofibrate (3–12 months)

#### Abbreviations

CI = confidence interval.

#### Sub-groups

Sub-group analysis was not performed as there was only one study evaluating statins.<sup>125</sup>

#### 7.3.7 GRADE

For the GRADE summary of findings table, the absolute change in LDL-c score was presented. Where absolute data is not reported, percentage changes are discussed (see *Table 116* to *Table 124, Appendix E*).

#### Table 50 GRADE summary of findings: Ezetimibe compared to placebo for hypercholesterolaemia without ASCVD

Outcomes	Anticipated al effects* (95%)	osolute Cl)	Relative effect	Number of participants	Certainty of the	Comments
	Risk with placebo	k with Risk with cebo ezetimibe		(studies)	evidence (GRADE)	
LDL-c (absolute change) follow up: 3 months	Mean LDL-c 197.50mg/dL	MD 46.68mg/ dL lower (53.46 lower– 39.9 lower)	-	252 (3 RCTs)	⊕⊕⊖⊖ LOW a,b,c,d	Ezetimibe statistically differed from placebo at 3 months. Effect size was moderate.
Withdrawal due to adverse events follow up: 2 weeks–3 months	30 per 1,000	36 per 1,000 (24–53)	RR 1.18 (0.79– 1.76)	3,569 (16 RCTs)	⊕⊕⊕⊖ MODERATE °	Ezetimibe did not statistically differ from placebo (no effect).
Serious adverse event follow up: 2 weeks–3 months	6 per 1,000	6 per 1,000 (2–22)	RR 0.98 (0.27– 3.57)	1297 (9 RCTs)	⊕⊕⊕⊖ MODERATE ⁰	Ezetimibe did not statistically differ from placebo (no effect).

#### Abbreviations

ASCVD = atherosclerotic cardiovascular disease, CI = confidence interval, LDL-c = low density lipoprotein-cholesterol, MD = mean difference, mg/dL = milligrams per decilitre, RCTs = randomised controlled trial, RR = risk ratio.

#### Notes

\* The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

 $\mathbf{a}$  = surrogate for MI, vascular events, mortality,  $\mathbf{b}$  = unclear applicability of trial population to Swiss context,  $\mathbf{c}$  = moderate levels of heterogeneity and inconsistency,  $\mathbf{d}$  = small sample size,  $\mathbf{e}$  = 95% CI around pooled estimates includes negligible effect and appreciable benefit/harm.

#### **GRADE Working Group grades of evidence**

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.

**Moderate certainty**: We are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: Our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect.

#### Table 51 GRADE summary of findings: Ezetimibe compared to statins for

Outcomes	Anticipated al effects* (95%)	osolute Cl)	Relative effect	Number of participants	Certainty of the	Comments
	Risk with statins	Risk with ezetimibe	(95% CI)	(studies)	evidence (GRADE)	
LDL-c (absolute change) follow up: 3 months	Mean LDL-c 121.49mg/dL	MD 10.77mg/dL higher (7.64 higher–13.9 higher)	-	129 (4 RCTs)	⊕⊕⊖⊖ LOW a,b,c	Ezetimibe statistically differed from statins at 3 months. Effect size was small.
Withdrawal due to adverse events follow up: 2 weeks–3 months	54 per 1,000	51 per 1,000 (26–98)	RR 0.95 (0.49– 1.82)	2,356 (9 RCTs)	⊕⊕⊕⊖ MODERATE d,e	Ezetimibe did not statistically differ from statins (no effect).
Serious adverse events follow up: 2 weeks–3 months	14 per 1,000	10 per 1,000 (3–32)	RR 0.70 (0.21– 2.36)	1,556 (4 RCTs)	⊕⊕⊕⊖ MODERATE d,e	Ezetimibe did not statistically differ from statins (no effect).

#### hypercholesterolaemia without ASCVD

#### Abbreviations

ASCVD = atherosclerotic cardiovascular disease, CI = confidence interval, LDL-c = low density lipoprotein-cholesterol, MD = mean difference, mg/dL = milligrams per decilitre, RCTs = randomised controlled trial, RR = risk ratio. Notes

\* The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

 $\mathbf{a}$  = surrogate for MI, vascular events, mortality,  $\mathbf{b}$  = unclear applicability of trial population to Swiss context,  $\mathbf{c}$  = small sample size,  $\mathbf{d}$  = losses to follow-up, but safety outcomes still likely captured,  $\mathbf{e}$  = 95% CI around pooled estimates includes negligible effect and appreciable benefit/harm.

#### **GRADE Working Group grades of evidence**

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.

**Moderate certainty**: We are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: Our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect.

### Table 52 GRADE summary of findings: Ezetimibe plus statins compared to statins for

Outcomes	tcomes Anticipated absolute effects* (95% CI)			Number of partici-	Certainty of the evidence	Comments
	Risk with statins	Risk with ezetimibe plus statins	(95% CI)	pants (studies)	(GRADE)	
3P-MACE follow up: 24 months	Ezetimibe plus 6 events vs 4 e	s statins vs statins events	NA	720 (1 RCT)	⊕⊕⊖⊖ LOW <sup>a,b,c,d</sup>	Unclear if ezetimibe plus statins differed to statins because statistical difference not reported.
Cardiovascular death follow up: 24 months	Ezetimibe plus 2/357 (0.5%) v	s statins vs statins vs 1/363 (0.2%)	NA	720 (1 RCT)	⊕⊕⊖⊖ LOW <sup>a,b,d</sup>	Unclear if ezetimibe plus statins differed to statins because statistical difference not reported.
Hospitalised for unstable angina	NR					
Coronary revascularisation follow up: 24 months	Ezetimibe plus 6 events vs 5 e	statins vs statins events	NA	720 (1 RCT)	⊕⊕⊖⊖ LOW <sup>a,b,c,d</sup>	Unclear if ezetimibe plus statins differed to statins because statistical difference not reported.
LDL-c (absolute change) follow up: 3–24 months	3 months Mean LDL-c 109.96mg/ dL 15 months Mean LDL-c 104.4mg/dL	3 months MD -16.72mg/dL lower (-22.34 lower to - 11.11 lower) 15 months MD -14.24mg/dL lower (-32.59 lower to - 4.81 lower)	NA	246–497 (13 RCTs)	⊕⊕⊖⊖ LOW b,e,f,g,h,i	Ezetimibe plus statins statistically differed from statins at 3 and 15 months. Effect size was small at both timepoints.
Withdrawal due to adverse event follow up: 2–24 months	41 per 1,000	48 per 1,000 (39–60)	RR 1.18 (0.95 to 1.45)	7,755 (21 RCTs)	⊕⊕⊕⊖ MODERATE <sup>9.j</sup>	Ezetimibe plus statins did not statistically differ from statins (no effect).
Serious adverse event follow up: 2 weeks–12 months	21 per 1,000	22 per 1,000 (14–37)	RR 1.08 (0.66 to 1.77)	5,516 (12 RCTs)	⊕⊕⊕⊖ MODERATE <sub>g,j,k</sub>	Ezetimibe plus statins did not statistically differ from statins (no effect).

#### hypercholesterolaemia without ASCVD

#### Abbreviations

ASCVD = atherosclerotic cardiovascular disease, CI = confidence interval, LDL-c = low density lipoprotein-cholesterol, 3P-MACE = 3-point major adverse cardiac events, MD = mean difference, mg/dL = milligrams per decilitre, NA = not applicable, NR = not reported, RCTs = randomised controlled trial, RR = risk ratio.

#### **Notes**

\* The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

**a** = losses to follow-up; important considering low event number, **b** = unclear applicability of trial population to Swiss context, **c** = not reported whether number of patients or events; cannot calculate risk, **d** = outcomes derived from one study, **e** = notable losses to follow-up, **f** = considerable levels of heterogeneity and inconsistency, **g** = non-overlapping Cls, **h** = surrogate for MI, vascular events, mortality, **I** = later timepoints informed by one study, **j** = losses to follow-up; event likely still captured appropriately, **k** = moderate levels of heterogeneity and inconsistency.

#### **GRADE Working Group grades of evidence**

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.

**Moderate certainty**: We are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: Our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect.

### Table 53 GRADE summary of findings: Ezetimibe plus statins compared to statins for

Outcomes	Anticipated a (95% CI)	bsolute effects*	Relative effect	Number of participants	Certainty of the	Comments
	Risk with statins	Risk with ezetimibe plus statins	(95% CI)	(studies)	evidence (GRADE)	
3P-MACE follow up: 7 years	211 per 1,000	192 per 1,000 (181–204)	HR 0.90 (0.84– 0.96)	18,144 (1 RCT)	⊕⊕⊖⊖ LOW a,b,c	Ezetimibe plus statins statistically differed from statins at 7 years. The effect size was small to moderate.
Cardiovascular death follow up: 7	59 per 1,000	59 per 1,000 (53–67)	HR 1.00 (0.89– 1.13)	18,144 (1 RCT)	⊕⊕⊖⊖ LOW a,b,c	Ezetimibe plus statins did not statistically differ from statins (no effect).
Hospitalised for unstable angina follow up: 7 years	16 per 1,000	17 per 1,000 (14–22)	HR 1.06 (0.85– 1.33)	18,144 (1 RCT)	⊕⊕⊖⊖ LOW a,b,c	Ezetimibe plus statins did not statistically differ from statins (no effect).
Coronary revascularisation follow up: 7 years	198 per 1,000	189 per 1,000 (178–199)	HR 0.95 (0.89– 1.01)	18,144 (1 RCT)	⊕⊕⊖⊖ LOW a,b,c	Ezetimibe plus statins did not statistically differ from statins (no effect).
LDL-c (absolute change) follow up: 3–24 months	3 months Mean LDL-c 84.61mg/dL 12 months Mean LDL-c 72.28mg/dL	3 months -17.22mg/dL lower (-24.34 lower to -10.22 lower) <i>12 months</i> -16.82mg/dL lower (-22.51 lower to -11.12 lower)	_	223–7,142 (9 RCTs)	⊕⊕⊖⊖ LOW a,d,e,f,g	Ezetimibe plus statins statistically differed from statins at 3 and 12 months. Effect size small at both timepoints.
Withdrawal due to adverse events follow up: 1–30 months	67 per 1,000	70 per 1,000 (65–76)	RR 1.05 (0.97– 1.13)	34,027 (30 RCTs)	⊕⊕⊕⊖ MODERATE f	Ezetimibe plus statins did not statistically differ from statins (no effect).
Serious adverse events follow up: 6 weeks–6 months	27 per 1,000	32 per 1,000 (27–38)	RR 1.20 (1.00– 1.44)	14,515 (29 RCTs)	⊕⊕⊕⊖ MODERATE f	Ezetimibe plus statins did not statistically differ from statins (no effect).

#### hypercholesterolaemia with ASCVD

#### Abbreviations

**ASCVD** = atherosclerotic cardiovascular disease, **CI** = confidence interval, **LDL-c** = low density lipoprotein-cholesterol, **3P-MACE** = 3-point major adverse cardiac events, **MD** = mean difference, **mg/dL** = milligrams per decilitre, **RCTs** = randomised controlled trial, **RR** = risk ratio.

#### Notes

\* The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

 $\mathbf{a}$  = notable losses to follow-up,  $\mathbf{b}$  = results reflective of one study in patients with ACS; unclear if reflective of all ASCVD patients in Switzerland,  $\mathbf{c}$  = results representative of Cannon (2015) trial,  $\mathbf{d}$  = considerable levels of heterogeneity and inconsistency within the model,  $\mathbf{e}$  = non-overlapping Cls,  $\mathbf{f}$  = highly heterogeneous population; unclear if reflective of ASCVD patients in Switzerland,  $\mathbf{g}$  = later timepoints informed by one study.

#### GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect

**Moderate certainty**: We are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: Our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect.

#### Table 54 GRADE summary of findings: Ezetimibe compared to placebo for hyperlipidaemia

Outcomes	Anticipated absolute effects* (95% Cl)		Relative effect	Number of participants	Certainty of the	Comments	
	Risk with placebo	Risk with ezetimibe	(95% CI)	(studies)	evidence (GRADE)		
LDL-c (absolute change) follow-up: 3 months	Ezetimibe vs placebo 102.1 ± 21.3mg/dL vs 133.0 ± 41.0mg/dL p<0.0001		-	20 (1 RCT)	⊕⊖⊖⊖ VERY LOW a,b,c,d,e,f	Ezetimibe statistically differed from placebo. Effect size was moderate.	
Withdrawal due to adverse events follow-up: 3 months	0 per 1,000	0 per 1,000	RR 3.16 (0.17– 59.57)	301 (2 RCTs)	⊕⊕⊕⊖ MODERATE <sup>e,g</sup>	Ezetimibe did not statistically differ from placebo (no effect).	
Serious adverse event follow-up: 3 months	Ezetimibe vs placebo 4/187 (2.1%) vs 0/64 (0.0%) p=NR		NA	251 (1 RCT)	⊕⊕⊕⊖ MODERATE f	Unclear if ezetimibe differed to placebo because statistical difference not reported.	

#### without ASCVD

#### Abbreviations

ASCVD = atherosclerotic cardiovascular disease, CI = confidence interval, LDL-c = low density lipoprotein-cholesterol, MD = mean difference, mg/dL = milligrams per decilitre, NA = not applicable, RCTs = randomised controlled trial, RR = risk ratio. Notes

\* The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

**a** = overlapping standard deviations, **b** = unclear applicability of trial population to Swiss context, **c** = one study; small sample size, **d** = notable losses to follow-up, **e** = 95% CI around pooled estimates includes negligible effect and appreciable benefit/harm, **f** = small sample size; low number of events, **g** = unclear; heterogeneity could not be calculated.

#### GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.

**Moderate certainty**: We are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: Our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect.

#### Table 55 GRADE summary of findings: Ezetimibe compared to statins for hyperlipidaemia

without ASCVD
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Outcomes	Impact	Number of participants (studies)	Certainty of the evidence (GRADE)	Comments
LDL-c (absolute change) follow up: 3 months	Ezetimibe vs statins 161.5 ± 18.6mg/dL vs 114.5 ± 21.7mg/dL p=NR	135 (1 RCT)	⊕⊕⊖⊖ LOW a.b.c.d	Unclear if ezetimibe differed to statins because statistical difference not reported.
Withdrawal due to adverse event follow up: 3 months	Ezetimibe vs statins 8/66 (12.1%) vs 8/69 (11.6%) p=NR	135 (1 RCT)	⊕⊕⊕⊖ MODERATE ₫	Unclear if ezetimibe differed to statins because statistical difference not reported.
Serious adverse event follow up: 3 months	Ezetimibe vs statins 0/66 (0.0%) vs 0/69 (0.0%) p=NR	135 (1 RCT)	⊕⊕⊕⊖ MODERATE ₫	Unclear if ezetimibe differed to statins because statistical difference not reported.

#### Abbreviations

ASCVD = atherosclerotic cardiovascular disease, CI = confidence interval, LDL-c = low density lipoprotein-cholesterol, MD = mean difference, mg/dL = milligrams per decilitre, NR = not reported, RCT = randomised controlled trial. Notes

\* The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

 $\mathbf{a}$  = notable losses to follow-up,  $\mathbf{b}$  = surrogate for MI, vascular events, mortality,  $\mathbf{c}$  = unclear applicability of trial population to Swiss context,  $\mathbf{d}$  = one study; small sample size.

#### GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.

**Moderate certainty**: We are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: Our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect.
# Table 56 GRADE summary of findings: Ezetimibe compared to fenofibrate for hyperlipidaemia

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect	Number of participants	Certainty of the	Comments	
	Risk with fenofibrate	Risk with ezetimibe	(95% CI)	(studies)	evidence (GRADE)		
LDL-c (percentage change) follow up: 3 months	Mean LDL- c -1.32%	9.72% lower (27.85 lower– 8.41 higher)	-	466 (2 RCTs)	⊕⊕⊖⊖ LOW a,b,c,d	Ezetimibe did not statistically differ from fenofibrate (no effect).	
Withdrawal due to adverse events follow up: 3 months	44 per 1,000	20 per 1,000 (7–57)	RR 0.46 (0.16– 1.30)	496 (2 RCTs)	⊕⊕⊕⊖ MODERATE e,f	Ezetimibe did not statistically differ from fenofibrate (no effect).	
Serious adverse events follow up: 3 months	4 per 1,000	18 per 1,000 (2–144)	RR 4.40 (0.46– 35.83)	496 (2 RCTs)	⊕⊕⊕⊖ MODERATE e,f	Ezetimibe did not statistically differ from fenofibrate (no effect).	

## without ASCVD

#### **Abbreviations**

ASCVD = atherosclerotic cardiovascular disease, CI = confidence interval, LDL-c = low density lipoprotein-cholesterol, MD = mean difference, mg/dL = milligrams per decilitre, NR = not reported, RCT = randomised controlled trial, RR = risk ratio. Notes

\* The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

 $\mathbf{a}$  = considerable levels of heterogeneity and inconsistency,  $\mathbf{b}$  = non-overlapping CIs,  $\mathbf{c}$  = surrogate for MI, vascular events, mortality,  $\mathbf{d}$  = unclear applicability of trial population to Swiss context,  $\mathbf{e}$  = small event number for sample size,  $\mathbf{f}$  = 95% CI around pooled estimates includes negligible effect and appreciable benefit/harm.

# **GRADE Working Group grades of evidence**

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.

**Moderate certainty**: We are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: Our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect.

Very low certainty: We have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect.

# Table 57 GRADE summary of findings: Ezetimibe plus statins compared to statins for

### hyperlipidaemia without ASCVD

Outcomes	Impact	Number of participants (studies)	Certainty of the evidence (GRADE)	Comments
LDL-c (absolute change) follow up: 3 months	Ezetimibe plus statins vs statins 89.7 ± 19.6mg/dL vs 114.5 ± 21.7mg/dL p=NR	133 (1 RCT)	⊕⊕⊖⊖ LOW a,b,c,d,e	Unclear if ezetimibe plus statins differed to statins because statistical difference not reported.
Withdrawal due to adverse events follow up: 3 months	Ezetimibe plus statins vs statins 5/64 (7.8%) vs 8/69 (11.6%) p=NR	133 (1 RCT)	⊕⊕⊕⊖ MODERATE ₫	Unclear if ezetimibe plus statins differed to statins because statistical difference not reported.
Adverse events follow up: 3 months	Ezetimibe plus statins vs statins 0/64 (0.0%) vs 0/69 (0.0%) p=NR	133 (1 RCT)	⊕⊕⊕⊖ MODERATE ₫	Unclear if ezetimibe plus statins differed to statins because statistical difference not reported.

# **Abbreviations**

ASCVD = atherosclerotic cardiovascular disease, CI = confidence interval, LDL-c = low density lipoprotein-cholesterol, MD = mean difference, mg/dL = milligrams per decilitre, NR = not reported, RCT = randomised controlled trial. Notes

\* The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

 $\mathbf{a}$  = notable losses to follow-up,  $\mathbf{b}$  = surrogate for MI, vascular events, mortality,  $\mathbf{c}$  = unclear applicability of trial population to Swiss context,  $\mathbf{d}$  = one study; small sample size,  $\mathbf{e}$  = overlapping standard deviations.

## **GRADE Working Group grades of evidence**

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.

**Moderate certainty**: We are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: Our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect.

Very low certainty: We have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect.

#### Table 58 GRADE summary of findings: Ezetimibe plus fenofibrate compared to fenofibrate for

Outcomes	Anticipated ab (95% CI)	solute effects*	Relative Number of effect participants		Certainty of the	Comments
	Risk with fenofibrate	k with ofibrate Risk with ezetimibe plus fenofibrate (95% CI)		(studies)	evidence (GRADE)	
LDL-c	3 months	3 months	NA	471	$\oplus \oplus \bigcirc \bigcirc$	Ezetimibe plus
(percentage	Mean LDL-c	-19.94% lower		(3 RCTs)	LOW a,b,c,d,e	tenotibrate statistically
follow up: 3–12 months	-1.32% (31.80 lower- 8.09 lower)					fenofibrate at 3 months in meta-
	12 months					analysis; differed at
	Mean LDL-c	12 months				12 months in 1 study.
	-22.0%	-13.40% lower				
		(16.06 lower– 10.74 lower)				
Withdrawal due to adverse event follow up: 3–12 months	52 per 1,000	38 per 1,000 (22–67)	RR 0.74 (0.43– 1.30)	1,070 (3 RCTs)	⊕⊕⊕⊖ MODERATE a,f	Ezetimibe plus fenofibrate did not statistically differ from fenofibrate (no effect).
Serious adverse event follow up: 3–12 months	31 per 1,000	53 per 1,000 (20–140)	RR 1.71 (0.64– 4.53)	1,070 (3 RCTs)	⊕⊕⊕⊖ MODERATE a,f	Ezetimibe plus fenofibrate did not statistically differ from fenofibrate (no effect).

#### hyperlipidaemia without ASCVD

# Abbreviations

**ASCVD** = atherosclerotic cardiovascular disease, **CI** = confidence interval, **LDL-c** = low density lipoprotein-cholesterol, **MD** = mean difference, **mg/dL** = milligrams per decilitre, **NA** = not applicable, **NR** = not reported, **RCT** = randomised controlled trial, **RR** = risk ratio.

#### <u>Notes</u>

\* The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

 $\mathbf{a}$  = notable losses to follow-up,  $\mathbf{b}$  = considerable levels of heterogeneity and inconsistency,  $\mathbf{c}$  = non-overlapping Cls,  $\mathbf{d}$  = surrogate for MI, vascular events, mortality,  $\mathbf{e}$  = unclear applicability of trial population to Swiss context,  $\mathbf{f}$  = 95% Cl around pooled estimates includes negligible effect and appreciable benefit/harm.

# GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.

**Moderate certainty**: We are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: Our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect.

Very low certainty: We have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect.

# 8 Costs, Cost-effectiveness and Budget Impact

#### 8.1 Summary Statement Costs, Cost-Effectiveness, and Budget Impact

Ezetimibe (monotherapy and combination therapy) is reimbursed by Swiss health insurance without limitation (except for ezetimibe plus atorvastatin). However, it is unclear whether the drug is cost effective when compared to statins. A Markov model has been developed to quantify the cost-effectiveness of ezetimibe plus statins compared to statins. The model uses incremental quality-adjusted life years (costs per QALYs) with univariate and probabilistic sensitivity analyses to evaluate uncertainties in the model. Results are presented as incremental cost-effectiveness ratios (ICER), with a hypothetical willingness-to-pay threshold set at CHF100,000 per QALY gained.

Models for patients with hypercholesterolaemia without ASCVD and patients with hyperlipidaemia with or without ASCVD could not be generated owing to the absence of MACE data. There was sufficient evidence to create a model for patients with hypercholesterolaemia and ASCVD. The results of the model were informed by the IMPROVE-IT trial and thus are more reflective of patients with ACS.<sup>52</sup> Using the results of the IMPROVE-IT trial, ezetimibe plus simvastatin reduced CHD-related surgeries, MI and strokes compared to simvastatin alone. Therefore, the estimated ICER for ezetimibe plus simvastatin vs simvastatin was CHF62,242 per QALY gained at 7 years. This decreased to CHF20,917 per QALY gained over a 20-year projection. Both ICERs are less than a hypothetical willingness-to-pay threshold of CHF100,000.

Univariate sensitivity analyses were used to explore different model assumptions, specifically different doses and types of statins (derived from Law [2003]<sup>192</sup>), costs of medicines, Swiss diagnosis-related group (DRG) cost weights for health states and assumed health state utilities. The analyses indicated that the ICER was most sensitive to medicine cost assumptions used in the model. Probabilistic sensitivity analyses (PSA) determined with 85% probability that ezetimibe plus simvastatin was superior (or cost-effective) compared to simvastatin over a 20-year projection.

Additional sensitivity analyses noted ezetimibe plus simvastatin was not cost-effective when compared to higher potency statins. This finding supports AGLA's current recommendation that ezetimibe should be limited to patients who are statin intolerant or have failed to reach treatment goals despite maximally tolerated statins. Therefore, budgetary impact analyses were performed to quantify the financial implication of limiting ezetimibe to these populations. In the absence of Swiss-specific data, two hypothetical substitution scenarios (10% and 25% of patients substituting from ezetimibe monotherapy and ezetimibe in combination with rosuvastatin or simvastatin to high potency statin [atorvastatin 40mg])

were utilised (Noting, there is uncertainty around the numbers of patients who belong to these subgroups.). If 10% of patients substituted from ezetimibe (monotherapy or combination therapy) to a high potency statin, there is a net savings of CHF2.0 million in 2020, increasing to CHF2.3 million by 2023. If 25% of patients substituted to high potency statin, there is a net savings of CHF5.0 million in 2020, increasing to CHF5.7 million by 2023.

#### 8.2 Methods

A Markov model was developed to quantify the cost-effectiveness of ezetimibe plus statins compared to statin monotherapy. The model was developed using TreeAgePro (TreeAge Software, Inc, One Bank Street Williamstown, MA, 01267 USA)<sup>193</sup> and data from the IMRPOVE-IT trial.<sup>52</sup>

Probabilistic sensitivity analysis was performed to account for uncertainty in the input parameters. (See *Table 59* for assumptions). The analysis involved 10,000 iterations which were used to calculate a 95% CI. The probability of the ICER being cost effective is based on a hypothetical willingness-to-pay threshold of CHF100,000. As this threshold is hypothetical, a cost-effective acceptability curve was provided for the lifetime projection, so the probability of the intervention being cost-effective at differing willingness-to-pays could be determined. This was an important consideration given many countries utilise different willingness to pay thresholds based on the severity of the health condition.<sup>194</sup>

ICERs were calculated using base-case unit costs and health outcomes reported as QALYs at 7 years (trial duration) and 20 years (lifetime). Costs and QALYs were discounted at 3% per annum in the base analysis, and a half-cycle correction was applied to both costs and health outcomes.

Health state utilities were estimated using values used in the economic model of Ara (2008).<sup>195</sup> The analysis took the perspective of the Swiss payer, so only direct costs were included. Annual costs for health states were taken from Swiss DRG costs,<sup>196</sup> the price of medicines were taken from the Swiss Spezialitätenliste and the volume and costs of medicines were taken from © COGE GmbH. Tarifpool. © SASIS AG, and TARMED was used for general doctor and monitoring costs.

Sensitivity of the results to different model assumptions was explored in univariate sensitivity analysis. Parameters included in univariate sensitivity analysis included discount rate, medicines regimen costs, dosing (e.g. statin types and doses [informed by Law (2003)<sup>192</sup>]), transition probabilities and DRG costs associated with MI, stroke, angina and CHD surgery. Normal distributions were assumed for most utility inputs in the probabilistic sensitivity analyses and triangular distributions for cost inputs based on average, high and low estimates for medicines and stroke, MI, angina and CHD surgery hospital costs.

#### 8.2.1 Economic Modelling Background

#### **Review of Economic Literature**

Twelve publications were identified from the systematic literature search (outlined in **Section 7.2.1**). Ten studies used Markov state transition models with long-term extrapolations and included similar health states: MI, angina, stroke, peripheral artery disease, heart failure, transient ischaemic attack and death. The studies also considered costs of medicines, and costs related to drug prescriptions and management of relevant clinical events and adverse effects. Most used the EQ-5D (EuroQOL 5 dimensions questionnaire) to infer quality-of-life changes and calculate incremental life gains.

As part of a systematic review for the NICE-supported HTA for ezetimibe, Ara (2008)<sup>195</sup> identified two published papers featuring Markov models by Cook (2004)<sup>197</sup> and Kohli (2006).<sup>198</sup> Cook (2004) developed a Markov model to evaluate the cost-effectiveness of ezetimibe in Germany, Spain and Norway.<sup>197</sup> The model compared ezetimibe plus statins to statin monotherapy and evaluated patients with CHD or diabetes who had not achieved treatment goals with their current statin dose. Statin monotherapy was either maintained at the current dose or up-titrated over the course of the model. Costs and benefits were discounted at an annual rate of 3% for the 3 countries. The ICER for ezetimibe plus statins compared to statin was less than €18,900 per life year gained (LYG) (CHF20,223) for CHD patients, and the ICER for ezetimibe plus statin compared to up-titrated statin was less than €27,300 (CHF29,211) per LYG.

The modelling study by Cook (2004)<sup>199</sup> appears to have influenced economic approaches to ezetimibe cost-effectiveness, as the subsequent studies of Davies (2017),<sup>200</sup> Laires (2015),<sup>200</sup> Reckless (2010)<sup>200</sup> and Van Nooten (2011)<sup>201</sup> all reference Cook (2004) in the methods or discussion sections. Kohli (2006)<sup>198</sup> used the Cook (2004)<sup>198</sup> used the Cook (2004)<sup>198</sup> model to examine the cost effectiveness of ezetimibe plus atorvastatin compared to atorvastatin (varying doses) in Canadian patients at high risk of coronary artery disease.<sup>198</sup> ICERs ranged from £26,200 to £45,900 per QALY gained (CHF21,746-38,097).

Ara (2008) developed a model to examine the cost-effectiveness of ezetimibe in combination with highdose statin therapy in patients with established CVD.<sup>202</sup> To calculate transition probabilities, the regression analyses of LDL-c and CVD from Baigent (2005)<sup>203</sup> were used. The calculated lifetime discounted cost per QALY gained was £27,475 (CHF22,804).

The Markov model submitted to the Australian Pharmaceutical Benefits Advisory Committee (PBAC) in 2017 was based on the results of the IMPROVE-IT trial and included a 70-year time horizon.<sup>204</sup> The ICER was \$72,297 (CHF46,993) per QALY gained for a seven-year model (base case), reducing to \$24,256 (CHF15,766) per QALY gained for a 70-year model. This substantial reduction in the ICER was

considered uncertain because many patients were older than 50 years and thus the time horizon exceeded average life expectancy. The reviewers also noted that the comparator (40mg simvastatin) was not applicable to Australia because patients were not up-titrated to the maximally tolerated statin prior to entry.

## Overview of economic model

A Markov model (summarised in *Table 59*) was developed to estimate the expected costs and QALYs associated with ezetimibe plus statins compared to statins for an average patient with hypercholesterolaemia and ASCVD. The model inputs/transition probabilities were largely sourced from the IMPROVE-IT trial<sup>52</sup> and are more reflective of individuals with ACS and ezetimibe plus simvastatin. Models evaluating patients with hypercholesterolaemia without ASCVD and patients with hyperlipidaemia with or without ASCVD were not undertaken because MACE outcomes were underreported in these populations. Similarly, there was insufficient MACE evidence to generate models for fenofibrate.

Perspective	Swiss payer
Patient population	Patients with hypercholesterolaemia and pre-existing ASCVD
Intervention	Ezetimibe in combination with simvastatin (10mg/40mg) (ezetimibe plus simvastatin)
Comparator	Simvastatin (40mg, 80mg), atorvastatin and rosuvastatin monotherapy
Type of economic evaluation	Cost-utility analysis
Sources of evidence	Trials, studies, Swiss DRG costs, TARMED, Swiss Spezialitätenliste, © COGE GmbH. Tarifpool. © SASIS AG
Time horizon	Duration of trial (7 years) and modelled lifetime analysis (20 years)
Outcomes	Quality-adjusted life years/ life years gained
Methods used to generate results	Cohort expected value analysis using Markov model
Discount rate	3% used for base and 0% and 6% sensitivity analyses
Software packages used	TreeAge Pro

#### Table 59 Summary of the economic evaluation

# Abbreviations

ASCVD = atherosclerotic cardiovascular disease, DRG = diagnosis-related group, FOPH = Federal Office of Public Health.

#### Type of economic evaluation

The Markov model outlined in *Figure* 77 was developed using TreeAge software. Health states include non-recurrent CVD (no CVD), stroke, angina, MI, CVD death, non–CVD death and CHD requiring surgery. This structure includes many of the states in the Cook (2004) model.<sup>197</sup> Each health state was assigned an expected cost using Swiss DRG weights and utilities based on EQ-5D values identified in Ara (2008).<sup>195</sup>

Ezetimibe plus simvastatin (10mg/40mg) was compared to simvastatin (40mg). The base model used the event data at seven years from the IMPROVE-IT trial (excluding adverse event data).<sup>52</sup> Sensitivity analyses extended annual probabilities for an additional 13 years to calculate the costs over a 20-year period. Other types and doses of statins (e.g. 80mg simvastatin, 40mg and 80mg atorvastatin or 20mg rosuvastatin) were assessed using univariate sensitivity analyses, with transition probabilities based on Law (2003).<sup>192</sup>



#### Figure 77 Markov structure for the cost utility model

#### **Abbreviations**

CHD = coronary heart disease, CVD = cardiovascular disease, MI = myocardial infarction.

# Sources of evidence

A summary of the clinical effectiveness results is presented in *Table 60*. There was sufficient MACE data to construct an economic model for patients with hypercholesterolaemia with ASCVD. There was insufficient data for patients with hypercholesterolaemia without ASCVD and hyperlipidaemia with and without ASCVD (these populations are discussed in the study limitations, see *Section 12.4*). Consequently, the base economic model reflects patients with hypercholesterolemia and ASCVD. (The model does not specifically include hyperlipidaemia with and without ASCVD or hypercholesterolaemia patients without ASCVD.)

There is considerable uncertainty using LDL-c levels to infer changes in mortality because the correlation is dependent on additional factors (e.g. baseline LDL-c levels)<sup>205</sup> and meta-regressions exploring this link include populations which are not applicable to Swiss context (i.e. Asian populations).<sup>206</sup> The EMA also cautions against inferring the effects of non-statin medication onto other populations who differ in their baseline LDL-c levels.<sup>72</sup> Furthermore, there was a limited number of studies evaluating LDL-c levels at longer timepoints (12 or 24 months) in the current HTA. These timepoints were often informed by one trial with relatively small sample size.

When these factors are considered, using LDL-c to calculate cardiovascular event rates would add further uncertainty to the economic model. There were no trials undertaken in Switzerland nor MACE data to inform other populations, so modelling reflects outcomes in the IMPROVE-IT trial.

Type of dyslipid- aemia	Without ASCVD	With ASCVD		
	<i>Ezetimibe vs statin</i> Statistically significant differences between ezetimibe and statin with respect to LDL-c (17.22%; 95% CI 11.23, 23.22%; p<0.00001) at 3 months, with results favouring statins. No study reported	<i>Ezetimibe vs statin</i> No study evaluated this comparison		
Hypercholesterolaemi	MACE outcomes. <b>Ezetimibe plus statin vs statin</b> Statistically significant differences between ezetimibe plus statin and statins with respect to LDL-c (MD -16.14%; -19.67, -12.60%; p<0.00001) at 3 months. When compared to statins, combination treatment of ezetimibe plus statin	<i>Ezetimibe plus statin vs statin</i> Ezetimibe plus statins improved LDL-c (MD - 13.41%; 95% CI -19.26, -7.56%; p<0.00001) at 3 months. Ezetimibe plus statin reduced incidence of 5P- MACE at 7 years post-intervention (HR 0.94; 95%)		
	resulted in similar MACE (non-fatal MI, non-fatal stroke, cardiovascular deaths) rates at 24 months. Trial not powered to detect group differences.	CI 0.89, 0.99; p=0.016). Reduction in MI, ischaemic stroke (p<0.05 for all outcomes) at 7 years, but not cardiovascular death, coronary revascularisation or hospitalisation for angina (p>0.05).		

Table 60 Clinical effectiveness result
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Type of dyslipid- aemia	Without ASCVD	With ASCVD
	Ezetimibe vs statin	Ezetimibe vs statin
	At 3 months, there were statistical differences in favour of statins in one study for LDL-c and total cholesterol.	No study evaluated this comparison
a	Ezetimibe plus statin vs statin	Ezetimibe plus statin vs statin
laem	Statistical difference not reported.	No study evaluated this comparison
lipic	Ezetimibe vs fenofibrate	Ezetimibe vs fenofibrate
Hyper	No difference in LDL-c between ezetimibe and fenofibrate.	No study evaluated this comparison
	Ezetimibe plus fenofibrate vs fenofibrate	Ezetimibe plus fenofibrate vs fenofibrate
	At 3 months, there were statistical differences in favour of ezetimibe plus fenofibrate for LDL-c, total cholesterol and triglycerides.	No study evaluated this comparison

Abbreviations ASCVD = atherosclerotic cardiovascular disease, CI = confidence interval, HR = hazard ratio, LDL-c = low density lipoprotein-cholesterol, MACE = major adverse cardiac events, MD = mean difference, MI = myocardial infarction.

# 8.3 Evidence Table

Model assumptions were derived for costs and QALY health outcomes, and are summarised in *Table 61* along with sources and the derivation of each assumption.

Assumption	Value		Source of Evidence	
Annual cost medicines use,	monitoring and do	octor visits		
	Base (CHF)	High (CHF)	Low (CHF)	
Ezetimibe (10mg), simvastatin (40mg)	663.48	846.73	480.24	Spezialitätenliste, See <b>Table 66</b>
Simvastatin (40mg)	507.66	535.36	479.97	Spezialitätenliste, See Table 66
Simvastatin (80mg)	479.97	NA	NA	Spezialitätenliste, See Table 66
Atorvastatin (40mg)	431.24	NA	NA	Spezialitätenliste, See Table 66
Atorvastatin (80mg)	431.24	NA NA		Spezialitätenliste, See Table 66
Rosuvastatin (20mg)	602.79	NA NA		Spezialitätenliste, See Table 66
Health state costs using Sw	iss DRG weights			
Angina	5,367	5,367 5,367		Swiss DRGs, See Table 68
Non-fatal MI	10,692	15,542 5,841		Swiss DRGs, See Table 68
Fatal MI	10,692	15,542	5,841	Swiss DRGs, See Table 68
Non-fatal stroke	15,258	28,212	3,978	Swiss DRGs, See Table 68
Fatal stroke	9,972	12,745	7,198	Swiss DRGs, See Table 68
CHD requiring surgery	31,930	64,562	9,118	Swiss DRGs, See Table 68
Health state utilities				
No CVD	0.82	Normal distributio	on (SD=0.14)	60–69-year olds from Swiss EQ- 5D survey from Perneger (2010) <sup>207</sup>
Angina	0.77	Normal distribution (SD=0.038)		Goodacre (2004), <sup>208</sup> cited in Ara (2008) <sup>195</sup>
Non-fatal MI	0.72	Normal distribution (SD=0.24)		Lacey and Walters (2003)209
Non-fatal stoke	0.63	Normal distribution (SD=0.04)		Ara (2008) <sup>195</sup>
CHD requiring surgery	0.76	Triangular distrib 0.79)	ution (0.73, 0.76,	Puskas (2004), <sup>210</sup> Shrive (2005) <sup>211</sup>
CVD and Non-CVD death	0.00	NA		Assumption

# Table 61 Summary of cost and utility evidence for the economic evaluation

# **Abbreviations**

**CHD** = coronary heart disease, **CVD** = cardiovascular disease, **DRG** = diagnosis-related group, **EQ-5D** = EuroQol 5 dimensions questionnaire, **MI** = myocardial infarction, **NA** = not applicable, **SD** = standard deviation.

Annual transition probabilities for coronary revascularisation (CHD-requiring surgery), MI, stroke and angina events were sourced from the IMPROVE-IT trial.<sup>52</sup> MI case fatality was 4% and stroke case fatality was 22%. The stroke fatality was the average difference between CHD and CVD deaths per group. This estimate was similar to the case fatality proportion in the South London Stroke Register (see Wolfe 2002).<sup>212</sup>

CHD deaths in the IMPROVE-IT trial encompassed deaths resulting from MI, atherosclerotic heart disease (sudden and non-sudden deaths) and coronary artery procedures such as surgery, percutaneous coronary intervention (PCI), or angiography. At 7 years, in the simvastatin monotherapy group there were 49 cumulative MI deaths (0.7%) and 412 sudden or non-sudden CHD deaths or procedure-related deaths (5.1%). In the ezetimibe plus simvastatin group there were 41 cumulative MI deaths (0.5%) and 399 sudden or non-sudden CHD deaths or procedure-related deaths (5.2%). Annual transition probabilities of 0.007 and 0.006 were included for the non-recurring CVD state to CVD death states (non-MI) for the simvastatin and ezetimibe plus simvastatin arm, respectively.

In the IMPROVE-IT trial, CHD requiring surgery encompassed urgent and non-urgent revascularisation procedures.<sup>52</sup> Urgent revascularisation was defined as coronary revascularisation (PCI or coronary artery bypass graft [CABG]) that occurred during a hospitalisation due to MI or recurrent unstable angina with an episode of ischaemic discomfort at rest lasting at least 10 minutes.<sup>52</sup> To avoid double counting, the non-fatal MI and angina health states included in this Markov model assumed that patients did not require revascularisation. Swiss DRGs were used that reflect non-invasive treatment for non-fatal MI and angina cases.

A background annual probability of non-CVD deaths (0.011) was applied to all health states. The probability was calculated by converting the cumulative proportion of non-CVD deaths from the IMPROVE-IT trial to annual probabilities (using the formula 1-(1-probability)^(1/7)) (*Table 62*). In the base analysis patient transitions are projected for 7 years and for 20 years in the lifetime analysis.

For the sensitivity analyses involving different type and doses of statins, the relative risks for CHD/stroke events in patients taking simvastatin (80mg), atorvastatin (40mg), atorvastatin (80mg) and rosuvastatin (20mg) were calculated from Law (2003).<sup>192</sup> The simvastatin (40mg) event rate in IMPROVE-IT<sup>52</sup> was changed using relative risks for each statin as part of a series of sensitivity analyses.

	Base analysis		Sensitivity analysis				
Annual transition probabilities	Ezetimibe (10mg), Simvastatin (40mg)	Simvastatin (40mg)	Simvastatin (80mg)	Atorvastatin (40mg)	Atorvastatin (80mg)	Rosuvastatin (20mg)	
Sourco	IMPROVE-	IMPROVE-	IMPROVE- IT <sup>52</sup> &	IMPROVE- IT <sup>52</sup> &	IMPROVE- IT <sup>52</sup> &	IMPROVE- IT <sup>52</sup> &	
Source	IT <sup>52</sup>	IT <sup>52</sup>	Law (2003) <sup>192</sup>	Law (2003) <sup>192</sup>	Law (2003) <sup>192</sup>	Law (2003) <sup>192</sup>	
No CVD-MI (non-fatal)	0.016	0.019	0.018	0.016	0.015	0.016	
No CVD-angina (non-fatal)	0.002	0.002	0.002	0.002	0.002	0.002	
No CVD-stroke (non-fatal)	0.005	0.006	0.005	0.005	0.005	0.005	
No CVD-CHD surgery	0.029	0.031	0.029	0.027	0.025	0.027	
MI-CVD death	0.044	0.044	0.044	0.044	0.044	0.044	
Angina-CVD death	0.000	0.000	0.000	0.000	0.000	0.000	
Stroke-CVD death	0.223	0.223	0.223	0.223	0.223	0.223	
No CVD-CVD death (not MI)	0.006	0.007	0.007	0.007	0.007	0.007	
All states-non-CVD death	0.011	0.011	0.011	0.011	0.011	0.011	
MI-no CVD	0.945	0.945	0.945	0.945	0.945	0.945	
Angina-no CVD	0.989	0.989	0.989	0.989	0.989	0.989	
Stroke-no CVD	0.766	0.766	0.766	0.766	0.766	0.766	
CHD-no CVD	0.989	0.989	0.989	0.989	0.989	0.989	

# Table 62 Summary of transition assumptions and evidence for the economic evaluation

# **Abbreviations**

**CHD** = coronary heart disease, **CVD** = cardiovascular disease, **MI** = myocardial infarction.

# 8.3.1 Applicability of Trials

This section addresses how the characteristics of patients included in the clinical evidence compare with circumstances of use in Switzerland (summarised in *Table 63*).

Parameter	Value	Sources/Comments					
Demographics	64 years	Patients were eligible for entry into the IMPROVE-IT trial if they					
	76% men	were older than 50 and had been hospitalised within preceding 10 days for ACS (acute MI or high-risk unstable apging). Additionally					
	LDL-c 50.7–123.7mg/dL (1.3–3.2 mmol/L)	patients required to have LDL cholesterol level of 50.7– 123.7mg/dL. <sup>52</sup>					
	Previous MI 21%						
	Previous PCI 20%						
	Previous CABG 9%						
Clinical usage	Ezetimibe (10mg) plus	Trial compared ezetimibe combination with fixed-dose statin.					
	simvastatin (40mg) vs simvastatin (40 mg)	PBAC review noted 34% of patients were being treated with a statin at beginning of trial and there was no evidence they had been treated using a maximally tolerated statin. <sup>204</sup>					
		Cannon (2015) noted that patients who had LDL-c levels >79mg/dL (2.0 mmol per litre) on 2 consecutive measurements had simvastatin dose increased to 80mg early in the trial. <sup>52</sup> During the trial, the US Food and Drug Administration limited new prescriptions of 80mg simvastatin, so patients unable to use 80mg dose. <sup>213</sup>					

Table 63 Features of patient populations in IMPROVE-IT trial

#### Abbreviations

ACS = acute coronary syndrome, CABG = Coronary artery bypass graft, LDL-c = low-density lipoprotein-cholesterol, MI = myocardial infarction, mg/dL = milligram per decilitre, mmol/L = millimoles per litre, PBAC = pharmaceutical benefits advisory committee, PCI = percutaneous coronary intervention. Source

Cannon (2015)52

# Demographics

Patients enrolled in the IMPROVE-IT trial had an average age of 64 years, 76% were men, 88% had received coronary angiography and 70% had undergone percutaneous coronary surgery. A total of 34% were taking statins at recruitment and 77% received statins during hospitalisation. It is unclear how this demographic profile relates to the applicable Swiss population. Limited Swiss-specific information was found for age-related LDL-c levels and number of patients with high cardiovascular risk (as per AGLA guidelines). The prevalence of high cholesterol in the Swiss Health survey was slightly higher among men than women (19% vs 16%) with the elderly (>65 years) reporting the highest level of any age group.<sup>29</sup>

Baseline LDL-c for patients entering the IMPROVE trial was 116mg/dL (3.0 mmol/L). The baseline LDL-c values were broadly similar to Swiss ACS patients in one study.<sup>33</sup> However, the average LDL-c for Swiss

patients using statin and ezetimibe medicines was unavailable. Cook (2004) reported that baseline LDLc varied across Germany, Norway and Spain.<sup>197</sup> For example, patients from Norway were less than 20% above their lipid goal (total cholesterol<193mg/dL [5mmol/L]), patients from Spain were 37–53% above their LDL-c goal and German patients were 48% above their lipid goal. Given this variation between countries and the limited information regarding Swiss LDL-c levels, it is difficult to determine how applicable are the baseline LDL-c levels in IMPROVE-IT to the Swiss context.

#### **Clinical Characteristics**

IMPROVE-IT patients received either ezetimibe plus simvastatin (10mg/40mg) or 40mg of simvastatin.<sup>52</sup> Up-titration to 80mg occurred in 27% of patients in the simvastatin monotherapy arm and in 6% of patients in the ezetimibe combination arm. In June 2011, the US Food and Drug Administration recommended limiting use of simvastatin (80mg) due to increased risk of myopathy.<sup>213</sup> This change in use limits the applicability to Swiss practice.

AGLA guidelines suggest ezetimibe should be used as a second-line treatment for patients who have not reached their goal despite using the maximum tolerated dose of statins or for statin-intolerant patients.<sup>17 21</sup> This did not occur across a wide range of patients in the IMPROVE-IT trial.<sup>52</sup>

# 8.3.2 Treatment Effectiveness

Base treatment effectiveness results were sourced from the IMPROVE-IT trial.<sup>52</sup> Cumulative event rates for each of the health states were converted to annual transition probabilities and included in the Markov model. The seven-year cumulative events at trial follow-up are summarised in *Table 64* for the model and from the IMPROVE-IT trial. In brief, at seven years, ezetimibe plus simvastatin significantly reduced the risk of MI, stroke and CHD requiring surgery (coronary revascularisation) compared to simvastatin. The differences increased when the annual transition probabilities were projected over 20 years.

# Table 64 Modelled and IMPROVE-IT trial cumulative events (percentage of patients)

	IMPROVE-IT <sup>52</sup>			Modelled 7-year			Modelled 20-year		
	Ezetimibe plus simvastatin	Simvastatin	Difference	Ezetimibe plus simvastatin	Simvastatin	Difference	Ezetimibe plus simvastatin	Simvastatin	Difference
Death from any cause	15.4%	15.3%	0.1%	14.33%	14.43%	-0.1%	35.9%	36.2%	-0.3%
Death from cardiovascular causes	6.9%	6.8%	0.1%	6.06%	6.16%	-0.1%	15.3%	15.6%	-0.3%
Death non-CVD	8.5%	8.5%	0.0%	8.27%	8.27%	0.0%	20.6%	20.6%	0.0%
Any MI	13.1%	14.8%	-1.7%	12.3%	14.0%	-1.7%	30.5%	34.6%	-4.1%
Any stroke	4.2%	4.8%	-0.6%	3.8%	4.3%	-0.5%	9.4%	10.7%	-1.3%
CHD requiring surgery	24.2%	25.6%	-1.4%	24.0%	25.6%	-1.6%	59.5%	63.2%	-3.7%
Angina	2.1%	1.9%	0.2%	1.9%	1.7%	0.2%	4.6%	4.1%	0.5%

<u>Abbreviations</u> CHD = coronary heart disease, CVD = cardiovascular disease, MI = myocardial infarction.

The IMPROVE-IT trial only evaluated simvastatin. To compare the effectiveness of ezetimibe plus simvastatin to other doses and types of statins the results from Law (2003) were used (*Table 65*).<sup>192</sup>

Law (2003) noted that the RCTs evaluating higher potency statins were under-powered to detect group differences in IHD. Therefore, the study used regression analyses to infer potential reductions in IHD from LDL-c levels (19.17857143 + 21.25 x mmol/l reduction LDL-c,  $R^2$ =0.97).<sup>192</sup> The results of the regression were used in this report (*Table 65*).

When compared to simvastatin (40mg), the reduced risk of ischaemic heart disease was 0.95 for simvastatin (80 mg), 0.88 for atorvastatin (40 mg), 0.82 for atorvastatin (80 mg) and 0.89 for rosuvastatin (20 mg). Risk reductions were also estimated for stroke. These values were applied to simvastatin (40mg) transition probabilities in the base analyses (see *Table 62*) as part of the sensitivity analyses that indirectly compares ezetimibe plus simvastatin to other statin types and doses.

Outcome	Simvastatin (40 mg)	Simvastatin (80 mg)	Atorvastatin (40 mg)	Atorvastatin (80 mg)	Rosuvastatin (20 mg)
Absolute reduction in LDL-c	68.83mg/dL (1.78mmol/L)	77.73mg/dL (2.01mmol/L)	91.26mg/dL (2.36mmol/L)	102.47mg/dL (2.65mmol/L)	89.71mg/dL (2.32mmol/L)
Reduction in serum LDL-c	37%	42%	49%	55%	48%
Expected IHD event decrease	57%	62%	69%	75%	68%
Expected stroke event decrease	17%	20%	23%	26%	23%

Table 65 Clinical effectiveness of different doses and types of statins, Law (2003)

#### **Abbreviations**

IHD = ischemic heart disease, LDL-c = low-density lipoprotein-cholesterol, mg/dL = milligram per decilitre, mmol/L = millimoles per litre.

Source

Law (2003)192

Baseline LDL-c levels differed between patients in the IMPROVE-IT trial and Law (2003).<sup>52 192</sup> This imbalance adds uncertainty to the model and, as a consequence, the risk reduction in Law (2003) may over- or under-estimate the effect of statins when compared to results from the IMROVE-IT trial. Correspondingly, results of the Law (2003) analysis are used in sensitivity analyses rather than as part of base model calculations.

# 8.3.3 Utility Measures

Each of the health states was assigned a utility weight derived from the literature (summarised in *Table 61*). Many of the utility weights were sourced from the Ara (2008) economic evaluation of ezetimibe for treatment of hypercholesterolaemia in the UK.<sup>195</sup>

#### CHD requiring surgery

The utility weight was an average of PCI and CABG from Shrive (2005)<sup>211</sup> and Puskas (2004).<sup>210</sup> Shrive (2005) determined a utility of 0.79 for PCI in patients age 65 and older from the Alberta provincial project for outcomes assessment in coronary heart disease (APPROACH) study.<sup>211</sup> Puskas (2004) determined a utility of 0.73 for CABG among 200 patients undergoing the procedure between 2000 and 2001.<sup>210</sup> An average utility of 0.76 was included in the base analysis, representing an average of the two surgical procedures.

#### Unstable angina

The IMPROVE-IT trial defined unstable angina as a patient requiring admission into hospital following an episode of ischaemic discomfort.<sup>52</sup> Ara (2008) reviewed several studies when developing utilities for unstable angina,<sup>195</sup> using a mean utility score of 0.77 based on UK patients' EQ-5D scores at 6 months post-diagnosis of unstable angina.<sup>208</sup> This value (and standard deviation) is included in *Table 61*.

#### Non-fatal MI

A mean utility of 0.72 for non-fatal MI was included in *Table 61*, along with the standard deviation estimated in Lacey and Walters (2003).<sup>209</sup> Fatal MI (CVD death) has a utility of zero. Ara (2008) also included a following-year utility of 0.8 for MI.<sup>195</sup> In our model, patients return to the 'no recurrent CVD' state following MI, so the utility associated with this state is uncertain. MI utility values are subject to sensitivity analysis to determine robustness of model results to this assumption, along with the standard deviation estimated in Lacey & Walters (2003).<sup>209</sup>

# Non-fatal stroke

Ara (2008) presented a meta-analysis of stroke utility estimates from 20 studies, generating an average utility of 0.63 when weighted by the proportions experiencing mild, moderate or severe stroke in a UK trial.<sup>214</sup> The severity of strokes occurring in IMPROVE-IT were not reported, although ischaemic stroke was far more common than haemorrhagic stroke.<sup>52</sup> The average of 0.63 and standard deviation of 0.04 were included in the base analysis for non-fatal stroke and subject to sensitivity analysis. Fatal stroke (CVD death) has a utility of zero.

#### Non-recurring CVD

Swiss general population EQ-5D values were included for the non-CVD health state. The values were sourced from Perneger (2010), who evaluated EQ-5D in Swiss adults from French-speaking regions in 2007.<sup>207</sup> Questionnaires were returned by 1,956 people (response 52.1%) with an average utility of 0.83 (SD 0.14) for 60–69 year-old men. This value is included as the baseline non-recurring CVD in the economic model. A sensitivity analysis was conducted where baseline utility varied by 10%.

# CVD and non-CVD death

A utility value of zero is included for the absorbing death state. Patients transition to this state as a result of CVD deaths (fatal stroke and MI) and non-CVD related causes.

# 8.3.4 Costs Input

Swiss DRG costs were applied to each health state in the model on an annual basis, along with calculations for medicines and services for the intervention and comparator (TARMED).

# Medicine costs

The annual costs of ezetimibe and statin medicines are presented in *Table 66*. Ezetimibe plus simvastatin (10mg/40mg) was costed based on commonly utilised brands. Prices were based on the 98- (or 100-) tablet pack, as many prescriptions use these pack sizes. Commonly used simvastatin (40mg, 80mg), rosuvastatin (20mg) and atorvastatin (40mg, 80mg) brands were used to estimate the annual cost of each regimen. Medicine costs were combined with annual doctor visit and monitoring costs from *Table 67* to generate total annual costs.

Medicine	Dose (mg) per day	Cost per pack (CHF)	mg per tablet	Tablets per pack	Medicine cost per year (CHF)	Doctor visit and monitor -ing (CHF)	Total per year (CHF)
Inegy Tablet 10mg/40mg, 98 tablets	10/40	180.45	10	98	672.08	174.65	846.73
Ezetimib-Simvastatin Mepha Tabl 10mg/40mg, 98 tablets	10/40	82.05	10	98	305.59	174.65	480.24
Zocor Filmtabl 40mg, 98 tablets	40	96.85	40	98	360.72	174.65	535.36
Simvastatin (40mg)	40	83.65	40	100	305.32	174.65	479.97
Simcora Filmtabl 40mg, 100 tablets							
Simvastatin (80mg)	80	83.65	80	100	305.32	174.65	479.97
Simcora Filmtabl 80mg, 100 tablets							
Rosuvastatin (20mg)	20	166.70	20	100	608.46	174.65	783.10
Crestor Filmtabl 20mg, 100 tablets							
Rosuvastatin (20mg)	20	67.90	20	100	247.84	174.65	422.48
Crestastatin Filmtabl 20mg, 100 tablets							
Atorvastatin	40	70.3	40	100	256.60	174.65	431.24
Mepha Lactabs 40mg, 100 tablets							
Atorvastatin	80	70.3	80	100	256.60	174.65	431.24
Mepha Lactabs 80mg, 100 tablets							

# Table 66 Annual costs for medicines and doctor visits (CHF)

**Abbreviations** 

CHF = Swiss francs Source Spezialitätenliste,<sup>68</sup> 1st July 2020.

# Costs of monitoring

Patients receive tests for liver function, cholesterol and CK. The costs of these tests, along with associated doctor visits are presented in *Table 67*, using TARMED positions for general doctor visits and laboratory testing. An average cost of CHF174.65 was added to annual medicine costs to generate annual intervention and comparator costs.

# Table 67 Annual costs for monitoring and doctor visits (CHF)

TARMED Position	Activity	Number of doctors' visits	Total time	Value for medical service (AL)	Value for technical service (TL)	Total	Tax point (TP) value CHF	Cost in CHF
GP services								
00.0010	Consultation, first 5 minutes (basic consultation)	1	5	10.42	8.19	18.61	0.90	16.75

TARMED Position	Activity	Number of doctors' visits	Total time	Value for medical service (AL)	Value for technical service (TL)	Total	Tax point (TP) value CHF	Cost in CHF
00.0015	Surcharge for GP services in doctor's office	1		10.88	0.00	10.88	0.90	9.79
00.0020	Consultation, every additional 5 minutes (consultation surcharge)	3	15	10.42	8.19	55.83	0.90	50.25
00.0050	Preliminary discussion of diagnostic/therapeutic interventions	1	5	10.42	8.19	18.61	0.90	16.75
00.0030	Consultation, last 5 minutes (consultation surcharge)	1	5	5.21	4.1	9.31	0.90	8.38
00.0141	Study of files in absence of patient	5	5	2.08	1.64	18.60	0.90	16.74
00.0415	Small examination by specialist for basic care	1	-	10.42	9.34	19.76	0.90	17.78
00.0710	Puncture, venous, for purpose of taking blood	1	-	0.00	0.00	0.00	0.90	0.00
00.0715	Puncture, venous, for purpose of taking blood	1	-	0.00	8.19	8.19	0.90	7.37
	Total AL plus TL	-	35	-	-	-	0.90	143.81
Analysis at	GP							
1230.01	Cholesterol, total	1	-	7.9	-	7.9	0.90	7.11
1410.01	HDL- Cholesterol	1	-	7.9	-	7.9	0.90	7.11
1731.01	Triglyceride	1	-	7.9	-	7.9	0.90	7.11
	LDL -Cholesterol	1	-	-	-	0.00	0.90	0.00
1249.01	СК	0.4	-	7.9	-	3.16	0.90	2.84
1047.01	Amylase	0.4	-	7.9	-	3.16	0.90	2.84
Total			-	-	-	-	-	27.02
Analysis at I	aboratory	•	•			•		
1230.00	Cholesterol, total	1	-	2.5	-	2.5	0.90	2.25
1410.10	HDL-cholesterol	1	-	3.2	-	3.2	0.90	2.88
1731.00	Triglyceride	1	-	2.8	-	2.8	0.90	2.52
1521.00	LDL-cholesterol	1	-	4	-	4	0.90	3.60
1249.00	СК	0.4	-	2.5	-	1	0.90	0.90
1047.00	Amylase	0.4	-	2.5	-	1	0.90	0.90
	Tax for labour	1	-	24	-	24	0.90	21.60
	Total	-	-	-	-	-	-	34.65
Costs: yearl	y control at GP and analysis at G	iP	CHF	170.83			·	
Costs: yearl	y control at GP but analysis at la	boratory	CHF	178.46				
Average			CHF	174.65				

# Abbreviations

AL= Taxpunktwert der ärztlichen Leistung (tax point value for medical service), CHF = Swiss franc, HDL-c = high-density lipoprotein-cholesterol, CK = creatine kinase, GP = general practitioner, LDL-c = low-density lipoprotein-cholesterol, Swiss FOPH = Swiss Federal Office of Public Health, TL = Taxpunkt der technischen Leistung (tax point value for technical service).

# Costs of health states

Swiss DRG weights (https://datenspiegel80.swissdrg.org, accessed 8/11/2020)<sup>215</sup> were used to calculate per procedure angina, non-fatal MI, fatal MI, non-fatal stoke, fatal stroke and CHD requiring surgery costs. The base, high and low cost are presented in *Table 68*. The high and low estimates were used as upper and lower bounds of triangular distributions in the PSA.

Assumption	Cost (CHF)			Source of Evidence				
Health state cost using Swiss DRG weights								
	Base	High	Low					
Angina	5,367	5,367	5,367	Swiss DRG, See Table 69				
Non-fatal MI	10,692	15,542	5,841	Swiss DRG, See Table 70				
Fatal MI	10,692	15,542	5,841	Swiss DRG, See Table 70				
Non-fatal stroke	15,258	28,212	3,978	Swiss DRG, See Table 71				
Fatal stroke	9,972	12,745	7,198	Swiss DRG, See Table 72				
CHD requiring surgery	31,930	64,562	9,118	Swiss DRG, See Table 73				

#### Table 68 Swiss DRG costs per procedure

#### Abbreviations

**CHF** = Swiss Francs, **CHD** = coronary heart disease, **DRG** = diagnostic reference group, **FOPH** = Federal Office of Public Health, **MI** = myocardial infarction.

# Unstable angina

The IMPROVE-IT trial defined unstable angina as an episode of ischaemic discomfort consistently lasting more than 10 minutes and resulting in the patient being hospitalised.<sup>52</sup> Swiss DRG Code F66Z (see *Table 69*) was used to calculate the cost of care associated with unstable angina. It was associated with an average length of hospital stay of 4.3 days.

#### Table 69 Angina, Swiss DRG cost per procedure

DRG	Description	Cost per procedure (CHF)	Average length of stay (days)
Angina			
DRG F66Z	Coronary arteriosclerosis	5,367	4.3

Abbreviations

**DRG** = diagnostic reference group.

# MI not requiring surgery

Swiss DRG codes and associated costs included in the costing model for MI are presented in **Table 70**. The average of the included costs was used for base cost calculations. Upper and lower values formed bounds of the triangular distribution used for the PSA.

	Table 7	'0 MI,	Swiss	DRG	cost	per	procedure
--	---------	--------	-------	-----	------	-----	-----------

DRG	Description	Cost per procedure (CHF)	Average length of stay (days)						
Acute MI with	Acute MI without surgery								
F60A	Acute MI without invasive cardiological diagnostics, with extremely severe complications, more than one day of occupancy	15,542	10.7						
F60B	Acute MI without invasive cardiological diagnostics, more than one day of occupancy	5,841	5.1						
Average		10,692	7.9						
Maximum		15,542	10.7						
Minimum		5,841	5.1						

Abbreviations

**DRG** = diagnostic reference group, **MI** = myocardial infarction.

# Non-fatal stroke

The IMPROVE-IT trial defined stroke as an acute new neurological deficit ending in death or lasting >24 hours.<sup>52</sup> Swiss DRG costs for non-fatal stroke were averaged (See *Table 71*), with CHF15,258 per procedure being used for base calculations. Upper and lower values formed bounds of the triangular distribution used for the PSA.

# Table 71 Non-fatal stroke, Swiss DRG costs per procedure

DRG	Description	Cost per procedure (CHF)	Average length of stay (days)				
Non-Fatal Stroke							
B70A	Apoplexy with complex neurological treatment of acute stroke >72 hours, with complicating diagnosis or difficult.	28,212	12.9				
B70B	Apoplexy with complex neurological treatment of acute stroke >72 hours. Complex diagnostics.	21,169	10				
B70C	Apoplexy with complex neurological treatment of acute stroke <73 hours, with complicating diagnosis or thrombolysis.	16,427	8.2				
B70D	Apoplexy with complex neurological treatment of acute stroke <73 hours. Complex treatment >72 hours.	14,509	7.4				

DRG	Description	Cost per procedure (CHF)	Average length of stay (days)
B70E	Apoplexy with other neurological complex treatment of acute stroke <73 hours. Complex diagnostics.	13,121	6.8
B70F	Apoplexy, more than one day of occupancy or thrombolysis with a complicating diagnosis.	13,664	8.8
B70G	Apoplexy, more than one occupancy day	10,987	7.3
B70J	Apoplexy with complex neurological treatment of acute stroke >23 hours to <48 hours, one occupancy day	3,978	1.0
B70K	Apoplexy with complex neurological treatment of acute stroke <24 hours, one day of occupancy	15,258	7.8
Average		15,258	7.8
Maximum		28,212	12.9
Minimum		3,978	1.0

<u>Abbreviations</u> DRG = diagnostic reference group.

# Fatal stroke

Swiss DRGs for fatal stroke were averaged (See Table 72), with CHF9,972 per procedure being used for base calculations. The weight corresponded to an average length of hospital stay of 2.9 days. Upper and lower values formed bounds of the triangular distribution used for the PSA.

Table 72 Fatal stroke	, Swiss DRG	i cost per	procedure
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DRG	Description	Cost per procedure (CHF)	Average length of stay (days)
Fatal Stroke			
B70H	Apoplexies, more than one day of occupancy or thrombolysis, died <5 days after admission, with complex neurological treatment of acute stroke or other complex neurological treatment	12,745	3.0
B70I	Apoplexy, more than one day of occupancy or thrombolysis, died <5 days after admission	7,198	2.7
Average		9,972	2.9
Maximum		12,745	3.0
Minimum		7,198	2.7

# Abbreviations

**DRG** = diagnostic reference group.

# CHD requiring surgery

This endpoint was investigator-determined in the IMPROVE-IT trial.<sup>52</sup> All PCI and CABG procedures performed >30 days after randomisation were included in this endpoint. Attempted revascularisation procedures, even if unsuccessful, were also included. Swiss DRG costs for PCI and CABG procedures were averaged and used for the base calculation. The mean cost was estimated to be CHF31,930 (See *Table 73*). Upper and lower values formed bounds of the triangular distribution used for the PSA.

DRG	Description	Cost per procedure (CHF)	Average length of stay (days)						
Coronary byp	Coronary bypass surgery								
F06A	Coronary bypass surgery, with multiple complex OR procedures or complicating procedures or implantation of a pacemaker	64,562	15.7						
F06B	Coronary bypass surgery, with complex vascular intervention or complex diagnosis with specific intervention	45,237	12.7						
F06C	Coronary bypass surgery, with specific intervention or extremely severe complications	41,958	11.4						
F06D	Coronary bypass surgery	34,723	9.6						
Percutaneous coronary angioplasty (PTCA)									
F24A	PTCA with multiple interventions or complicating procedures, and extremely severe complications, or certain diagnosis	36,945	11.2						
F24B	PTCA with multiple interventions or complicating procedures or a specific diagnosis with extremely severe CC, more than one	25,587	8.2						
F24C	PTCA with three or more stents or complex procedure	16,158	3.5						
F24D	PTCA with two stents	13,085	3.8						
F24F	PTCA, age >15 years	9,118	2.5						
Average		31,930	8.7						
Maximum		64,562	15.7						
Minimum		9,118	2.5						

Table	73 CHD	requiring	surgery,	Swiss	DRG	cost per	procedu	Jre

**Abbreviations** 

DRG = diagnostic reference group, PCTA = percutaneous coronary angioplasty.

# 8.4 Results: Cost-Effectiveness

# 8.4.1 Hypocholesterolaemia with ASCVD

# ICER

The incremental cost effectiveness of ezetimibe plus simvastatin vs simvastatin monotherapy comparisons at 7 and 20 years are presented in *Table 74*. The ICER at 7 years was CHF62,242 and at 20 years, CHF20,917. The ICER was less than the hypothetical willingness to pay threshold of CHF100,000.

# Table 74 Incremental cost-effectiveness of ezetimibe plus simvastatin vs simvastatin at 7 and 20 years

	Cost per patient (CHF)	Incremental cost (CHF)	QALYs	Incremental QALYs	ICER (CHF per QALY gained)			
7 years (IMPROVE-IT trial follow-up)								
Ezetimibe plus simvastatin	15,099		5.49					
Simvastatin	14,757	342	5.48	0.01	62,242			
20 years (lifetime projection)								
Ezetimibe plus simvastatin	38,308		10.71					
Simvastatin	37,851	456	10.69	0.02	20,917			
Ezetimibe plus simvastatin Simvastatin	38,308 37,851	456	10.71 10.69	0.02	20,917			

Abbreviations

**QALY** = quality-adjusted life year.

# Univariate Sensitivity Analysis

Sensitivity of the results to different model assumptions was explored in a univariate sensitivity analysis for the 7- and 20-year models.

A tornado graph for ezetimibe plus simvastatin compared to simvastatin at seven years is presented in *Figure 78*. ICER estimates were most affected by high and low medicine costs, utility estimates for the no recurring CVD health state, a 10% change in the statin arm transitions to surgery and costs assumed for CHD patients requiring surgery.



# Figure 78 Ezetimibe plus simvastatin compared to simvastatin: 7-year incremental costeffectiveness tornado graph

#### Abbreviations

CHF = Swiss francs, CVD = cardiovascular disease, ICER = incremental cost effectiveness ratio, MI = myocardial infarction. Notes

The bracketed numbers refer to the minimum (low) and maximum (high) cost, probability or utility value of the assessed parameters, see *Section 8.3.4*.

A tornado graph for ezetimibe plus simvastatin compared to simvastatin at 20 years is presented in *Figure 79*. ICER estimates were most affected by high and low medicine costs, relative risks of transition to stroke, surgery and MI for statins, a 10% change in the statin arm transitions to surgery, and costs assumed for CHD patients requiring surgery. Changes in cost weights for MACE events (revascularisation, stroke, MI and angina) and discounting did not have a large impact on the calculated ICER.





#### effectiveness tornado graph

#### Abbreviations

CHF = Swiss Francs, CHD = coronary heart disease, CVD = cardiovascular disease, ICER = incremental cost effectiveness ratio, MI = myocardial infarction.

#### <u>Notes</u>

The bracketed numbers refer to the minimum (low) and maximum (high) cost, probability or utility value of the assessed parameters, see *Section 8.3.4*.

Ezetimibe plus simvastatin was also compared to statins of different types and intensity using the transition data in *Table 62* and *Table 66*. The expected IHD event decrease was applied to the no CHD-MI and the no CHD-CHD surgery transition probabilities, while the expected stroke event decrease was applied to the no CHD-stroke transition. Only ezetimibe in combination with simvastatin was considered for the analyses. Ezetimibe monotherapy and ezetimibe in combination with other statins or fenofibrate were not evaluated in this analysis.

The ICER for ezetimibe plus simvastatin versus simvastatin (80mg) was CHF117,063 over a 20-year horizon, while the ICERs for ezetimibe plus simvastatin against atorvastatin (40mg), atorvastatin (80mg) and rosuvastatin (20mg) were CHF1,133,631, CHF-1,082,447 and CHF223,854, respectively. These lower costs medicines yielded similar effectiveness. The results suggest ezetimibe plus simvastatin is not cost effective against higher potency statins using the indirect comparison provided in Law (2003).<sup>192</sup> This finding supports AGLA recommendations, noting baseline imbalances in LDL-c between Law (2003).<sup>192</sup> and the IMPROVE-IT trial<sup>52</sup> limits the applicability of the results.

#### Probabilistic Sensitivity Analyses

Inputs were specified as distributions for the 20-year projection (described in *Table 61*). A mean expected ICER of CHF34,173 per QALY gained (95% CI, from PSA CHF-255,300, CHF384,418, *Figure 80*) was estimated for ezetimibe plus simvastatin compared to simvastatin. Using a hypothetical willingness-to-pay threshold of CHF100,000/QALY, ezetimibe plus simvastatin reported an 85% probability of being cost effective when compared with simvastatin.



Incremental Cost-Effectiveness, EZ + Statin v. Statin



<u>Abbreviations</u> Ez = ezetimibe, WTP = willingness to pay. The cost-effectiveness acceptability curve is presented for the ezetimibe plus simvastatin compared to simvastatin at 20 years in *Figure 81*. It is evident that ezetimibe plus simvastatin has a greater than 85% chance of being cost-effective at willingness-to-pay thresholds of greater than CHF100,000. At willingness-to-pay thresholds of CHF50,000 and CHF80,000 there is a 71% and an 81% chance of ezetimibe plus simvastatin being cost-effective, respectively.



CE Acceptability Curve

# Figure 81 Ezetimibe plus simvastatin compared to simvastatin at 20 years: cost-effectiveness acceptability curve

#### acceptability

<u>Abbreviations</u> CE = cost-effectiveness, Ez = ezetimibe, WTP = willingness to pay.

# 8.4.2 Key Drivers of the Economic Model

Key drivers of the model are summarised in **Table 75**. Univariate sensitivity analyses demonstrated the assumption that medicines cost was a key driver of model value. Variations in the costs of most health-states had a negligible impact on the estimated ICER. This result was likely because cost offsets due to differences in MACE outcomes were minor when compared with the cumulative difference in cost of medicines.

# Table 75 Key drivers of the economic model

Description	Method/Value	Impact
Ezetimibe plus simvastatin prices on the Spezialitätenliste	The cost of Inegy 10/40mg (98 tablets) was CHF180.45 in 2020 whereas Mepha 10/40mg (98 tablets) was CHF82.05. The base economic model used an average of these costs. Sensitivity analyses included the minimum and maximum price as upper and lower bounds.	HighThe large range in annual medicine costsper patient had the largest impact on theICER.There were relatively small treatmentdifferences in the IMPROVE-IT trial.52
Costs weights for CHD patients requiring surgery	The Swiss DRG weights for PCI and CABG procedures were averaged for the health state cost of a CHD patient requiring surgery. Higher and lower weights associated with PCI and CABG were used to generate bounds for the sensitivity analysis.	Moderate The use of high and low weights for surgery costs had a moderate impact on the ICER.
Use of high-potency statins	The IMPROVE-IT trial compared ezetimibe plus simvastatin to simvastatin. The impact of other statins on the ICER was evaluated using sensitivity analysis. The clinical effectiveness of the other statins was informed by Law (2003) and was extrapolated to infer stroke and IHD rates. <sup>192</sup> Treatment costs were taken from popular brands of atorvastatin and rosuvastatin on the Spezialitätenliste.	High Compared to ezetimibe plus simvastatin, atorvastatin and rosuvastatin had similar reductions in LDL-c and MACE (as inferred via regression analysis in Law, 2003) but were less costly. Correspondingly, ezetimibe plus simvastatin was not cost- effective or dominated.

## Abbreviations

**CABG** = coronary artery bypass grafting, **CHD** = coronary heart disease, **CHF** = Swiss franc, **DRG** = diagnosis-related group, **ICER** = incremental cost effectiveness ratio, **IHD** = ischaemic heart disease, **LDL-c** = low density lipoprotein-cholesterol, **MACE** = major adverse cardiac event, **PCI** = percutaneous coronary intervention.

The estimated ICERs are broadly similar to the results of other economic studies. For example, analyses in Europe (Germany, Spain, Norway) using the Cook (2004) model for CHD patients, resulted in ICERs of less than €18,900/LYG (CHF20,223) for statin monotherapy and less than €27,300/LYG (CHF29,211) for the up-titrated statin comparison.<sup>197</sup> A Canadian study of patients at high risk of a CHD event, which compared ezetimibe plus atorvastatin with atorvastatin titration, found ICERs ranged from £26,200 to £45,900 per QALY (CHF21,746–38,097).<sup>198</sup> Ara (2008) undertook a cost-effectiveness analysis of long-term ezetimibe monotherapy in statin-intolerant patients with CVD and estimated an ICER of £23,026 per QALY (CHF19,111).<sup>202</sup>

# 8.5 Results: Budget Impact

Ezetimibe plus simvastatin was cost-effective compared to simvastatin (40mg) alone in patients with hypercholesterolaemia and ASCVD at 7- and 20-years. However, sensitivity analyses noted ezetimibe plus simvastatin was not cost-effective against higher potency statins. This finding supports AGLA's recommendations that ezetimibe should be limited to patients with statin intolerance and those who fail to reach treatment goals despite using maximally tolerated statins.

Therefore, to gauge the potential financial impact (from a payer perspective) of limiting ezetimibe use in Switzerland, hypothetical scenario analyses are performed. The first scenario assumes 10% of patients currently availing ezetimibe monotherapy and ezetimibe in combination with rosuvastatin or simvastatin would substitute to a high potency statin (atorvastatin 40mg/day) and the second scenario assumes 25% of patients would substitute to a high potency statin (atorvastatin 40mg/day). There was no Swiss information to inform these scenario's, so broad hypothetical assumptions are presented to infer the financial impact.

# 8.5.1 Assumptions for Budgetary Impact Analysis

# Number of patients currently treated with ezetimibe

Use of ezetimibe in Switzerland was provided by © COGE GmbH. Tarifpool. © SASIS AG for major product types. The number of packs, tablets and estimated patients in 2019 are presented in *Table 76*.

Description	Row	Value	Source							
Ezetimibe free products (ezetimibe monotherapy and ezetimibe in free combination with statins)										
Packs per year (10 mg)	А	134,248	© COGE GmbH. Tarifpool. © SASIS AG, 2019							
Tablets per year	В	11,991,934	Tarifpool pack data multiplied by pack size							
Average cost CHF per tablet	С	1.16	Average cost per tablet Tarifpool data							
Payer cost per year CHF	D	13,934,627	[Row B x C]							
Number of patients (Ezetimibe 10mg day)	E	32,855	[Row B / 365]							
Ezetimibe + simvastatin										
Ezetimibe + simvastatin (10/10mg)										
Packs per year (10/10 mg)	F	16,493	© COGE GmbH. Tarifpool. © SASIS AG, 2019							
Tablets per year	G	1,440,193	Tarifpool pack data multiplied by pack size							
Average CHF per tablet	Н	1.76	Average cost per tablet Tarifpool data							
Payer cost per year CHF (10/10 mg)	I	2,540,794	[Row G x H]							
Number of patients (10/10mg day)	J	3,946	[Row G / 365]							
Ezetimibe + simvastatin (10/20mg)										
Packs per year (10/20 mg)	К	40,556	© COGE GmbH. Tarifpool. © SASIS AG, 2019							
Tablets per year	L	3,818,716	Tarifpool pack data multiplied by pack size							

		-		
Table 7	'6 Ezetimibe	usage in	Switzerland	in 2019
	• ==••••••••	adage		

Description	Row	Value	Source
Average CHF per tablet	М	1.95	Average cost per tablet Tarifpool data
Payer cost per year CHF (10/20 mg)	Ν	7,434,915	[Row L x M]
Number of patients (10/20mg day)	0	10,462	[Row L / 365]
Ezetimibe + simvastatin (10/40mg)			
Packs per year (10/40 mg)	Р	40,550	© COGE GmbH. Tarifpool. © SASIS AG, 2019
Tablets per year	Q	3,822,115	Tarifpool pack data multiplied by pack size
Average CHF per tablet	R	2.23	Average cost per tablet Tarifpool data
Payer cost per year CHF (10/40 mg)	S	8,505,682	[Row Q x R]
Number of patients (10/40mg day)	Т	10,472	[Row Q / 365]
Total payer cost, Ezetimibe + Simvastatin CHF	U	18,481,391	Row I+N+S
Total patients, Ezetimibe + Simvastatin	V	24,880	Row J+O+T
Ezetimibe + rosuvastatin			
Ezetimibe + rosuvastatin (10/10mg day)			
10/10 mg Packs	W	9,547	© COGE GmbH. Tarifpool. © SASIS AG, 2019
Tablets	Х	723,802	Tarifpool pack data multiplied by pack size
Average CHF per tablet	Y	1.27	Average cost per tablet Tarifpool data
Payer cost per year CHF (10/10 mg)	Z	921,293	[Row X x Y]
Number of patients (10/10mg day)	AA	1,983	[Row X / 365]
Ezetimibe + rosuvastatin (10/20mg day)			
10/20 mg Packs	AB	22,307	© COGE GmbH. Tarifpool. © SASIS AG, 2019
Tablets	AC	1,733,964	Tarifpool pack data multiplied by pack size
Average CHF per tablet	AD	1.42	Average cost per tablet Tarifpool data
Payer cost per year CHF (10/20 mg)	AE	2,461,220	[Row AC x AD]
Number of patients (10/20mg day)	AF	4,751	[Row AC / 365]
Ezetimibe + rosuvastatin total payer cost per year CHF	AG	3,382,513	Row Z+AE
Ezetimibe + rosuvastatin total patients	AH	6,734	Row AA+AF
Ezetimibe + atorvastatin			
Ezetimibe + atorvastatin (10/10mg day)			
10/10 mg Packs	Al	11,568	© COGE GmbH. Tarifpool. © SASIS AG, 2019
Tablets	AJ	881,710	Tarifpool pack data multiplied by pack size
Average CHF per tablet	AK	1.77	Average cost per tablet Tarifpool data
Payer cost per year CHF (10/10 mg)	AL	1,557,293	[Row AJ x AK]
Number of patients (10/10mg day)	AM	2,416	[Row AJ / 365]
Ezetimibe + atorvastatin (10/20mg day)			
10/20 mg Packs	AN	16,457	© COGE GmbH. Tarifpool. © SASIS AG, 2019
Tablets	AO	1,274,020	Tarifpool pack data multiplied by pack size
Average CHF per tablet	AP	1.76	Average cost per tablet Tarifpool data

Description	Row	Value	Source
Payer cost per year CHF (10/20 mg)	AQ	2,247,553	[Row AO x AP]
Number of patients (10/20mg day)	AR	3,490	[Row AO / 365]
Ezetimibe + atorvastatin (10/40mg day)			
10/40 mg Packs	AS	43,028	© COGE GmbH. Tarifpool. © SASIS AG, 2019
Tablets	AT	3,552,350	Tarifpool pack data multiplied by pack size
Average CHF per tablet	AU	1.73	Average cost per tablet Tarifpool data
Payer cost per year CHF (10/40 mg)	AV	6,136,925	[Row AT x AU]
Number of patients (10/40mg day)	AW	9,732	[Row AT / 365]
Ezetimibe + atorvastatin (10/80mg day)			
10/80 mg Packs	AX	11,684	© COGE GmbH. Tarifpool. © SASIS AG, 2019
Tablets	AY	971,390	Tarifpool pack data multiplied by pack size
Average CHF per tablet	AZ	1.75	Average cost per tablet Tarifpool data
Payer cost per year CHF (10/80 mg)	BA	1,700,879	[Row AY x AZ]
Number of patients (10/80mg day)	BB	2,661	[Row AY / 365]
Ezetimibe + atorvastatin total payer cost per year CHF	BC	11,642,650	Row AL+AQ+AV+BA
Ezetimibe + atorvastatin total patients	BD	18,300	Row AM+AR+AW+BB
Total (all ezetimibe medicines)			
Number of ezetimibe patients	BE	82,768	Row E+I+M+Q+V
Payer cost of ezetimibe use CHF	BF	47,441,181	Row D+R+AA+AR

#### Abbreviations

**CHF** = Swiss franc.

The number of patients was estimated by dividing numbers of tablets by 365 days, to generate patients per year. The calculated number of patients was greatest for ezetimibe free products (ezetimibe monotherapy and ezetimibe in free combination with statins) (32,855 patients), followed by ezetimibe plus simvastatin (24,880 patients), ezetimibe plus atorvastatin (18,299 patients) and ezetimibe plus rosuvastatin (6,734 patients). In total, 82,768 patients were estimated to use ezetimibe free (ezetimibe monotherapy and ezetimibe in free combination with statins) and fixed combination products in 2019. There is a high degree of uncertainty about the actual numbers of patients as rates of adherence and discontinuation are unknown.

The current annual cost of ezetimibe products to the payer was CHF47.4 million in 2019. The volume of ezetimibe medicines from 2017 to 2019 was provided by © COGE GmbH, Tarifpool, © SASIS AG. The trends in ezetimibe sales between 2017 and 2019 were inconsistent. It was estimated overall sales were CHF44.5 million in 2017, CHF42.4 million in 2018 and CHF47.4 million in 2019. There were large differences in annual sales growth among ezetimibe monotherapy and combination products as inferred

by overall sales. The budget impact projection assumes the use of ezetimibe monotherapy and combination products increases by 4% per year, which reflects the averaged 2017 to 2019 sales growth.

Prices for ezetimibe and statins have been decreasing, and the use of different brands has varied. Average product costs were varied in sensitivity analyses to reflect possible changes in brand utilisation.

The average cost for each product class was multiplied by growth assumptions from 2019 to 2023 to generate cost to the payers of ezetimibe over five years. These projected costs are presented in *Table* **77**.

The payer cost for ezetimibe products was estimated to be CHF55.5 million in 2023, representing an increase of CHF8.1 million compared to 2019 (CHF47.4 million).

	Unit	Row	2019	2020	2021	2022	2023	Source		
Estimated ezetimibe patients										
Ezetimibe monotherapy <sup>a</sup>	No.	А	32,855	34,169	35,536	36,957	38,435	<i>Table 76</i> , Row E increasing 4% pa		
Ezetimibe + simvastatin (10mg)	No.	В	3,946	4,104	4,268	4,438	4,616	<i>Table 76</i> , Row J increasing 4% pa		
Ezetimibe + simvastatin (20mg)	No.	С	10,462	10,881	11,316	11,769	12,239	<i>Table 76</i> , Row O increasing 4% pa		
Ezetimibe + simvastatin (40mg)	No.	D	10,472	10,890	11,326	11,779	12,250	<i>Table 76</i> , Row T increasing 4% pa		
Ezetimibe + rosuvastatin (10mg)	No.	E	1,983	2,062	2,145	2,231	2,320	<i>Table 76</i> , Row AA increasing 4% pa		
Ezetimibe + rosuvastatin (20mg)	No.	F	4,751	4,941	5,138	5,344	5,558	<i>Table 76</i> , Row AF increasing 4% pa		
Ezetimibe + atorvastatin (10mg)	No.	G	2,416	2,512	2,613	2,717	2,826	<i>Table 76</i> , Row AM increasing 4% pa		
Ezetimibe + atorvastatin (20mg)	No.	Н	3,490	3,630	3,775	3,926	4,083	<i>Table 76</i> , Row AR increasing 4% pa		
Ezetimibe + atorvastatin (40mg)	No.	I	9,732	10,122	10,527	10,948	11,386	<i>Table 76</i> , Row AW increasing 4% pa		
Ezetimibe + atorvastatin (80mg)	No.	J	2,661	2,768	2,879	2,994	3,113	<i>Table 76</i> , Row BB increasing 4% pa		
Total	No.	К	82,768	86,078	89,521	93,102	96,826	Addition		
(Patients)								Row A-J		
Projected Ezetin	Projected Ezetimibe payer costs									
Ezetimibe monotherapy <sup>a</sup>	CHF	L	13,934,627	14,492,012	15,071,692	15,674,560	16,301,543	Row A x <b>Table 76</b> Row C x 365		

Table 77 Projected ezetimibe costs (CHF), 2019–2023

	Unit	Row	2019	2020	2021	2022	2023	Source
Ezetimibe + simvastatin (10mg)	CHF	М	2,540,794	2,642,426	2,748,123	2,858,048	2,972,370	Row B x <b>Table 76</b> Row H x 365
Ezetimibe + simvastatin (20mg)	CHF	N	7,434,915	7,732,312	8,041,604	8,363,268	8,697,799	Row C x <b>Table 76</b> Row M x 365
Ezetimibe + simvastatin (40mg)	CHF	0	8,505,682	8,845,909	9,199,746	9,567,735	9,950,445	Row D x <b>Table 76</b> Row R x 365
Ezetimibe + rosuvastatin (10mg)	CHF	Ρ	921,293	958,145	996,471	1,036,329	1,077,783	Row E x <b>Table 76</b> Row Y x 365
Ezetimibe + rosuvastatin (20mg)	CHF	Q	2,461,220	2,559,669	2,662,056	2,768,538	2,879,279	Row F x <b>Table 76</b> Row AD x 365
Ezetimibe + atorvastatin (10mg)	CHF	R	1,557,293	1,619,585	1,684,368	1,751,743	1,821,813	Row G x <b>Table 76</b> Row AK x 365
Ezetimibe + atorvastatin (20mg)	CHF	S	2,247,553	2,337,455	2,430,953	2,528,191	2,629,319	Row H x <b>Table 76</b> Row AP x 365
Ezetimibe + atorvastatin (40mg)	CHF	Т	6,136,925	6,382,402	6,637,698	6,903,206	7,179,334	Row I x <b>Table 76</b> Row AU x 365
Ezetimibe + atorvastatin (80mg)	CHF	U	1,700,879	1,768,914	1,839,671	1,913,258	1,989,788	Row J x <b>Table 76</b> Row AZ x 365
Total (CHF)	CHF	V	47,441,181	49,338,828	51,312,381	53,364,877	55,499,472	Addition Row L-U

<u>Abbreviations</u> CHF = Swiss Francs, No = number, pa = per annum.

<u>Notes</u>

\* = fixed combinations.
a = ezetimibe monotherapy and ezetimibe in free combination with statins.
# 8.5.2 Financial Implications

The financial implications of limiting ezetimibe monotherapy and combination therapy to patients who are statin intolerant or unable to achieve treatment goals were examined using budget impact analysis from a payer perspective.

There was uncertainty around the number of patients currently availing ezetimibe who belong to each of these sub-populations. In the absence of these estimates, 2 scenarios are presented. In the first scenario, it is assumed that 10% of the current 64,468 patients estimated to be availing ezetimibe monotherapy or ezetimibe in combination with rosuvastatin or simvastatin (Rows A-F of **Table 77**) would substitute to a high potency statin (atorvastatin 40mg/day). The second scenario assumed 25% of the current 64,468 patients estimated to be availing ezetimibe monotherapy and ezetimibe in combination with rosuvastatin (atorvastatin 40mg/day).

There was no published information reporting the number of Swiss patients who were statin intolerant or unable to achieve treatment goals following maximally tolerated statins. Therefore, the scenarios presented are hypothetical and are presented to gauge the potential financial implications of limiting access to ezetimibe. Ezetimibe in combination with atorvastatin is not included in the substitution analysis because the product is already limited on the Spezialitätenliste.

The average per year medicines cost per patient for ezetimibe monotherapy and ezetimibe in combination with rosuvastatin or simvastatin is estimated to be CHF555, while atorvastatin 40mg/day (Atorvastatin Mepha Lactabs 40 mg 100 Stk) is estimated to cost CHF256 per year. Substitution results in a CHF299 payer cost saving per patient per year.

The five-year net budget impact of limiting access to ezetimibe is presented in *Table 78*. If 10% of patients using ezetimibe monotherapy and ezetimibe combination therapies (rosuvastatin or simvastatin) substitute to a high potency statin, then a cost savings of CHF2.0 million would occur in 2020, increasing to CHF2.3 million by 2023. If 25% of patients substituted to a high potency statin, then a cost savings of CHF5.7 million by 2023.

# Table 78 Net ezetimibe costs (CHF) in Switzerland 2019–2023

Net cost		Row	2019	2020	2021	2022	2023	Source
Base analysis	5							
Ezetimibe monotherap y and ezetimibe + S/R patients	No.	A	64,468	67,046	69,728	72,517	75,418	<i>Table 77,</i> sum Rows A-F
Ezetimibe + AT patients	No.	В	18,300	19,032	19,793	20,585	21,408	<b>Table 77</b> , sum Rows G-J
Ezetimibe monotherap y and ezetimibe + S/R payer costs	CHF	С	35,798,531	37,230,472	38,719,691	40,268,479	41,879,218	<i>Table 77</i> , sum Rows L-Q
Ezetimibe + AT payer costs	CHF	D	11,642,650	12,108,356	12,592,690	13,096,398	13,620,254	<b>Table 77</b> , sum Rows R-U
Total payer costs	CHF	E	47,441,181	49,338,828	51,312,381	53,364,877	55,499,472	Addition Row C-D
Scenario 1: E	zetimibe limite	ed to 90% of cu	irrent ezetimib	e monotherap	y and ezetimib	e + S/R patient	S	
Patients								
Ezetimibe monotherap y and ezetimibe + S/R patients	No.	F	64,468	60,342	62,755	65,266	67,876	90% of Row A from 2020
Ezetimibe + AT patients	No.	G	18,300	19,032	19,793	20,585	21,408	Row B no change
High potency statins	No.	Н	0	6,705	6,973	7,252	7,542	10% of Row A from 2020
Payer costs								
Projected ezetimibe monotherap y and ezetimibe + S/R payer cost	CHF	1	35,798,531	33,507,425	34,847,722	36,241,631	37,691,296	Row F times average annual cost of CHF555 per patient
Projected ezetimibe + AT payer costs	CHF	J	11,642,650	12,108,356	12,592,690	13,096,398	13,620,254	Row G times average annual cost of CHF638 per patient
Substitute medicines usage	CHF	К	0	1,720,378	1,789,193	1,860,761	1,935,192	Row H times average annual cost of CHF256 per patient
Total	CHF	L	47,441,181	47,336,159	49,229,606	51,198,790	53,246,741	Sum Rows
Cost Difference	CHF	М	0	2,002,669	2,082,776	2,166,087	2,252,730	Row E-L
Scenario 2: E	zetimibe limite	ed to 75% of cu	ırrent ezetimib	e monotherap	y and ezetimib	e + S/R patient	s	
Patients								
Ezetimibe monotherap	No.	N	64,468	50,285	52,296	54,388	56,564	75% of Row A

Net cost		Row	2019	2020	2021	2022	2023	Source
y and ezetimibe + S/R patients								from 2020
Ezetimibe + AT patients	No.	0	18,300	19,032	19,793	20,585	21,408	Row B no change
High potency statins	No.	Ρ	0	16,762	17,432	18,129	18,855	25% of Row A from 2020
Payer costs								
Projected ezetimibe monotherap y and ezetimibe + S/R payer cost	CHF	Q	35,798,531	27,922,854	29,039,768	30,201,359	31,409,413	Row N times average annual cost of CHF555 per patient
Projected ezetimibe + AT payer costs	CHF	R	11,642,650	12,108,356	12,592,690	13,096,398	13,620,254	Row O times average annual cost of CHF638 per patient
Substitute medicines usage	CHF	S	0	4,282,592	4,453,895	4,632,051	4,817,333	Row P times average annual cost of CHF256 per patient
Total	CHF	T	47,441,181	44,313,802	46,086,354	47,929,808	49,847,000	Sum Rows Q-S
Cost	CHF	W	0	5,025,026	5,226,027	5,435,069	5,652,471	Row E-T

## **Abbreviations**

**CHF** = Swiss Francs, **ezetimibe + AT** = ezetimibe plus atorvastatin, **Ez + S/R** = ezetimibe plus simvastatin and ezetimibe plus rosuvastatin.

The results of the budget impact analysis are limited to medication costs. The IMPROVE-IT trial demonstrated that ezetimibe plus simvastatin reduced number of MIs, strokes and numbers of patients requiring surgery compared to simvastatin monotherapy. These benefits of avoided medical events were not costed in the model, so the cost impacts for payers are likely to be overstated. The cost-effectiveness analysis indicated event rates were marginally higher if patients were assumed to avail simvastatin (results of IMPROVE-IT trial), correspondingly, these benefits are not likely to be substantial.

## Sensitivity Analysis

Some of the key assumptions used in the budget impact analysis are uncertain. The base analysis included cost of using ezetimibe monotherapy and ezetimibe combination products. Ezetimibe monotherapy can be prescribed with statins (free combination), however, there is no data to reveal the number of patients using free combinations. A scenario is included in the sensitivity analysis (*Table 79*) where half of ezetimibe free product use is assumed to comprise 40mg per day of simvastatin. Under this assumption, the net cost to the payer increases from CHF47.4 million to CHF52.4 million in 2019.

Growth of ezetimibe products is variable. The budget impact assumed the use of ezetimibe monotherapy and combination products would increase by 4% per year. A scenario was included in the sensitivity analysis which projected a 0% growth rate. The use of different ezetimibe products has also changed in the last few years, with greater adoption of lower-cost products (i.e. generics). It is unclear whether average prices will continue to decrease. Scenarios are included where the average price decreases by 2%, 5% and 10% per year for ezetimibe free (monotherapy and in free combination with statins) and fixed combination products. The net payer costs were most sensitive to alterations in the price of ezetimibe products and the concurrent use of free statin combinations (with ezetimibe monotherapy).

Scenario	2020	2021	2022	2023
Ezetimibe limited to 90% of current patients (i.e. 10% substitute to high potency statin)	2,002,669	2,082,776	2,166,087	2,252,730
50% of free ezetimibe product use associated with simvastatin, 40mg	7,168,217	7,454,945	7,753,143	8,063,269
No growth in usage of ezetimibe high potency statin combinations	2,002,669	2,002,669	2,002,669	2,002,669
Ezetimibe monotherapy and combination products, 2% annual price decline	1,928,208	1,929,446	1,929,276	1,927,614
Ezetimibe monotherapy and combination products, 5% annual price decline	1,816,517	1,705,259	1,591,758	1,475,897
Ezetimibe monotherapy and combination products, 10% annual price decline	1,630,364	1,347,102	1,074,811	812,504

Table 79 Net pa	yer cost sensitivit	y analysis (CHF)
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Abbreviations

CHF = Swiss franc.

# 9 Legal, Social and Ethical Issues

## 9.1 Summary Statement Legal, Social and Ethical Issues

The literature addressing legal, social and ethical issues associated with ezetimibe was limited, therefore, the scope was broadened to include issues associated with statins. Many of these issues are likely applicable to ezetimibe given that combination therapies also include statins.

Limiting access to ezetimibe is unlikely to result in any legal or ethical issues.

Patients had mixed or negative opinions about statin therapy, which led to high rates of non-adherence. Non-adherence to statins is a common problem in the management of dyslipidaemia, increasing the risk of cardiovascular morbidity and mortality. Methods to increase statin adherence included improved patient-physician communication, regular medical appointments and referrals to a specialist.

Transitioning from statins to ezetimibe monotherapy may improve adherence to medication because statins-associated adverse events (e.g. myopathy) are avoided.

Older adults using statins represent an at-risk group, as they are often under-treated owing to complexity of medical care in this population.

## 9.2 Methods

Literature identified from systematic and non-systematic searches was used to address legal, social and ethical issues. The search terms used for the systematic search are outlined in *Appendix A*, *Section* **15.1**, *Table 93* to *Table 95*. The non-systematic search involved targeted searches of Google and PubMed using the following terms: 'access', 'autonomy', 'benefits', 'burden', 'dyslipidaemia', 'hyperlipidaemia', 'hypercholesterolaemia', 'ezetimibe', 'harm', 'hypercholesterolaemia', 'expectations', 'lipid lowering therapy', 'perception' and 'statin'. The non-systematic searches were conducted by a single reviewer who identified an additional 27 studies. A PRISMA chart was not provided owing to the use of systematic and non-systematic searches. Results of the literature searches were summarised using narrative synthesis.

# 9.3 Evidence Table

There were no studies evaluating legal issues.

Twenty-seven studies were included in the assessment of social and ethical issues (*Table 80*). The studies consisted of primary (k=11) and secondary research (k=16). Primary research studies were

performed mostly in the USA (k=5) or the UK (k=3) with frequently studied populations being general practitioners and patients with dyslipidaemia or CVD. Primary research consisted of surveying or interviewing patients and physicians to ascertain perception of statins and potential barriers leading to non-adherence. Additional primary research focused on identifying how statins are portrayed in internet and print media.

Secondary research studies included analyses of databases (k=3), systematic reviews (k=6) and published literature (k=7). The reviews summarised available evidence regarding patient perception, and the reasons for non-adherence to statin therapy and the consequences of this. The database analyses aimed to evaluate the prescribing practices of physicians, patient and physician attitudes and beliefs related to cholesterol management, and the reasons leading to discontinuation of statins.

There was limited primary and secondary research addressing social issues associated with ezetimibe. Most studies considered the broader context of statins. Therefore, in the absence of literature addressing ezetimibe, studies pertaining to statins and other lipid-lowering treatments were presented. Studies evaluating statins are likely more applicable to ezetimibe combination therapy than to ezetimibe monotherapy given that combination therapies include statins. Further, many of the perceptions and issues associated with statins are more reflective of the underlying disease than the treatment itself. Consequently, many of the concerns will likely persist for individuals using ezetimibe.

Additional studies providing epidemiological information were not included in the table because they did not specifically address social or ethical issues.

Study; country	Indication; sample size	Design; follow-up; setting	Interview/survey topics
Borne 2019 <sup>216</sup>	Elderly (>80 years old)	Analysis of French Health Insurance database	Overuse of statin in older adults
Bui 2019 <sup>217</sup> USA	NA	Literature review	Predictors of statin non- adherence
Chan 2010 <sup>218</sup> USA	Patients using statins n=14,257	Analysis of Blue Cross Blue Shield databases	Predictors of statin non- adherence
Chee 2014 <sup>219</sup> Singapore	NA	Literature review	Patients' perspectives and attitudes to taking statins
Cherubini 2012 <sup>220</sup> Italy	NA	Literature review	Factors associated with under-prescribing in older adults
Chisnell 2017 <sup>221</sup> UK	News media reporting on statins n=67 articles	Content analysis British newspapers	Perception of statins in the media
Choudhry 2011 <sup>222</sup> USA	Patients with recent MI n=5,855	RCT, post-discharge, 2.5 years	Cost of statins and impact on health outcomes

 Table 80 Characteristics of included studies for social issues

Study; country	Indication; sample size	Design; follow-up; setting	Interview/survey topics
Cournot 2006 <sup>223</sup> France	Patients with CHD age ≥35 n=3,928 Cardiologists n=1,001	Analysis of ELIAGE and ELICOUER studies	Factors associated with under-prescribing in older adults
Clough 2019 <sup>224</sup> USA	Primary care providers n=164 Patients using statins n=16,802	Survey Community based North Carolina network	Primary care providers' beliefs of statin for primary prevention and prescription
De Vera 2014 <sup>225</sup> Canada	Patients using statins k=28	Systematic review Prospective observation studies	Statin non-adherence and health outcomes
Fung 2010 <sup>226</sup> USA	Patients using statins n=18	Interview, content analysis	Patients' perspectives and attitudes to taking statins
Golder 2020 <sup>227</sup> UK, USA	Twitter posts relating to statins n=11,852 posts	Analysis of twitter posts	Perception of statins in the media
Hope 2019 <sup>228</sup> UK	Patients with hypercholesterolaemia, hypertension, diabetes or arthritis using statins k=19	Systematic review Original trial or observational study	Predictors of statin non- adherence
Ingersgaard 2020 <sup>229</sup> Denmark	Patients using statins k=9	Systematic review	Predictors of statin non- adherence
luga 2014 <sup>230</sup> USA	NA	Literature review	Healthcare costs due to non-adherence
Ju 2018 Australia	Patients at risk of CVD n=888	Systematic review of qualitative studies	Patients' perspectives and attitudes to taking statins
Kedward 2003 <sup>231</sup> UK	General practitioners n=26	Survey Practices in mid/south Bedfordshire	General practitioner perception of statins and factors related to non- adherence
Kruger 2018 <sup>232</sup> Germany	General practitioners n=16	Survey Rural and urban practices	General practitioner perception of statins and factors related to non- adherence
Lansberg 2018 <sup>233</sup> Netherland	NA	Literature review	Predictors of statin non- adherence
Naderi 2012 <sup>234</sup> UK	Patients using drugs for cardiovascular diseases k=20 n=376,162	Systematic review and meta-analysis 24 months	Proportion of patients adhering to statins
Nordestgaard 2018 <sup>235</sup> Denmark	News media reporting on statins	Literature review Newspapers	Perception of statins in the media
Mann 2007 <sup>236</sup>	First time statin users	Survey	Patients' perspectives and attitudes to taking statins

Study; country	Indication; sample size	Design; follow-up; setting	Interview/survey topics
USA	n=71	6 months	
		Medical centre	
Maningat 2013 <sup>237</sup>	NA	Literature review	Predictors of statin non-
USA			adherence
Strandberg 2014 <sup>238</sup>	Patients with	Systematic review/clinical	Treatment of
Finland	hypercholesterolaemia	guidance	hypercholesterolaemia in
	and/or ASCVD	Searched 1990 to 2014	older adults
	k=26		
Turner 2016 <sup>239</sup>	Patients using high-potency	Observational,	Statin non-adherence and
UK	statins	retrospective	health outcomes
	n=1,005	16 months	
Wei 2013 <sup>240</sup>	Patients using statins	Internet-based survey	Predictors of statin non-
USA	n=10,138		adherence
Welmer 2013 <sup>241</sup>	Participants in Swedish	Prospective, observational	Cardiovascular burden in
Sweden	National Study on Aging and Care in Kungsholmen	design, participants' house or institution	older patients
	n=2,725		

## Abbreviations

**ASCVD** = atherosclerotic cardiovascular disease, **CHD** = coronary heart disease,  $\mathbf{k}$  = number of studies,  $\mathbf{n}$  = number of patients, **NA** = not applicable, **RCT** = randomised controlled trial, **UK** = United Kingdom, **USA** = United States of America.

# 9.4 Legal Results

No legal issues were identified from systematic and non-systematic searches.

# 9.5 Social Results

# 9.5.1 Patient and Physician Perception

No literature was identified evaluating patient and physician perceptions of ezetimibe. When considering lipid-lowering treatments more broadly, physicians had mixed views about statins. Clinicians acknowledged that statins reduced cardiovascular morbidity and mortality in primary and secondary prevention populations and often used risk calculators (as recommended by guidelines) to determine whether pharmacological treatment was required.<sup>224 242</sup> However, others (typically general practitioners) lacked confidence in their knowledge of the guidelines, and some failed to adhere to the guidelines – many patients eligible for statins did not receive a prescription.<sup>224 232 242</sup> (It should be noted, however, that there are multiple reasons leading to under-prescribing). Physicians also expressed concerns regarding patient compliance to statins, cost of medication, increased workload associated with statins (additional blood tests and follow-up appointments) and increased risk of adverse events.<sup>231 232</sup> Clinicians also noted that statins often encouraged risky behaviour such as relaxation of lipid-lowering

diets. Many preferred to implement lifestyle changes before prescribing statins, especially in lower-risk patients (i.e. primary prevention).<sup>231</sup>

Patient perception of statins was polarised, with individuals reporting positive and negative opinions of the medication.<sup>227</sup> This mixed perception reflects previous experience with statins (particularly if an adverse event was experienced), family and clinician opinions, and intake of news media.<sup>221 235 243</sup> The media portrayal of statins is country specific, for example, mostly negative stories in the UK and positive stories in Denmark.<sup>235</sup> Positive perception of statins (e.g. 'it will help reduce my cholesterol') tended to result in higher rates of compliance<sup>236</sup> whereas negative perceptions often led to non-adherence and thereby poor treatment outcomes.<sup>228</sup>

# 9.5.2 Statin Non-Adherence

Adherence to statins is a major challenge in the management of dyslipidaemias and ASCVD, and nonadherence is increasingly common. Recent meta-analyses estimated 50% of primary prevention populations and 44% of secondary prevention populations were non-adherent.<sup>234</sup> However, prevalence estimates varied considerably across the literature.<sup>244</sup> Further analyses identified several demographic factors associated with poor compliance. For example, patients more likely to be non-adherent were younger than 50 or older than 70, female, African American or Hispanic, had lower health literacy, had low socioeconomic status and were not seeing a specialist.<sup>218</sup> <sup>229</sup> <sup>245</sup> Non-adherence is concerning because of its association with increased cardiovascular morbidity and mortality and increased healthcare costs.<sup>225</sup> <sup>230</sup> <sup>239</sup>

Multiple patient and provider factors led to non-adherence. From a patient perspective, key reasons underlying non-adherence were concerns regarding the safety of statins (e.g. muscle and liver damage), lack of knowledge about dyslipidaemias and how statins work, imperceptible benefits, medication cost, medical distrust, and desire to avoid over-medicalisation.<sup>226</sup><sup>233</sup><sup>240</sup><sup>243</sup> Clinicians reported that poor health literacy, the nocebo effect and poor media coverage were additional patient-related factors contributing to non-adherence.<sup>232</sup>

To improve adherence, a multifaceted approach engaging patients, physicians and other healthcare workers is required.<sup>219</sup> Better communication between patients and physicians is key. Effectively communicating the importance of statins (i.e. reasons for prescribing and how they work) and emphasising that benefits will often be imperceptible, is expected to aid in promoting adherence.<sup>232 237</sup> Listening to patients' concerns regarding adverse events, maintaining regular medical appointments and referring to specialists should also promote adherence.<sup>233 237</sup> Other healthcare workers, such as pharmacists, can promote better medication-taking behaviour by simplifying prescribing processes and providing additional information about the medication.<sup>217</sup> Removing co-payments to reduce medication cost is also expected to increase statin accessibility and thus increase statin adherence rates.<sup>218 222</sup>

Transitioning from statins to ezetimibe (monotherapy) may improve adherence due to the avoidance of statin-associated myopathy.<sup>246</sup> However, it is unclear whether ezetimibe combination therapies would reduce myopathy as they contain statins.

## 9.6 Ethical Results

## 9.6.1 Symptoms and Burden of Disease Attributable to Dyslipidaemia and ASCVDs

Dyslipidaemias are asymptomatic or slightly symptomatic (tendon xanthomas) and individuals are often unaware they have the disorder until they have a blood test or experience cardiac events such as stroke or MI manifesting as chest pain, shortness of breath, numbness or weakness in the arms or legs, fatigue or light-headedness.<sup>2</sup> <sup>247</sup> Even if treated, these events can result in significant morbidity and death.<sup>248</sup> The degree of impairment is related to the type and duration of the event, however, most stroke and MI survivors report long-term disabilities that reduce their independence, mobility and ability to work, and increase their reliance on caregivers. These factors significantly reduce quality of life.<sup>241</sup> <sup>249</sup> <sup>250</sup>

# 9.6.2 Vulnerable Patient Groups

Literature addressing the use of ezetimibe in vulnerable patient groups was limited, therefore, the results were expanded to include vulnerable patients using statins.

In Switzerland, the incidence of high cholesterol and CVD is highest amongst older adults.<sup>30</sup> In spite of this, older adults are often under-treated<sup>220</sup> suggesting these individuals represent a vulnerable patient group. Older adults are often inadequately treated because they overuse or are not adherent to lipid-lowering therapies (see **Section 9.5.2**) and clinicians do not prescribe the appropriate medication.<sup>216 218</sup> <sup>223</sup> This is concerning because non-adherence has been found to increase the risk of cardiovascular morbidity and mortality.<sup>225 230 239</sup>

Under-prescribing in older adults reflects the complexity of medical management in this patient group. For example, older adults are more likely to experience statin-induced adverse events such as myopathy, fatigue or cognitive impairment.<sup>251</sup> These events increase caregiver dependency and may increase the likelihood of institutionalisation.<sup>251</sup> Other factors found to contribute to under-prescribing include lack of indication,<sup>223</sup> perceived lack of benefit owing to shorter life expectancy, frailty and dangers associated with polypharmacy.<sup>220 238</sup>

From a social perspective, older adults with ASCVD have poorer mental and physical health and often have difficulties performing daily tasks such as walking across a room or transferring to bed.<sup>252</sup> These limitations detrimentally impact the individual and can lead to a loss of independence and quality of life.<sup>253 254</sup>

## 9.6.3 Perceived Benefits and Harms of Ezetimibe

## Non-maleficence: a norm of avoiding causation of harm

A key ethical concern when considering an intervention is avoidance or minimisation of harm. In this context, harm included adverse physical and psychological consequences of ezetimibe.

The results from **Section 7** indicated ezetimibe monotherapy had an equivalent safety profile to placebo and statins in patients with hypercholesterolemia or hyperlipidaemia. Common adverse events included gastrointestinal disturbances (diarrhoea, constipation and nausea), headaches and muscle pain (myalgia). When reported, these events were generally mild and self-limiting. Ezetimibe plus statins also had comparable safety to statins in patients who had hypercholesterolaemia and ASCVD. In patients with hypercholesterolaemia without ASCVD, ezetimibe plus statins led to more treatment-related adverse events. There was no common event underlying this increased prevalence.

It is unclear how accurately these results reflect current practice as this HTA does not specifically address the known side effects of statins, specifically myopathy, which reportedly occur in 1% of statin users, and are more common at higher doses.<sup>255</sup>

Any medical treatment may cause distress if individuals' expectations are not met. Alternatively, for patients who believe ezetimibe improves their condition, impeding access to the technology could cause psychological distress if the desired medication cannot be obtained.

# Beneficence: a group of norms for providing benefits and balancing benefits against risks and costs

The primary goal of lipid-lowering therapies is to prevent cardiovascular morbidity and mortality.<sup>7</sup> Dyslipidaemia is generally asymptomatic, however consequent ASCVD can significantly impair an individual's quality of life and/or result in death. Results from *Section 7* highlighted that ezetimibe plus statins significantly reduced composite measures of cardiovascular morbidity and mortality in patients with hypercholesterolemia and ASCVD. However, when evaluating the outcomes separately, ezetimibe plus statins reduced some markers of morbidity (MI and stroke) but had no effect on cardiovascular mortality. The safety profile of ezetimibe plus statins was similar to statins in patients with hypercholesterolaemia and ASCVD. Therefore, the risk/benefit is likely in favour of ezetimibe plus statins.

For patients with hypercholesterolemia and hyperlipidaemia, there was limited information to determine whether ezetimibe plus statin and ezetimibe monotherapy reduces mortality as most results were limited to surrogate outcomes. In patients with hypercholesterolaemia and no ASCVD, ezetimibe plus statins increased the risk of treatment-related adverse events. Given higher-intensity statins have been shown to reduce cardiovascular morbidity and mortality in lower-risk groups,<sup>256</sup> ezetimibe plus statins should

be considered for individuals who cannot achieve treatment goals, are contraindicated, or unable to tolerate statins (as per AGLA guidelines).<sup>17 21</sup>

# 10 Organisational Issues

## **10.1 Summary Statement Organisational Issues**

In Saskatchewan, Canada, where ezetimibe use is not restricted to specific populations (similar to the current situation in Switzerland), ezetimibe was prescribed as a first-line treatment in nearly a quarter of all new users (inconsistent with guidelines). Factors associated with inappropriate prescribing were age and sex of the patient, presence of comorbidities and specialty of the physician. However, in Ontario, Canada and Demark, factors associated with ezetimibe prescribing were previous use of high-potency statins, suggesting clinicians were prescribing in accordance with guidelines.

In Switzerland, there is regional and demographic variability in the screening, diagnosis and treatment of dyslipidaemia, with Leman and Ticino having the highest rates and Eastern and Central Switzerland reporting the lowest rates. Differences in health policies, risk calculators and healthcare expenditure may underscore the regional variation.

## 10.2 Methods

Literature identified from systematic and non-systematic searches was used to address organisational issues. The search terms used for the systematic search are outlined in *Appendix A*, *Section 15.1, Table 96*. The non-systematic search involved targeted searches of PubMed and Google using the following terms: 'dyslipidaemia', 'hyperlipidaemia', 'hypercholesterolaemia', 'statin', 'ezetimibe', 'education', 'cost', 'access', 'adherence' and 'burden'. The non-systematic searches were conducted by a single reviewer who identified an additional five studies. A PRIMSA chart was not provided owing to the use of systematic and non-systematic searches. Results of the literature searches were summarised using narrative synthesis.

## 10.3 Evidence Table

Six studies were included for the assessment of organisational issues (*Table 81*). The studies were all secondary research involving the analyses of databases. Three studies were performed in Switzerland and evaluated the Swiss Health survey and the CoLaus database (random sample of the Lausanne population). One study evaluated healthcare expenditure but did not specify from where the information was obtained. The remaining studies were performed in Canada (k=2) or Denmark (k=1). These trials identified demographic factors associated with the prescription of ezetimibe and the prevalence of inappropriate ezetimibe prescription.

Study; country	Indication; sample size	Design; follow-up; setting	Interview/survey topics
Alsabbagh, 2014 <sup>257</sup> Canada	New lipid-lowering therapy users n=17,870	Analysis of health administrative database 2004–2011	Analyse of use and cost of ezetimibe
Marques-Vidal 2012 <sup>28</sup> Switzerland	Swiss private households n=17,8797	Analysis of Swiss Health Survey 2007	Regional variation in screening, diagnosis and treatment of CVD risk factors
Reich 2012 <sup>258</sup> Switzerland	NA	Database analysis 1997–2007	Healthcare expenditure across regions
Firmann 2010 <sup>32</sup> Switzerland	Patients with dyslipidaemia n=6,084	Analysis of CoLaus database	Demographic factors associated with dyslipidaemia treatment
Clemens 2018 <sup>259</sup> Canada	Patients hospitalised for acute MI n=71,125	Database analysis 2005–2014	Factors associated with ezetimibe prescription
Wallach-Kildemoes 2015 <sup>260</sup> Denmark	Patients with prescription filled for statin or ezetimibe n=589,006	Analysis of Danish National Prescription registry 2010–2012	Impact of sociodemographic factors on ezetimibe initiation as second-line treatment

Table 81 Characteristics of included studies for organisational issues

## Abbreviations

CVD = cardiovascular disease, n = number of patients, MI = myocardial infarction, NA = not applicable.

# 10.4 Organisational Results

# 10.4.1 Ezetimibe Prescriptions in Practice

Inappropriate utilisation of ezetimibe was reported in one study. Analysis of the provincial health administrative databases noted 23% of first-time lipid-lowering therapy users were prescribed ezetimibe (instead of statins) as a first-line treatment.<sup>257</sup> Furthermore, of previous statin users, 33% had not increased their statin dose and 89% had only used one type of statin before being prescribed ezetimibe. Of the clinicians prescribing ezetimibe, 10% were responsible for half of the inappropriate prescriptions. Non-specialists were more likely to prescribe ezetimibe as a first-line treatment, and patients who were older, female, and had type 2 diabetes or hypertension were more likely to receive ezetimibe as a first-line treatment. The authors noted that Saskatchewan was the only province in Canada that did not restrict access to ezetimibe (similar to the current situation in Switzerland).

## 10.4.2 Patient-Related Factors Associated with Ezetimibe Prescriptions

Two studies identified patient-related factors associated with ezetimibe use. In Ontario, Canada, prescriptions for ezetimibe was associated with rural patients and those with coronary artery disease. Ezetimibe prescriptions were also associated with previous use of high-potency statins, suggesting clinicians were prescribing in accordance with guidelines.<sup>259</sup>

In Demark, prescribing ezetimibe as a second-line treatment was associated with female patients, older adults, those with higher incomes and those with previous use of a high-intensity statin. Patients with comorbidities such as type 2 diabetes or hypertension, patients with peripheral artery disease, or those who had experienced stroke were less likely to be prescribed ezetimibe as a supplement to or replacement for statins.<sup>260</sup>

# 10.4.3 Regional and Demographic Variation in the Screening and Treatment of Dyslipidaemia in Switzerland

In Switzerland, in 2007, there was regional variability in the screening, diagnosis and treatment of hypercholesterolaemia. Leman and Ticino reported the highest screening and diagnosis rates for hypercholesterolaemia and CVD risk factors (diabetes and hypertension), and Eastern and Central Switzerland reported the lowest rates. Treatment rates were also highest in Leman and Ticino and lowest in Eastern and Central Switzerland, noting that less than half of the patients diagnosed with hypercholesterolaemia received treatment.<sup>28</sup>

These regional differences suggest there were potential barriers preventing patients from accessing appropriate care in Eastern and Central Switzerland. The differences were thought to relate to specific health policies, the use of different risk calculators (PROCAM vs SCORE) and lower healthcare expenditure in German-speaking regions.<sup>28</sup> Given healthcare expenditure is correlated with density of general practitioners and specialists, there may have been fewer clinicians in the German-speaking regions, leading to comparatively lower diagnosis and treatment rates.<sup>258</sup>

From a Swiss patient perspective, individuals were more likely to be diagnosed with dyslipidaemia and receive treatment if they were male, older (age 55–75 years), obese, had a history of CVD or diabetes and were considered high risk (as determined by PROCAM).<sup>32</sup> Of patients diagnosed with dyslipidaemia, 40% received treatment, of which 60% achieved treatment goals and 30% nearly achieved their goals (10% not specified). Demographic variables associated with a patient's treatment-response included sex, PROCAM score and history of CVD and/or diabetes.<sup>32</sup>

# 11 Additional Issues

Six clinical practice guidelines were identified from the literature (*Table 82*). All the guidelines recommended ezetimibe as a second-line treatment for patients who failed to achieve treatment goals using maximal tolerated statin or who were contraindicated or intolerant to statins. The organisations were from Australia, Europe and North America.

The AGLA guidelines were updated after the submission of the draft HTA report. Ezetimibe is still recommended as a second-line treatment in high- or very-high risk patients who failed to achieve treatment goals using a maximal tolerated statin.<sup>261</sup> The treatment goals for high- or very-high-risk patients have been revised in the updated guidelines. For high risk patients, the initial LDL-c treatment goals has reduced from 100mg/dL to 70mg/dL and for very-high-risk patients the goals have reduced from 70mg/dL to 55mg/dL. The revised goals reflect a more aggressive treatment strategy with the aim to reduce LDL-c levels as much as possible.<sup>261</sup>

Table 82 Summary	of	clinical	guidelines	and	recommendations	regarding	ezetimibe
(monother	ару а	and comb	ination thera	pies)			

Organisation	Indication	Strength of recommendation	Position in treatment pathway
AGLA 2018, <sup>17 21</sup> AGLA 2020 <sup>261</sup>	Indicated for high- or very-high-risk patients who fail to achieve goals with maximal tolerated statin	NR	2 <sup>nd</sup> line
	Indicated for patients who are intolerant to statins	NR	2 <sup>nd</sup> line
American Heart Association/American College of Cardiology 2019 <sup>78</sup>	Indicated for patients with ASCVD and very-high-risk patients who fail to reach treatment goals (LDL-c ≥70mg/dL)	NR	2 <sup>nd</sup> line
Canadian Cardiovascular Society 2016 <sup>262</sup>	Strongly recommended for adults 50 years or older with CKD	High-quality evidence	1 <sup>st</sup> line (combination)
	Indicated for primary or secondary prevention in patients who fail to achieve goals with maximal tolerated statin	NR	2 <sup>nd</sup> line
European Society of Cardiology and the European Atherosclerosis	Recommended for patients with dyslipidaemia who fail to reach treatment goals with maximal tolerated dose of statins	С	2 <sup>nd</sup> line
Society 2019 <sup>7</sup>	Recommended for patients with FH and ASCVD (high risk) who fail to achieve treatment goals	С	2 <sup>nd</sup> line
	Should be considered for patients with dyslipidaemia and diabetes	В	2 <sup>nd</sup> line
	Recommended for patients with ACS and high-risk	В	2 <sup>nd</sup> line
	Should be considered for patients with statin intolerance	B	2 <sup>nd</sup> line
	Recommended for patients with stage 3–5 CKD (non-dialysis)	A	∠ <sup>™</sup> line

Organisation	Indication	Strength of recommendation	Position in treatment pathway
	Strongly recommended for primary prevention and secondary prevention in patients who fail to achieve goals with maximal tolerated statin	High-quality evidence	2 <sup>nd</sup> line
National Heart Foundation of Australia & Cardiac Society of Australia and New Zealand 2016 <sup>263</sup>	Indicated for patients with ACS who fail to achieve goals with maximal tolerated statin or are intolerant to statins	NR	2 <sup>nd</sup> line
NICE 2016 <sup>264</sup>	Indicated for patients with severe hypercholesterolaemia who fail to reach treatment goals with maximally tolerated statins (LDL-c ≥100mg/dL)	NR	2 <sup>nd</sup> line

# Abbreviations

ACS = acute coronary syndrome, AGLA = Arbeitsgruppe Lipide und Atherosklerose, ASCVD = atherosclerotic cardiovascular disease, CKD = chronic kidney disease, FH = familial hypercholesterolaemia, LDL-c = low density lipoprotein-cholesterol, mg/dL = milligram per decilitre, NICE = National Institute of Clinical Excellence, NR = not reported.

<u>Notes</u>

**A** = data sourced from randomised clinical trials or meta-analyses.

**B** = data sourced from single randomised clinical trials or large non-randomised studies.

**C** = consensus of opinion of experts and/or small studies, retrospective studies or registries.

# 12 Discussion

The objective of this HTA is to evaluate the clinical and economic effectiveness of ezetimibe monotherapy or combination therapy, and to consider social, legal, ethical and organisational issues associated with its use. To address the clinical effectiveness of ezetimibe a systematic search of published literature was undertaken. The search identified 30 RCTs in patients with hypercholesterolaemia without ASCVD, 42 RCTs in patients with hypercholesterolaemia and ASCVD, and 5 RCTs in patients with hyperlipidaemia without ASCVD. There were no studies evaluating patients with hyperlipidaemia and ASCVD. The studies varied with respect to eligibility requirements, length of follow-up, comparator, type of intervention (monotherapy or combination therapy) and risk of bias. Ezetimibe plus statins compared to statins was the most frequently studied comparison, both in patients with hypercholesterolaemia and ASCVD and patients with hypercholesterolaemia without ASCVD. Few studies compared ezetimibe (monotherapy or combination therapy) to fenofibrate or placebo, or evaluated timepoints beyond 3 months. The quality of evidence ranged from low to moderate.

## 12.1 Findings of the Clinical Evaluation

## Hypercholesterolaemia without ASCVD

The assessment of clinical effectiveness was limited to surrogate markers for comparisons involving ezetimibe monotherapy. Ezetimibe was superior to placebo but inferior to statins in the absolute or percentage change in LDL-c, HDL-c and total cholesterol, and the number of patients achieving LDL-c goals at 3 months. No study evaluated ezetimibe monotherapy beyond 3 months, so its long-term effectiveness is uncertain.

In one study, ezetimibe plus statins did not reduce MACE outcomes or markers of vascular damage compared to statins, although the study was not designed or powered to detect differences in MACE. Compared to statins, ezetimibe plus statins significantly improved LDL-c, HDL-c and total cholesterol levels, and increased the number of patients achieving LDL-c goals at 3 months. The statistical effect persisted for LDL-c and total cholesterol at 12 months, with the effect size increasing for the percentage change but not the absolute change. (This inconsistency relates to the number of studies included at later timepoints for the measures; 5 studies provided evidence for the absolute change at 12 months, whereas the percentage change was informed by only 1 study and is therefore subject to more uncertainty.) At 12 months there were no differences in HDL-c. The change in triglycerides was inconsistent. Most trials reporting the percentage change found statistical differences between ezetimibe plus statins and statins. Most trials reporting the absolute change found statistical differences between ezetimibe

Relying on surrogate markers to assess the clinical effectiveness of ezetimibe in this population makes its impact on MACE outcomes and thus overall clinical relevancy uncertain. Further, inferring clinical relevancy (reductions in MACE) from meta-regressions linking LDL-c to reduction in major vascular events is inappropriate for comparisons involving ezetimibe monotherapy and ezetimibe combination therapies because it was uncertain whether they produced a sustained reduction in LDL-c at later timepoints.<sup>72</sup>

To investigate sources of heterogeneity, sub-group analysis was applied to statin type. Of the 19 studies evaluating ezetimibe plus statins, 15 utilised simvastatin. Consequently, the results of the ezetimibe plus simvastatin sub-group mirrored the pooled estimate – there were significant reductions in LDL-c and total cholesterol and increases in HDL-c in favour of the combination treatment. The effect size was also comparable to the pooled estimate, as indicated by overlapping confidence intervals. The impact of other statins, or other planned sub-groups, could not be determined owing to insufficient study numbers.

Ezetimibe monotherapy had a similar safety profile to both placebo and statins. Ezetimibe plus statins increased the risk of treatment-related adverse events relative to statins but the incidence of other safety outcomes was similar. The type of event leading to the increased incidence of treatment-related adverse events could not be determined owing to under-reporting of safety information in the included trials. Importantly, no study reported rhabdomyolysis, a serious adverse event associated with statins.<sup>255</sup> Generally, the analyses were sufficiently powered to detect group differences (as inferred by post-hoc power calculations). However, uncertainties remain because common side effects (e.g. myopathy) where not specifically evaluated in this report, so it is unclear how applicable the safety results are to clinical practice. The American Heart Association notes the incidence of discontinuations, common adverse events (e.g. myopathy) and serious adverse events increases as doses and intensities of statins increase.<sup>265</sup> Further, the incidence of adverse events increases as doses of statin in the intervention and comparator groups often differed and RCTs often pooled doses when assessing safety. Therefore, it is uncertain whether ezetimibe is comparatively safer than lower or higher-intensity statins.

The results for this population are in accordance with AGLA guidelines if its assumed that the trial population reflects moderate-to-high-risk groups.<sup>21</sup> For example, ezetimibe was superior to no treatment (placebo) and inferior to first-line treatments (statins). This suggests ezetimibe is an appropriate second-line treatment and may be useful in patients who are contraindicated or intolerant to statins. Adding ezetimibe to statins further reduced LDL-c albeit at an increased risk of adverse events. This suggests that combination therapies may be appropriate under specific circumstances (i.e. patients who failed to achieve LDL-c goals and thus have an increased cardiovascular risk). Nevertheless, these conclusions

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are uncertain owing to applicability concerns (see **Section 7.3.4**), and no study specifically evaluated patients intolerant to statins or those who failed to reach treatment goals. It is unclear whether those patients would respond differently to ezetimibe than did the patients included in the analysis for this HTA.

#### Hypercholesterolaemia with ASCVD

The patient population was heterogenous, including patients with a range of indications such as hypercholesterolaemia with established CHD (or risk equivalent), ACS, recent MI or those undergoing elective vascular surgery. In spite of the diverse population, the safety and effectiveness results were largely representative of patients with ACS because the IMPROVE-IT trial was heavily weighted in the meta-analyses and was the only study powered to detect differences in MACE. It is unclear how representative patients with ACS are to the broader population, given ACS is often the end result of different forms of ASCVD.<sup>2</sup> Treatment effects may differ in patients with more mild disease.

The IMPROVE-IT trial showed that ezetimibe plus statin significantly reduced the incidence of 3P-MACE, MI and stroke at seven years compared to statins. There were no differences between treatments in cardiovascular death, unstable angina or coronary revascularisation.<sup>52</sup> Secondary analyses of the IMPROVE-IT trial determined that older adults, individuals with diabetes, and individuals with a high cardiovascular risk benefited more from ezetimibe plus statin, as inferred by a greater reduction in MACE, MI and stroke compared to younger adults, non-diabetics and low-to-moderate-risk individuals. However, baseline imbalances confounded the result. Two studies that reported MACE outcomes at 12 and 24 months found no difference between ezetimibe plus statin and statin groups, although the studies were not powered to detect treatment effects.

Ezetimibe plus statins significantly reduced LDL-c and total cholesterol levels and increased the number of patients achieving LDL-c goals at early timepoints. At later timepoints, the effect was inconsistent, with statistical differences observed for the absolute but not percentage change in LDL-c and total cholesterol. (The inconsistency again relates to the small number of trials informing later timepoints for the percentage change.) There were no differences in HDL-c, and limited differences in triglycerides. Thus, it is unclear whether ezetimibe has pleiotropic effects in this patient population.<sup>44</sup>

The type of statin was investigated to ascertain sources of heterogeneity in the lipid outcomes. As with the hypercholesterolaemia without ASCVD population, most studies evaluating the percentage change in lipids used simvastatin. For absolute changes, atorvastatin was the most commonly used statin. In general, the results of these sub-groups mirrored the pooled estimate. Much of the heterogeneity is likely attributable to the diverse population included in the analyses. These populations differed in their treatments (i.e. moderate- or high-intensity statins), baseline lipid levels and overall cardiovascular risk.

The rate of adverse events for ezetimibe plus statins was similar to that for statins, and lower than the rate observed in the hypercholesterolaemia without ASCVD population. Common adverse events experienced by both groups related to myopathy and gastrointestinal discomfort, which is consistent with previous literature and practice.<sup>255</sup>

The results from this population are in accordance with AGLA guidelines if its assumed that the trial population reflects high- to very-high-risk groups. For example, when added to statins, ezetimibe reduced LDL-c, increased the number of patients achieving treatment goals and decreased the incidence of long-term cardiac events (MI and stroke). This suggests that ezetimibe should be added to statins if patients cannot achieve treatment goals using statins alone. Nevertheless, applicability concerns (see **Section 7.3.4**) and the uncertainty of patients with ACS representing all ASCVD patients limit the generalisability of this conclusion.

## Hyperlipidaemia without ASCVD

The evidence base evaluating hyperlipidaemia without ASCVD was small. Comparisons were limited to one or two unique trials with relatively small sample sizes that evaluated surrogate markers at 3 months. Ezetimibe monotherapy significantly improved LDL-c and total cholesterol levels compared to placebo but was generally no different to fenofibrate. Ezetimibe was inferior to statins regarding changes in LDLc, total cholesterol, triglycerides and number of patients achieving LDL-c goals. The difference between ezetimibe plus statins and statins was uncertain due to under-reporting of statistics by Stein (2008).<sup>125</sup> Ezetimibe plus fenofibrate was superior to fenofibrate as inferred by a greater reduction in LDL-c and total cholesterol, and an increase in the number of patients achieving goals at 3 months. The statistical difference persisted to 12 months, however the effect size may have been exaggerated because approximately 30% of patients in the fenofibrate group withdrew due to lack of efficacy. The results reinforce the benefit of combination therapy when treating hyperlipidaemia. Fenofibrate primarily reduce triglycerides (and LDL-c to a lesser extent), whereas ezetimibe mainly reduces LDL-c. Together these treatments potentially correct all deficits of hyperlipidaemia.<sup>42 266</sup> However, the clinical meaningfulness of the results is uncertain given that most comparisons had limited follow-up and no study reported MACE outcomes. The safety profile was generally similar among all treatment groups. Again, it is unclear how well the results reflect clinical practice.

The small evidence base limits the ability to determine whether this patient population is in accordance with AGLA guidelines.

## 12.2 Comparison to Previous Literature

The results from this HTA are broadly congruent with recently published studies evaluating ezetimibe combination therapies.<sup>267-269</sup> There are slight differences in the effect sizes, measures of heterogeneity

and GRADE score for LDL-c and MACE outcomes. The differences are likely attributable to the different methods of analysis and pooling of timepoints. For example, the meta-analyses in Savarese (2015),<sup>267</sup> Yu (2020)<sup>268</sup> and Zhan (2018)<sup>269</sup> treated each timepoint as an independent event or only considered a single timepoint (final follow-up). By contrast, the current HTA utilised mixed-effect meta-regression models, which incorporated time as a covariate factor. This likely resulted in a more precise effect estimate. However, a problem with this meta-analysis was that heterogeneity estimated in the model was assumed to be the same across different follow-up timepoints. This may over- or under-estimate heterogeneity at specific timepoints.

The differences in effect size likely reflect the inclusion of additional trials and the pooling of multiple patient populations in the existing analyses.<sup>268 269</sup> The current HTA aimed to reflect the Swiss population and thus studies with predominately Asian and African populations were excluded. Zhan (2018) and Yu (2020) included all ethnicities. This may increase heterogeneity as ethnicities differ in their cardiovascular risk profiles and their response to statins.<sup>97-99</sup> Further, to elucidate the effect of ezetimibe on different populations, the meta-analyses delineated between patients with hypercholesterolaemia, hypercholesterolaemia with ASCVD, and hyperlipidaemia. Zhan (2018) explored patients with and without ASCVD in sub-group analyses, Yu (2020) considered patients with hypercholesterolaemia with and without ASCVD, while Savarese (2015) pooled all populations together. The differences in GRADE scores reflect the different levels of heterogeneity and inconsistency (owing to the different statistical approaches), the uncertain applicability to the Swiss context, and reliance on surrogate markers.

Few meta-analyses evaluated ezetimibe monotherapy compared to placebo<sup>270</sup> and no studies evaluated patients with hyperlipidaemia with ASCVD or compared ezetimibe monotherapy to statins or fenofibrate.

# 12.3 Quality and Applicability of Evidence

The quality of outcomes as inferred by GRADE was low to moderate. The reasons for downgrading were common across all the populations and included risk-of-bias concerns, inconsistency and indirectness. The main bias concern was losses to follow-up that may over- or under-estimate the treatment effect owing to an enriched patient population. This effect was more apparent in extension trials. The moderate to considerable levels of heterogeneity and inconsistency add to the uncertainty and reflect the different indications, treatment goals, cardiovascular risks and medications used in the trials. The ability to investigate sources of heterogeneity using sub-group analyses was constrained as there were insufficient studies to meta-analyse most statin types or other sub-groups (e.g. age or diabetes status). While not meta-analysed, the triglyceride results were inconsistent as there was no clear direction of effect. This may be attributable to the use of different statistical tests (parametric and non-parametric) across the studies.

The main quality concern relates to the indirectness of the population. In Switzerland, ezetimibe monotherapy and combination therapies are indicated for patients with primary hypercholesterolaemia, mixed/combined hyperlipidaemia or homozygous sitosterolemia.<sup>46</sup> <sup>47</sup> <sup>49</sup> Atozet (ezetimibe plus atorvastatin) is limited on the Spezialitätenliste to patients who have a high or very high cardiovascular risk and have not reached treatment goals on maximum tolerated statins.<sup>68</sup> AGLA further suggests ezetimibe should be considered if an individual is intolerant to statins or cannot achieve treatment goals despite using maximally tolerated statins, and has a high or very high cardiovascular risk.<sup>17 21</sup> The evaluated evidence was not stratified in accordance with AGLA risk groups and it was infrequently reported whether patients had previously used statins (or had been up-titrated to the maximal dose). Only one study evaluated statin intolerant patients. Thus, the evaluated population may reflect a comparatively different population to those seen in Swiss practice.

Another quality concern relates to the indirectness of the outcomes. The primary goal in treating lipid disorders is the prevention of cardiovascular morbidity and mortality.<sup>72</sup> There was sufficient evidence to infer ezetimibe plus statins impact on cardiovascular morbidity and mortality in patients with hypercholesterolemia and ASCVD (hence this population tended to have a higher GRADE scores for these outcomes). However, there was insufficient evidence to infer ezetimibe's effects on mortality and morbidity in patients with hypercholesterolemia or hyperlipidaemia without ASCVD. The EMA cautions against inferring the effects of non-statin medication onto other populations who differ in their baseline LDL-c levels.<sup>72</sup> Therefore, the clinical effectiveness of ezetimibe was inferred by surrogate markers in patients with hypercholesterolemia without ASCVD or hyperlipidaemia without ASCVD (and was a common reason to downgrade the guality of reported outcomes). The use of surrogate markers is contentious because the magnitude of change in surrogate markers does not always correlate to the magnitude of clinical benefit<sup>271</sup> (more so for HDL-c, total cholesterol and triglycerides). Furthermore, surrogates may not accurately capture the risk-benefit profile of medications, and surrogates often overestimate the treatment effect.<sup>272</sup> The latter point is particularly relevant for ezetimibe. The incidence of cardiovascular morbidity and mortality in studies is low, particularly in lower-risk populations.<sup>272</sup> Even in trials of higher-risk patients (such as Cannon 2015), the improvements are often relatively small. This suggests that larger sample sizes with longer follow-up periods will be required to detect group differences in populations such as hypercholesterolemia without ASCVD and hyperlipidaemia without ASCVD.

Imprecision was a key concern for comparisons within the hyperlipidaemia population. The evidence base was generally limited to one or two unique trials per comparison, with notable losses to follow-up. The lack of information is unlikely to be addressed in the near future. A search of clinical trials databases identified four trials anticipated to be completed by 2024. All four trials are evaluating ezetimibe

(monotherapy or combination therapy) to rosuvastatin. No studies are evaluating MACE outcomes or using fenofibrate. An additional thirteen ongoing trials are being conducted in patients with ASCVD and eight in patients with hypercholesterolaemia. Most of these will be completed in the next four years.

# 12.4 Limitations of Economic Analyses

A Markov model was developed to quantify the cost-effectiveness of ezetimibe plus statins compared to statins in patients with hypercholesterolaemia with ASCVD. There were several limitations and uncertainties in the economic analysis. The IMPROVE-IT trial involved the comparison of ezetimibe (10mg) plus simvastatin (40mg) to simvastatin (40mg). The AGLA guidelines indicate ezetimibe should be prescribed to patients who do not reach their treatment goals or who are intolerant to statins. In the IMPROVE-IT trial, only 34% of enrolled patients had previously received a statin; 27% up-titrated over the course of the trial. Thus, the applicability of IMPROVE-IT results to Swiss clinical practice is uncertain. Sensitivity analysis was included to indirectly compare higher doses of simvastatin and other more potent statins (atorvastatin and rosuvastatin) to ezetimibe and simvastatin using the results from Law (2003). However, baseline characteristics (e.g. LDL-c) differ between the studies in Law (2003) and patients enrolled in the IMPROVE-IT trial. These baseline imbalances potentially confound the results of the sensitivity analyses.

The clinical review found no differences in MACE outcomes for patients with hypercholesterolaemia without ASCVD (one under-powered study). No studies evaluated MACE outcomes in hyperlipidaemia patients. Despite there being differences in LDL-c within hypercholesterolaemia and hyperlipidaemia populations, it is uncertain whether these differences would translate to improvements in MACE outcomes over the long-term. The economic analysis did not include these sub-populations, which likely account for large numbers of patients in Switzerland.

The budget impact analysis comprised two hypothetical scenarios to calculate the net cost savings to payers if ezetimibe was limited. In the absence of data, it was assumed that 10% and 25% of patients would transition to higher potency statins from ezetimibe. A more accurate calculation of net costs would involve an estimate of the number of Swiss patients prescribed ezetimibe due to statin intolerance or not attaining lipid goals, or having hyperlipidaemia. However, there was no published literature reporting these numbers. The price and use of different ezetimibe medicines and statins has been changing in Switzerland over the last three years. Future projections of costs are subject to uncertainty with differing regimes and brands likely to be used over the next five years.

## 12.5 Legal, Social, Ethical and Organisational Issues

There were limited legal and ethical issues associated with restricting access to ezetimibe. When considering lipid-lowering treatments more broadly, statin non-adherence was the main social concern.

Non-adherence increases the risk of cardiovascular morbidity and mortality and is caused by multiple patient and physician barriers (see *Section 9.5.2*). The causes and consequences of non-adherence are likely generalisable to ezetimibe combination therapies (which also contain statins). However, it is unclear whether non-adherence is a concern for ezetimibe monotherapies because existing analyses have reported that cholesterol absorption inhibitors and other lipid-lowering medications (fenofibrate) are not factors associated with non-adherence.<sup>273</sup> Higher compliance rates among patients using cholesterol absorption inhibitors may relate to the avoidance of statin-associated muscle symptoms.

Key organisational concerns relate to inappropriate prescribing of ezetimibe and regional variability in the treatment of hypercholesterolaemia in Switzerland. Analysis of prescription databases determined ezetimibe was prescribed against guideline recommendations (as a first-line treatment) in a quarter of new lipid-lowering therapy users in Saskatchewan, Canada. Non-specialists were more likely to prescribe ezetimibe as a first-line treatment compared to specialists (see *Section 10.4.1*). This reinforces the results from surveys indicating that some general practitioners are not confident in their knowledge of dyslipidaemia guidelines.<sup>274</sup> This issue is likely applicable to Switzerland because ezetimibe monotherapy and ezetimibe in combination with simvastatin are not restricted to specific indications on the Spezialitätenliste. It is unclear to what extent inappropriate prescribing of ezetimibe occurs in Switzerland. However, restricting access to specific indications would circumvent the problem.

In Switzerland, there is regional variation in the diagnosis, screening and treatment of hypercholesterolaemia, with the highest rates in Leman and Ticino. This finding is not unique to cardiovascular disease, as other chronic disease such as type 2 diabetes also vary between regions.<sup>275</sup> Further, the utilisation of healthcare resources (hospital and nursing home stays) also vary between regions and are thought to underscore differences in the number of services, and the age and density of populations within each region.<sup>276</sup>

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# 13 Conclusions

The clinical effectiveness and safety of ezetimibe monotherapy and combination therapies were informed by a moderate-sized evidence base for patients with hypercholesterolaemia without ASCVD, a large evidence base for patients with hypercholesterolaemia and ASCVD, and a small evidence base for patients with hyperlipidaemia without ASCVD. There were no studies evaluating ezetimibe in patients with hyperlipidaemia and ASCVD. The quality of included studies was moderate to high (as inferred by risk-of-bias), but the quality of reported outcomes—as inferred by GRADE—ranged from low to moderate. Quality concerns involved risk-of-bias concerns (mainly losses to follow-up), moderate to considerable heterogeneity in the meta-analyses, reliance on surrogate markers to infer clinical effectiveness, and the uncertain applicability of the evidence base to Swiss practice.

## Hypercholesterolaemia without ASCVD

Comparisons involving ezetimibe monotherapy were limited to surrogate markers at 3 months.

At 3 months, ezetimibe was superior to placebo but inferior to statins with respect to the absolute and percentage change in LDL-c, HDL-c, total cholesterol and number of patients achieving LDL-c goals. The impact on triglycerides could not be accurately determined because statistical significance was infrequently reported. Compared to statins, ezetimibe plus statins significantly improved LDL-c, HDL-c and total cholesterol and increased the number of patients achieving LDL-c goals at 3 months. The statistical effect persisted to 12 months for LDL-c and total cholesterol. However, results were subject to considerable heterogeneity and later timepoints were often informed by only one study. There were inconsistent differences in triglycerides and limited differences in markers of vascular damage. One study reported that the incidence of 3P-MACE and coronary revascularisation was similar between ezetimibe plus statin and statin groups (noting the study was not powered to detect differences). To investigate causes of heterogeneity, the types of statins underwent sub-group analysis. Ezetimibe plus simvastatin reduced LDL-c and total cholesterol and increased HDL-c to the same extent as the pooled estimate. The remaining statin types were not meta-analysed owing to insufficient study numbers.

Ezetimibe had a comparable safety profile to placebo and statins at the end of follow-up. The incidence of adverse events (serious, any, and withdrawal due to) was similar between ezetimibe plus statin and statin groups. However, ezetimibe plus statin significantly increased the incidence of treatment-related adverse events. The type of events accounting for the increased incidence was not reported.

#### Hypercholesterolaemia with ASCVD

Ezetimibe plus statins compared to statins was the only assessed comparison in this patient population. Furthermore, the results largely reflect patients with ACS because the IMPROVE-IT trial was heavily weighted in the meta-analyses and was the only study powered to detect group differences in MACE. At 3 months, ezetimibe plus statins significantly improved LDL-c and total cholesterol levels and increased the number of patients achieving LDL-c goals compared to statins. At later timepoints, the improvement was inconsistent, with significant differences noted for the absolute but not percentage changes in LDL-c and total cholesterol. There were no differences in HDL-c, and limited differences in triglycerides across all timepoints. Compared to statins, ezetimibe plus statins significantly reduced the incidence of 3P-MACE, MI and stroke at seven years. There were no statistical differences between the groups in cardiovascular death, unstable angina or coronary revascularisation or any safety outcome. Secondary analyses of the IMPROVE-IT trial reported that older adults, individuals with diabetes, and individuals with a high cardiovascular risk profile benefited most from ezetimibe plus statins.

## Hyperlipidaemia without ASCVD

The evidence base was generally limited to surrogate outcomes (lipid and triglyceride levels) at 3 months, with one to two studies informing each comparison. Ezetimibe monotherapy was superior to placebo, inferior to statins, and no different to fenofibrate with respect to improvements in LDL-c, total cholesterol and triglycerides. The statistical difference between ezetimibe plus statins and statins was not reported so it was unclear whether the groups differed. Ezetimibe plus fenofibrate significantly reduced LDL-c, total cholesterol and triglycerides and increased the number of patients achieving LDL-c goals compared to fenofibrate monotherapy. The incidence of adverse events (serious, any, and withdrawal due to) was generally similar across all comparisons. Owing to the limited evidence base, the concordance of the HTA with AGLA guidelines is uncertain.

Economic models for patients with hypercholesterolaemia without ASCVD, patients with hyperlipidaemia with ASCVD, and patients with hyperlipidaemia without ASCVD could not be generated owing to the absence of MACE data. There was sufficient evidence to create a model for patients with hypercholesterolaemia and ASCVD. The results of the model were informed by the IMPROVE-IT trial and thus are reflective of patients with ACS and patients using ezetimibe plus simvastatin or simvastatin (medium-potency statin). The analysis found ezetimibe plus simvastatin to be cost-effective compared to simvastatin at 7- and 20-year projections. There is uncertainty surrounding the applicability of these results to other population groups, such as hyperlipidaemia patients and patients with hypercholesterolaemia without ASCVD (i.e. lower risk).

The main social issue related to increased cardiovascular morbidity and mortality due to statin nonadherence. This concern applies to patients receiving ezetimibe combination therapies because these therapies contain statins.

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# **15 Appendices**

#### 15.1 Appendix A: Source of Literature (databases and websites)

#### Table 83 Databases searched and number of search results

Source	Location	Search results Inception–31 December 2019	Updated search results 31 December 2019–4 May 2020
PubMed	https://www.ncbi.nlm.nih.go v	2,616	363
Embase	https://www.embase.com/	8,285	1,012
The Cochrane Library (inc. CENTRAL)	https://www.cochranelibrary .com/	1,696	124
CINAHL	https://www.ebscohost.com /nursing/products/cinahl- databases/cinahl-complete	1,339	47
York CRD (inc. HTA, NHS EED, DARE)	https://www.crd.york.ac.uk/ CRDWeb/	40	0
CEA Registry	http://healtheconomics.tufts medicalcenter.org/cear4/ho me.aspx	15	0
Econlit	https://www.aeaweb.org/ec onlit/	1	0
ETHMED	http://www.ethicsweb.eu/se arch_ets	10	5
	Total	14,002	1,551

#### **Abbreviations**

**CEA registry** = cost-effectiveness analysis registry, **CINAHL** = Cumulative Index of Nursing and Allied Health Literature, **CRD** = centre for review and dissemination, **DARE** = Database of Abstracts of Reviews of Effects, **HTA** = health technology assessment, **inc**. = including, **NHS EED** = National Health Service Economic Evaluation Database.

Number	Query	Initial search Inception–31 December 2019	Updated search 31 December 2019–4 May 2020
1	Ezetimib*	3,362	361
2	Ezetrol	3,356	361
3	Zetia	3,359	361
4	SCH?58235	3,356	
5	'58235, SCH'	1	0
6	SCH58235	3,355	361
7	Niemann Pick C1-like 1 protein inhibitor	87	3
8	NPC1L1 inhibitor	113	8
9	Atozet	1	0
10	Inegy	549	10
11	Vytorin	575	18
12	Ezetimibe[Mesh]	2,062	65
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]	3,384	363
14	Filters human	2,616	-

#### Table 84 Search strategy – Medline (PubMed)

Number	Query	Initial search Inception-31 December 2019	Updated search 31 December 2019–4 May 2020
1	Ezetimib*.mp.	10,963	1,012
2	Ezetrol.mp.	254	4
3	Zetia.mp.	387	8
4	SCH?58235.mp.	5	0
5	'58235, SCH'.mp.	5	0
6	SCH58235.mp.	0	0
7	'Niemann Pick C1 like 1 protein inhibitor'.mp.	3	0
8	'NPC1L1 inhibitor'.mp.	27	1
9	Atozet.mp.	5	0
10	Inegy.mp.	96	2
11	Vytorin.mp.	467	19
12	ezetimibe/	9,645	894
13	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12	10,979	1,012
14	limit 13 to human	9,671	-
15	limit 14 to (conference abstracts and conference abstract status and conference abstract)	1,093	-
16	limit 14 to conference paper	188	-
17	limit 14 to conference review	5	-
18	14 not (15 or 16 or 17)	8,385	-

#### Table 85 Search strategy – Ovid/Embase

Number	Query	Initial search	Updated search
		Inception-31 December 2019	31 December 2019–4 May 2020
1	Ezetimib*	1,686	124
2	Ezetrol	37	0
3	Zetia	28	1
4	SCH?58235	2	0
5	'58235, SCH'	16	1
6	SCH58235	3	0
7	'Niemann pick C1 like 1 protein inhibitor'	3	0
8	'NPC1L1 inhibitor'	5	1
9	Atozet	0	0
10	Inegy	13	1
11	Vytorin	96	9
12	MeSH descriptor: [Ezetimibe] explode all trees	737	2
13	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12	1,696	124

## Table 86 Search Strategy – The Cochrane Library

Number	Query	Initial search	Updated search
		Inception-31 December 2019	31 December 2019–4 May 2020
1	Ezetimib*	1,086	37
2	Ezetrol	4	0
3	Zetia	18	4
4	SCH?58235	0	19
5	'58235, SCH'	3	0
6	SCH58235	429	19
7	'Niemann pick C1-like 1 protein inhibitor'	296	9
8	'NPC1L1 inhibitor'	3	1
9	Atozet	0	0
10	Inegy	3	0
11	Vytorin	71	0
12	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11	1,339	47

## Table 87 Search strategy – Cumulative Index of Nursing and Allied Health Literature

# Table 88 Search Strategy – York Centre for Reviews and Dissemination

Number	Query	Initial search Inception–31 December 2019	Updated search 31 December 2019–4 May 2020
1	Ezetimibe	35	0
2	Ezetrol	3	0
3	Zetia	1	0
4	SCH?58235	0	0
5	58235, SCH	0	0
6	SCH58235	0	0
7	Niemann Pick C1-like 1 protein inhibitor	0	0
8	NPC1L1 inhibitor	0	0
9	Atozet	0	0
10	Inegy	1	0
11	Vytorin	0	0
	Total	40	0

#### Table 89 Search strategy – Ethicsweb

Number	Query	Initial search Inception–9 November 2019	Updated search 31 December 2019–4 May 2020
1	Ezetimibe	8	0
2	Ezetrol	1	0
3	Zetia	1	0
4	SCH?58235	0	0
5	'58235, SCH'	0	0
6	SCH58235	0	0
9	Atozet	0	0
10	Inegy	0	0
11	Vytorin	0	0
	Total	10	0

# Table 90 Search strategy – Cost-effectiveness Analysis Registry

Number	Query	Initial search Inception–23 September 2019	Updated search 31 December 2019–4 May 2020
1	Ezetimibe	14	0
2	Ezetrol	0	0
3	Zetia	0	0
4	SCH?58235	0	0
5	58235, SCH	0	0
6	SCH58235	0	0
7	Niemann–Pick C1-like 1 protein inhibitor	0	0
8	NPC1L1 inhibitor	0	0
9	Atozet	0	0
10	Inegy	0	0
11	Vytorin	1	0
	Total	15	0

Number	Query	Initial search	Updated search
		Inception–23 September 2019	31 December 2019–4 May 2020
1	Ezetimibe	1	0
2	Ezetrol	0	0
3	Zetia	0	0
4	SCH?58235	0	0
5	'58235, SCH'	0	0
6	SCH58235	0	0
7	'Niemann-Pick C1-like 1 protein inhibitor'	0	0
8	NPC1L1 inhibitor	0	0
9	Atozet	0	0
10	Inegy	0	0
11	Vytorin	0	0
12	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11	1	5

#### Table 91 Search strategy – Econlit

## Table 92 Clinical trial registries

Clinical trial registries	Initial search Inception–31 December 2019	Updated search Inception–7 September 2020
ClinicalTrials.gov	9	19
Cochrane Central Register of Controlled Trials	0	0
EU Clinical Trials Registry	8	6
WHO International Clinical Trials Registry Platform (ICTRP)	0	0
Australian New Zealand Clinical Trials Registry	0	0

## Additional Legal, Social, Ethical and Organisational Searches

Number	Query	PubMed	Embase
1	Personal autonomy [mh]	6,001	4444
2	Human rights [mh]	78,824	78,208
3	Human rights[tiab]	10,317	9,386
4	(free will)	68,397	92,235
5	(self determination)	30,373	16,527
6	Parental consent [mh]	1,287	980
7	Third-party consent [mh]	2,318	18,305
8	Presumed consent [mh]	283	18,305
9	Informed consent by minors [mh]	137	18,305
10	Consent [tiab]	62,536	127,136
11	Privacy [tw]	20,399	26,388
12	Confidentiality [mh]	28,295	9,069
13	Confidentiality[tiab]	11286	13,662
14	Personally identifiable information [mh]	21	43
15	Health record, personal [mh]	1,473	3
16	(personal information)	38,169	53,832
17	Jurisprudence [mh]	128,158	20,451
28	Law enforcement [mh]	1,896	2,247
19	Law[tiab]	90,305	101,272
20	Laws[tiab]	29,770	32,041
21	Legislation, drug [mh]	17,340	6,542
22	Legislation, pharmacy [mh]	801	46,399
23	Legislation, food [mh]	1366	46,399
24	Legislation as topic [mh]	91,067	46,399
25	Legislation[tiab]	36,749	42,296
26	Civil rights [mh]	12,229	8,047
27	Authority[tiab]	22,398	29,353
28	Legal case [pt]	11,012	0
29	Legal guardians [mh]	1,772	64
30	Legal [tiab]	90,753	100,090
31	Liability, legal [mh]	7,471	6,559
32	Legal services [mh]	21	102
33	Access to information [mh]	4,199	3,035
34	Social justice [mh]	5,596	4,030
35	Health equity [mh]	928	1,380

# Table 93 Search string for legal issues (24 June 2020)

Number	Query	PubMed	Embase
36	Human rights abuses [mh]	1,025	1,055
37	Patient rights [mh]	41,534	35,794
38	Rights to human [mh]	2	8
39	Ownership [mh]	9,673	549,850
40	Intellectual property [mh]	6,140	7,701
41	Intellectual property[tiab]	2,200	2,938
42	Licensure [mh]	9,730	31,488
43	License[tiab]	7624	11,823
44	Liability, legal [mh]	7,471	6,559
45	Liability [tiab]	19,116	23,587
46	Legislation[mh]	91,088	46,399
47	Legislation as topic [mh]	91,067	46,399
48	Medical device legislation [mh]	166	413
49	Legislation, nursing [mh]	2,042	46,399
50	Legislation, medical [mh]	8,893	23,408
51	Legislation, hospital [mh]	2,637	46,399
52	Legislation, food [mh]	1,366	46,399
53	Legislation, drug [mh]	17,340	6,542
54	Conflict of interest [mh]	5,766	4,208
55	Guaranty[tiab]	123	230
56	Regulation[tiab]	841,456	1,013,518
57	Acquisition	159,410	195,680
58	Conflict of interest[tiab]	4,052	5,902
59	1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 PR 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20 OR 21 OR 22 OR 23 OR 24 OR 25 OR 26 OR 27 OR 28 OR 29 OR 30 OR 31 OR 32 OR 33 OR 34 OR 35 OR 36 OR 37 OR 38 OR 39 OR 40 OR 41 OR 42 OR 43 OR 44 OR 45 OR 46 OR 47 OR 48 OR 49 OR 50 OR 51 OR 52 OR 53 OR 54 OR 55 OR 56 OR 57 OR 58	1,619,766	2,557,677
60	59 AND (dyslipid* OR hypercholesterol* OR hyperlipid*)	83,939	10,789
61	60 AND (statin OR ezetimibe)	82	29

Number	Query	PubMed	Embase
1	Patient experience[tiab]	5,993	9,933
2	Quality of life [mh]	88,177	105,811
3	Social aspects of [tiab]	2,333	2,961
4	Medical decision-making process [mh]	94,591	192
5	Patient education as topic [mh]	516,156	0
6	Patient education[tiab]	19,224	26,921
7	Patient attitude[tiab]	160	1,546
8	Patient preference [tiab]	4,465	6,704
9	Patient decision[tiab]	1658	200
10	Patient acceptance[tiab]	2912	3,814
11	Patient satisfaction [tiab]	36,331	50,738
12	Patient-focused [tiab]	1,601	2,244
13	Patient-centred [tiab]	6,117	7,797
14	Patient advocacy [tiab]	1,368	1,949
15	Consumer satisfaction [tiab]	759	865
16	Consumer participation [tiab]	394	377
17	Consumer preference [tiab]	396	365
18	Consumer attitude[tiab]	41	49
19	Self-perception	149,623	5,701
20	Self-care	191,801	65,151
21	Self-efficacy	62,706	33,660
22	Attitude to health	539 837	113,543
23	Health education	703,995	863,783
24	Health knowledge	320,894	358,775
25	Informed choice	49,397	8,976
26	Shared decision making	11,968	19,050
27	Empowerment	12,794	19,201
28	Quality of Life	397,141	684,717
29	Adaptation, psychological	134,226	21,964
30	Coping	163,815	93,582
31	1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20 OR 21 OR 22 OR 23 OR 24 OR 25 OR 26 OR 27 OR 28 OR 29 OR 30	1,841,089	2,088,902
32	Focus group	116,377	30,762
33	verbal communication	29,899	16,343
34	qualitative	289,355	323,547
35	survey	1,459,653	1,380,252

## Table 94 Search string for social issues (24 June 2020)

Number	Query	PubMed	Embase
36	32 OR 33 OR 34 OR 35	1,816,292	1,794,783
37	31 AND 36	3,079,396	3,487,115
38	37 AND (dyslipid* OR hypercholesterol* OR hyperlipid*)	88,127	16,778
39	38 AND (statin OR ezetimibe)	90	42

## Table 95 Search string for ethical issues (24 June 2020)

Number	Query	PubMed	Embase
1	Ethics[mh]	91,267	108,843
2	Medical ethics[tiab]	6 214	6,598
3	Ethical theory [mh]	1,156	986
4	Bioethics[mh]	7,258	6,790
5	Bioethics[tiab]	16,462	10,157
6	Morals[mh]	103,920	12,306
7	Morality[tiab]	4,385	4,847
8	Ethical theory[tiab]	296	297
9	Principle-based ethics[mh]	12,096	108,843
10	Patient rights [mh]	41,534	35,794
11	Patient autonomy[tiab]	2,307	2,754
12	Personal autonomy [mh]	6,001	4,444
13	Autonomy[tiab]	29,120	35,439
14	Social justice [mh]	5,596	4,030
16	Ethical issues [tiab]	11,866	13,990
17	Normative [tiab]	29,101	36,890
18	1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17	958,258	216,874
19	18 AND (dyslipid* OR hypercholesterol* OR hyperlipid*)	85,064	311
20	19 AND (statin OR ezetimibe)	85	8

Number	Query	PubMed	Embase
1	Information storage and retrieval [mh]	58,093	9
2	(information management)	355,366	329,205
3	Health information systems [mh]	988	7,763
4	Health information management [mh]	1,300	7,763
5	Health information exchange [mh]	634	7,763
6	Information literacy [mh]	4,210	215
7	Health equity [mh]	928	1,380
8	(work process)	197,829	180,864
9	(work flow)	61,087	61,627
10	Medical Education[mh]	122,968	172,559
11	Education, professional, retraining [mh]	930	9,417
12	Education, public health professional [mh]	637	172,561
13	Health information interoperability[mh]	102	80
14	Communication [mh]	166,056	191,278
15	Health communication [mh]	1,734	11,383
16	Quality assurance, health care [mh]	149,206	554,669
18	Implementation science [mh]	214	519
19	Organization culture [mh]	19,605	730
20	(human skills)	192,855	195,291
21	Sustainability[tiab]	23,633	27,588
22	(system structure)	446,562	320,759
23	Acceptance[tiab]	68,980	91,419
24	1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20 OR 21 OR 22 OR 23 OR 24	1,694,774	1,978,148
25	24 AND (dyslipid* OR hypercholesterol* OR hyperlipid*)	83,568	9,388
26	25 AND (statin OR ezetimibe)	82	36

## Table 96 Search string for organisational issues (24 June 2020)

#### 15.2 Appendix B: List of Notable Excluded Trials

Averna, M., L. Missault, H. Vaverkova, M. Farnier, M. Viigimaa, Q. Dong, A. Shah, A. O. Johnson-Levonas, W. Taggart and P. Brudi (2011). "Lipid-altering efficacy of switching to ezetimibe/simvastatin 10/20 mg versus rosuvastatin 10 mg in high-risk patients with and without metabolic syndrome." *Diab Vasc Dis Res*<u></u> 8(4): 262-270. doi: 210.1177/1479164111418136. *Wrong comparisons.* 

Brudi, P., J. P. Reckless, D. P. Henry, T. Pomykaj, S. T. Lim, R. Massaad, K. Vandormael and A. O. Johnson-Levonas (2009). "Efficacy of ezetimibe/simvastatin 10/40 mg compared to doubling the dose of low-, medium- and high-potency statin monotherapy in patients with a recent coronary event." *Cardiology* 113(2): 89-97. doi: 10.1159/000172795. *Wrong comparisons.* 

Kosoglou, T., P. Statkevich, J. C. Fruchart, L. J. C. Pember, L. Reyderman, D. L. Cutler, M. Guillaume, S. E. Maxwell and E. P. Veltri (2004a). "Pharmacodynamic and pharmacokinetic interaction between fenofibrate and ezetimibe." *Current Medical Research and Opinion* 20(8): 1197-1207. *No effectiveness data for this comparison.* 

Kosoglou, T., P. Statkevich, I. Meyer, D. L. Cutler, B. Musiol, B. Yang, Y. Zhu, S. E. Maxwell and E. P. Veltri (2004). "Effects of ezetimibe on the pharmacodynamics and pharmacokinetics of lovastatin." *Curr Med Res Opin.* 20(6): 955-965. doi: 910.1185/030079904125003872. *Lovastatin not licenced in Switzerland.* 

Kouvelos, G. N., E. M. Arnaoutoglou, H. J. Milionis, V. D. Raikou, N. Papa and M. I. Matsagkas (2015). "The effect of adding ezetimibe to rosuvastatin on renal function in patients undergoing elective vascular surgery." *Angiology*. 66(2): 128-135. doi: 110.1177/0003319713519492. *Repeat of Kouvelos 2013*.

Lakoski, S. G., F. Xu, G. L. Vega, S. M. Grundy, M. Chandalia, C. Lam, R. S. Lowe, M. E. Stepanavage, T. A. Musliner, J. C. Cohen and H. H. Hobbs (2010). "Indices of cholesterol metabolism and relative responsiveness to ezetimibe and simvastatin." *J Clin Endocrinol Metab.* 95(2): 800-809. doi: 810.1210/jc.2009-1952. *Wrong comparisons.* 

Moriarty, P. M., P. D. Thompson, C. P. Cannon, J. R. Guyton, J. Bergeron, F. J. Zieve, E. Bruckert, T. A. Jacobson, S. L. Kopecky, M. T. Baccara-Dinet, Y. Du, R. Pordy and D. A. Gipe (2015). "Efficacy and safety of alirocumab vs ezetimibe in statin-intolerant patients, with a statin rechallenge arm: The ODYSSEY ALTERNATIVE randomized trial." *J Clin Lipidol.* 9(6): 758-769. doi: 710.1016/j.jacl.2015.1008.1006. *No effectiveness data for this comparison.* 

Olszewska-Banaszczyk, M., P. Jackowska, P. Gorzelak-Pabiś, E. Pytel, M. Koter-Michalak and M. Broncel (2018). "Comparison of the effects of rosuvastatin monotherapy and atorvastatin-ezetimibe combined therapy on the structure of erythrocyte membranes in patients with coronary artery disease." *Pharmacol Rep.* 70(2): 258-262. doi: 210.1016/j.pharep.2017.1011.1004. *Wrong outcomes.* 

Pandey, A. S., S. Bissonnette, S. Boukas, E. Rampakakis and J. S. Sampalis (2011). "Effectiveness and tolerability of ezetimibe co-administered with statins versus statin dose-doubling in high-risk patients with persistent hyperlipidemia: The EZE(STAT)2 trial." *Archives of Medical Science* 7(5): 767-775. *Wrong study design.* 

Pearson, G. J., G. A. Francis, J. S. Romney, D. M. Gilchrist, A. Opgenorth and G. T. Gyenes (2006). "The clinical effect and tolerability of ezetimibe in high-risk patients managed in a specialty cardiovascular risk reduction clinic." *Canadian Journal of Cardiology* 22(11): 939-945. *Wrong study design*.

Piorkowski, M., S. Fischer, C. Stellbaum, M. Jaster, P. Martus, A. J. Morguet, H. P. Schultheiss and U. Rauch (2007). "Treatment with ezetimibe plus low-dose atorvastatin compared with higher-dose atorvastatin alone: is sufficient cholesterol-lowering enough to inhibit platelets?" *J Am Coll Cardiol.* 49(10): 1035-1042. doi: 1010.1016/j.jacc.2006.1010.1064. *Wrong outcomes*.

Westerink, J., J. E. Deanfield, B. P. Imholz, W. Spiering, D. C. Basart, B. Coll, J. J. Kastelein and F. L. Visseren (2013). "High-dose statin monotherapy versus low-dose statin/ezetimibe combination on fasting and postprandial lipids and endothelial function in obese patients with the metabolic syndrome: The PANACEA study." *Atherosclerosis*. 227(1): 118-124. doi:

110.1016/j.atherosclerosis.2012.1011.1028. Wrong outcomes.

## 15.3 Appendix C: List of Included Trials

# 15.3.1 Hypercholesterolaemia without ASCVD

## Table 97 Hypercholesterolaemia without ASCVD: characteristics of included RCTs assessing

Study; country; trial ID	Inclusion criteria; sample size	Design; setting; follow-up	Intervention; comparator	Effectiveness and safety outcomes
Alvarez-Sala 2008136	Hypercholesterolaemia	RCT, open-label	Fluvastatin (80mg)	Effectiveness
Spain	LDL-c: ≥130mg/dL Triglycerides: ≤400mg/dL	Multicentre	Fluvastatin (80mg) plus ezetimibe (10mg)	<ul> <li>LDL-c, HDL-c, total cholesterol, triglycerides</li> </ul>
		3 months		Safety
	n=89			<ul> <li>Withdrawal, AE, SAE</li> </ul>
Ballantyne 2003126	Primary	RCT, double-	Atorvastatin (10, 20,	Effectiveness
	nypercholesterolaemia	blind	40 or 80mg)	LDL-c, HDL-c, total
007	LDL-c: 145–250mg/dL	Multicentre	Atorvastatin (10, 20,	Cholesteron
NCT03867110	Triglycerides: ≤350ma/dL	2 months	40 or 80mg) plus ezetimibe (10mg)	Safety
		5 monuns		<ul> <li>Mortality, withdrawal, AE.</li> </ul>
	n=628		Ezetimibe (10mg)	TAE
			Placebo	
Ballantyne 2004b146	Primary hypercholesterolaemia	RCT, double-	Atorvastatin (10mg	Effectiveness
USA	nyperenoiesteroidennia	study <sup>126</sup>	increa to comy)	<ul> <li>LDL-c, HDL-c, total cholesterol.</li> </ul>
	LDL-c: >NCEP-ATP III	Multicentre	Simvastatin (10mg	triglycerides
NCT03867110	Triglycerides:	Multicentie	ezetimibe (10mg)	Safety
	≤350mg/dL	6 months	Circulantatia (20ma	<ul> <li>Mortality,</li> </ul>
	n=788		tittered to 80mg) plus ezetimibe (10mg)	withdrawal, AE, SAE, STAE, TAE
Bays 2004 <sup>127</sup>	Primary	RCT, double-	Ezetimibe (10mg)	Effectiveness
USA + 22 countries <sup>a</sup>	LDL-c: 145–250mg/dL	International,	Simvastatin (10, 20, 40 or 80mg)	• LDL-c, HDL-c, total cholesterol, triglycerides
NR	Triglycerides: ≤350ma/dl	multicentre		Safaty
	0000g/ 0.1	3 months	Simvastatin (10, 20, 40 or 80mg) plus	<ul> <li>Mortality.</li> </ul>
	n=1528		ezetimibe (10mg)	withdrawal, AE, SAE, STAE, TAE
			Placebo	

#### clinical effectiveness and safety

Study; country; trial ID	Inclusion criteria; sample size	Design; setting; follow-up	Intervention; comparator	Effectiveness and safety outcomes
Bays 2008 <sup>106</sup> USA + 22 other countries <sup>a</sup> NR	Primary hypercholesterolaemia LDL-c: 145–250mg/dL Triglycerides: ≤350mg/dL n=768	RCT, double- blind, extension study <sup>107</sup> International, multicentre 15 months	Simvastatin (10, 20, 40 or 80mg) Simvastatin (10, 20, 40 or 80mg) plus ezetimibe (10mg)	Effectiveness <ul> <li>LDL-c, HDL-c, total cholesterol, triglycerides</li> </ul> <li>Safety <ul> <li>Mortality, withdrawal, AE, SAE STAE TAE</li> </ul> </li>
Chirinos 2010 <sup>170</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) plus ezetimibe (10mg)	• Withdrawal, SAE
Davidson 2002 <sup>128</sup> USA NR	Primary hypercholesterolaemia LDL-c: 145–250mg/dL Triglycerides: ≤350mg/dL n=668	RCT, double- blind Multicentre 3 months	Ezetimibe (10mg) Simvastatin (10, 20, 40 or 80mg) Simvastatin (10, 20, 40 or 80mg) plus ezetimibe (10mg) Placebo	Effectiveness • LDL-c, HDL-c, total cholesterol, triglycerides Safety • Mortality, withdrawal, AE, SAE, TAE
Davidson 2013 <sup>169</sup> USA NCT00701727	Hypercholesterolaemia LDL-c: 130–200mg/dL Triglycerides: <350mg/dL n=26	RCT, double- blind, cross-over Single-centre 7 weeks	Ezetimibe (10mg) Placebo	Safety • SAE
Dujovne 2002 <sup>129</sup> USA Protocol P00474	Primary hypercholesterolaemia LDL-c: 130–200mg/dL Triglycerides: ≤350mg/dL n=892	RCT, double- blind Multicentre 12 weeks	Ezetimibe (10mg) Placebo	<ul> <li><i>Effectiveness</i></li> <li>LDL-c, HDL-c, total cholesterol, triglycerides</li> <li><i>Safety</i></li> <li>Withdrawal, AE</li> </ul>
Florentin 2011 <sup>141</sup> Greece NR	Primary hypercholesterolaemia LDL-c: ≥ NCEP–ATPIII recommendations Triglycerides : NR n=100	RCT, double- blind Single-centre 3 months	Simvastatin (10mg) plus ezetimibe (10mg) Simvastatin (40mg)	<ul> <li><i>Effectiveness</i></li> <li>LDL-c, HDL-c, total cholesterol, triglycerides</li> <li><i>Safety</i></li> <li>Withdrawal</li> </ul>

Study; country; trial ID	Inclusion criteria; sample size	Design; setting; follow-up	Intervention; comparator	Effectiveness and safety outcomes
Goldberg 2004 <sup>107</sup> USA + 22 countries <sup>a</sup> NR Kastelein 2008 <sup>120</sup> America, Africa and Europe <sup>b</sup> NCT00552097	Primary hypercholesterolaemia LDL-c: 145–250mg/dL Triglycerides ≤350mg/dL n=887 Familial hypocholesterolaemia LDL-c: >210mg/dL; or <210mg/dL + existing lipid-lowering therapy Triglycerides: NR	RCT, double- blind International, multicentre 3 months RCT, double blind International, multicentre 24 months	Ezetimibe (10mg) Simvastatin (10, 20, 40 or 80mg) Simvastatin (10, 20, 40 or 80mg) plus ezetimibe (10mg) Placebo Simvastatin (80mg) plus ezetimibe (10mg) Simvastatin (80mg) plus placebo	Effectiveness • LDL-c, HDL-c, total cholesterol, triglycerides Safety • Withdrawal, AE, SAE, STAE, TAE Effectiveness • LDL-c, HDL-c, total cholesterol, triglycerides • Vascular damage • MACE Safety • Mortality, withdrawal, AE, TAE
	n=720			TAE
Kerzner 2003 <sup>130</sup> USA NR	Primary hypercholesterolaemia LDL-c: 145–250mg/dL Triglycerides ≤350mg/dL n=136	RCT, double blind Multicentre 3 months	Ezetimibe (10mg) Placebo	Effectiveness • LDL-c, HDL-c, total cholesterol Safety • Mortality, withdrawal, AE, TAE
Knopp 2003 <sup>131</sup> USA NR	Primary hypercholesterolaemia LDL-c: ≥130mg/dL Triglycerides: ≤250mg/dL n=827	RCT, double- blind Multicentre 3 months	Ezetimibe (10mg) Placebo	Effectiveness <ul> <li>LDL-c, HDL-c, total cholesterol, triglycerides</li> </ul> Safety <ul> <li>Mortality, withdrawal, AE</li> </ul>
Koren 2014 <sup>132</sup> Africa, America, Asia, Europe ° NCT01763827	Primary hypercholesterolaemia LDL-c: 100–190mg/dL Triglycerides: ≤400mg/dL n=299	RCT, double- blind Multicentre 3 months	Ezetimibe (10mg) Placebo	Effectiveness • LDL-c, triglycerides Safety • Mortality, withdrawal, AE, SAE, STAE

Study; country; trial ID	Inclusion criteria; sample size	Design; setting; follow-up	Intervention; comparator	Effectiveness and safety outcomes
Koren 2012 <sup>104</sup>	Primary hypercholesterolaemia	RCT, double- blind	Ezetimibe (10mg)	Effectiveness <ul> <li>LDL-c, HDL-c, total</li> <li>cholesterol</li> </ul>
USA, Australia, Belgium, Denmark, Canada	LDL-c: 100–190mg/dL Triglycerides: ≤400mg/dL	Multicentre 3 months	Placebo	Safety
NCT01375777	n=135			withdrawal, AE, SAE, STAE, TAE
Kosoglou 2004 <sup>167</sup>	Hypercholesterolaemia	RCT, single- blind	Ezetimibe (10mg) plus placebo	Safety • Mortality
France	LDL-c: ≥130mg/dL Triglycerides: ≤400ma/dL	Single-centre	Rosuvastatin (10mg)	• AE, SAE
NK	n=40	2 weeks	(10mg)	
			Rosuvastatin (10mg) plus Placebo	
			Placebo plus placebo	
Krysiak 2012a <sup>134</sup>	Primary hypercholesterolaemia	RCT, double-	Ezetimibe (10mg)	Effectiveness
Poland	with	Multicentre	Simvastatin (40mg)	<ul> <li>LDL-c, HDL-c, total cholesterol, triglycerides</li> </ul>
NR	LDL-c: 130mg/dL Triglycerides: <150mg/dL	3 months	Simvastatin (40mg) plus ezetimibe (10mg)	Safety <ul> <li>Withdrawal, AE</li> </ul>
	n=104		Placebo	
Krysiak 2012b <sup>135</sup>	Hypercholesterolaemia	RCT, double- blind	Ezetimibe (10mg)	
Poland	LDL-c: 130mg/dL Triglycerides:	Multicentre	Simvastatin (40mg)	cholesterol, triglycerides
NR	<150mg/dL	3 months	Simvastatin (40mg) plus ezetimibe (10mg)	Safety
	n=178		(Tonig)	<ul> <li>Withdrawal, AE</li> </ul>
		DOT 1. 11	Placebo	
Kusters 2015 <sup>121</sup>	Familial hypercholesterolaemia or ponfamilial	blind	Ezetimibe (10mg)	<ul> <li>Effectiveness</li> <li>LDL-c, HDL-c, total</li> </ul>
d	hypercholesterolaemia	International, multicentre	Placebo	cholesterol, triglycerides
NCT00867165	LDL-c dependent on family history	3 months		Safety <ul> <li>Withdrawal, AE,</li> <li>SAE, TAE</li> </ul>
	Children			
	n=138			

Study; country; trial ID	Inclusion criteria; sample size	Design; setting; follow-up	Intervention; comparator	Effectiveness and safety outcomes
Liberopoulos 2013 <sup>142</sup> Greece NR Masana 2005 <sup>138</sup> NR NR	Primary hypercholesterolaemia LDL-c: >NCEP-ATP III Triglycerides: NR n=50 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	RCT, double- blind Single-centre 3 months RCT, double- blind, extension study <sup>180</sup> Multicentre 12 months	Simvastatin (10mg) plus ezetimibe (10mg) Simvastatin (40mg) Simvastatin (10, 20, 40, 80mg) plus ezetimibe (10mg) Simvastatin (10, 20, 40, 80mg) plus placebo	<ul> <li><i>Effectiveness</i></li> <li>LDL-c, HDL-c, total cholesterol, triglycerides</li> <li><i>Safety</i></li> <li>Withdrawal</li> <li><i>Effectiveness</i></li> <li>LDL-c, HDL-c, total cholesterol, triglycerides</li> <li><i>Safety</i></li> <li>Mortality, withdrawal, AE, SAE, TAE</li> </ul>
Melani 2003 <sup>133</sup> USA NCT00079638	n=433 Primary hypercholesterolaemia LDL-c: 155–251mg/dL Triglycerides: ≤354mg/dL n=538	RCT, double- blind Multicentre 3 months	Placebo Pravastatin (10, 20 or 40mg) Pravastatin (10, 20 or 40mg) plus ezetimibe (10mg)	<i>Effectiveness</i> • LDL-c, HDL-c, total cholesterol, triglycerides <i>Safety</i> • Mortality, withdrawal, AE, TAE
Moutzouri 2011 <sup>143</sup> Greece NR	Primary hypercholesterolaemia LDL-c: ≥NCEP–ATP III guidelines Triglycerides: <500mg/dL n=153	RCT, open-label Single-centre 3 months	Rosuvastatin (10mg) Simvastatin (40mg) Simvastatin (10mg) plus ezetimibe (10mg)	Effectiveness • LDL-c, HDL-c, total cholesterol, triglycerides
Ose 2007 <sup>139</sup> USA + 24 countries <sup>a</sup> Protocol 038-10	Primary hypercholesterolaemia LDL-c: 145–250mg/dL Triglycerides: ≤350mg/dL n=1104	RCT, double- blind, extension study <sup>127</sup> International, multicentre 14 weeks (26 weeks total)	Simvastatin (10, 20, 40 or 80mg) plus ezetimibe (10mg) Simvastatin (10, 20, 40 or 80mg)	<ul> <li>Effectiveness</li> <li>LDL-c, HDL-c, total cholesterol, triglycerides</li> <li>Safety</li> <li>Withdrawal, AE, SAE, TAE</li> </ul>

Study; country; trial ID	Inclusion criteria; sample size	Design; setting; follow-up	Intervention; comparator	Effectiveness and safety outcomes
Robinson 2014 <sup>109</sup> Europe, North America, Australia <sup>e</sup> NCT01763866	Primary hypercholesterolaemia LDL-c: ≥150mg/dL (no statin); 100mg/dL (low– moderate intensity statin); 80mg/dL (high intensity statin) Triglycerides: ≤400mg/dL	RCT, double- blind International, multicentre 3 months	Atorvastatin (10 or 80mg) plus ezetimibe (10mg) Atorvastatin (10 or 80mg) plus placebo	Effectiveness • LDL-c, HDL-c, total cholesterol, triglycerides Safety • Mortality, withdrawal, AE, SAE
Strony 2008 <sup>140</sup> USA NR	Primary hypercholesterolaemia LDL-c: 145–250mg/dl Triglycerides: <350mg/dL n=109	RCT, double- blind, extension study <sup>128</sup> Multicentre 12 months	Simvastatin (10, 20, 40 or 80mg) plus ezetimibe (10mg) Simvastatin (10, 20, 40 or 80mg) plus Placebo	Effectiveness • LDL-c, HDL-c, total cholesterol Safety • Mortality, withdrawal, AE, SAE, STAE, TAE
Sudhop 2002 <sup>168</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	Safety <ul> <li>Withdrawal, SAE</li> </ul>
Sudhop 2009 <sup>108</sup> NR NCT00652301	Hypercholesterolaemia LDL-c: 130–180mg/dL Triglycerides: <250mg/dL n=41	RCT, double- blind, cross-over Centres NR 6 months	Ezetimibe (10mg) Simvastatin (20mg) Simvastatin (20mg) plus Ezetimibe (10mg) Placebo	Safety <ul> <li>Mortality, withdrawal, STAE, TAE</li> </ul>
van der Graff 2008 <sup>122</sup> The Netherlands NCT00129402	Adolescents with familial hypercholesterolaemia LDL-c value based on genotype Triglycerides: ≤350mg/dL n=248	RCT, double- blind Multicentre 12 months	Simvastatin (10, 20 or 40mg) plus ezetimibe (10mg) Simvastatin (10, 20 or 40mg) plus placebo	Effectiveness • LDL-c, HDL-c, total cholesterol, triglycerides Safety • Mortality, withdrawal, AE

#### **Abbreviations**

AE = adverse event, HeFH = Heterozygous familial hypercholesterolaemia, HDL-c = high density lipoprotein-cholesterol, 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, SAE = serious adverse event, STAE = serious treatment-related adverse event, TAE = treatment-related adverse event.

#### <u>Notes</u>

**a** = Remaining countries not reported.

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

**c** = Belgium, Canada, Denmark, Korea, South Africa, Turkey, Taiwan and USA.

d = Canada, Columbia, France, Greece, Israel, Italy, Norway, Netherlands and USA.

e = Australia, Belgium, Canada Czech Republic, Denmark, France, Germany, Hong Kong, Hungary, Italy, Netherlands, Russia, Spain, Sweden, Switzerland, UK and 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.

## 15.3.2 Hypercholesterolaemia with ASCVD

# Table 98 Hypercholesterolaemia with ASCVD: characteristics of included RCTs assessing

Study; country; trial ID	Inclusion criteria; sample size	Design; setting; follow-up	Intervention; comparator	Safety outcomes
Averna 2010 <sup>186</sup> Italy NCT00423579	Primary hypercholesterolaemia with CHD LDL-c: 100–160mg/dL despite treatment Triglycerides: ≤350mg/dL n=120	RCT, double- blind Multicentre 6 weeks	Simvastatin (40mg) plus ezetimibe (10mg) Simvastatin (40mg) plus placebo	Safety • Withdrawal, AE, SAE, STAE, TAE
Ballantyne 2004a <sup>137</sup> USA NCT00525824	Primary hypercholesterolaemia with established (or at risk of) CHD LDL-c: 145–250mg/dL Triglycerides: ≤350mg/dL	RCT , double- blind Multicentre 12 months	Ezetimibe (10mg) plus Atorvastatin (10mg) Atorvastatin (10mg) plus Placebo	Effectiveness • LDL-c, HDL-c total cholesterol, triglycerides Safety • Withdrawal, AE, TAE
Ballantyne 2007 <sup>110</sup> Austria, Germany, Switzerland, South Africa, USA D3569C00006	H=240 Hypercholesterolaemia with CHD LDL-c: 160–250mg/dL Triglycerides: ≤400mg/dL n=469	RCT, open-label International, multicentre 6 weeks	Rosuvastatin (40mg) Rosuvastatin (40mg) plus ezetimibe (10mg)	Safety • Mortality, withdrawal, AE, SAE, STAE, TAE
Ballantyne 2019 <sup>147</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 3 months	Ezetimibe (10mg) Placebo	Effectiveness • LDL-c, total cholesterol, Safety • Withdrawal, AE, SAE, STAE, TAE Safety
Bardini 2010 <sup>171</sup> Italy	I ype 2 diabetes with CHD LDL-c: 100–160mg/dL Triglyceride:	RC1, double- blind	Simvastatin (20mg)	<ul> <li>Mortality, withdrawal, AE, SAE, TAE</li> </ul>

## clinical effectiveness and safety

Study; country; trial ID	Inclusion criteria; sample size	Design; setting; follow-up	Intervention; comparator	Safety outcomes
Protocol 04037	≤350mg/dL n=93	Multicentre 6 weeks	Simvastatin (20mg) plus ezetimibe (10mg)	
Barrios 2005 <sup>187</sup>	Hypercholesterolaemia with CHD	RCT, double- blind	Atorvastatin (20mg)	Safety <ul> <li>Withdrawal, AE,</li> <li>SAE, STAE, TAE</li> </ul>
Asia and Europe <sup>a</sup>	LDL-c: 100–160mg/dL Triglycerides: ≤350mg/dl	International, multicentre	Simvastatin (20mg) plus ezetimibe (10mg)	
	n=435	6 weeks		
Bays 2011 <sup>173</sup>	Hypercholesterolaemia with high risk of CHD or	RCT, double- blind	Rosuvastatin (40mg)	Safety • Mortality, withdrawal AE
America, Europe <sup>b</sup> NCT00783263	LDL-c : >NCEP-ATP III guidelines	International, multicentre	Rosuvastatin (40mg) plus ezetimibe (10mg)	SAE, STAE, TAE
	Triglycerides: ≤350mg/dL	6 weeks		
	n=440			
Bays 2013 <sup>172</sup> America and Europe °	Primary hypercholesterolaemia with high risk of CVD	RCT, double- blind	Atorvastatin (20mg) Atorvastatin (10mg)	<ul> <li>Safety</li> <li>Mortality, withdrawal, AE,</li> <li>SAE STAE TAE</li> </ul>
NCT01154036	LDL-c: 166–190md/dL Triglycerides: NR	International, multicentre	plus ezetimibe (10mg)	OAL, OTAL, TAL
	n=1547	6 weeks	Rosuvastatin (10mg)	
Bays 2015 <sup>148</sup>	Primary hypercholesterolaemia with high risk of CVD	RCT, double- blind	Atorvastatin (40mg)	Effectiveness <ul> <li>LDL-c</li> </ul>
Australia, America and Europe <sup>d</sup> NCT01730040	LDL-c: >70mg/dL high risk CVD; >100mg/dL	International, multicentre	Atorvastatin (20mg) plus ezetimibe (10mg)	Safety • Mortality, withdrawal, SAE, AF
	with diabetes/kidney disease despite therapy Triglycerides: NR	6 months	Rosuvastatin (40mg)	
	n=355			
Blagden 2007 <sup>174</sup>	Primary hypercholesterolaemia with CHD	RCT, double- blind	Atorvastatin (10mg) plus ezetimibe (10mg)	<ul> <li>Safety</li> <li>Mortality, withdrawal, AE,</li> </ul>
NR	LDL-c: 130–209mg/dL	Multicentre		SAE, STAE, TAE

Study; country; trial ID	Inclusion criteria; sample size	Design; setting; follow-up	Intervention; comparator	Safety outcomes
	Triglycerides: ≤368mg/dL n=148	6 weeks	Atorvastatin (10mg) plus Placebo	
Brohet 2005 <sup>124</sup>	Hypercholesterolemia with CHD	RCT, double- blind	Simvastatin (10 or 20mg)	Safety <ul> <li>Mortality,</li> </ul>
Europe <sup>e</sup> NR	LDL-c: 100–160mg/dL	International, multicentre	Simvastatin (10 or 20mg) plus ezetimibe (10mg)	SAE, STAE, TAE
	n=418	6 weeks		
Cannon 2015 <sup>52</sup> Australia, Europe, North and South	ACS LDL: >125mg/dL and 100mg/dL for patients	RCT, double- blind International,	Simvastatin (40mg) plus ezetimibe (10mg)	<ul> <li>Effectiveness</li> <li>LDL-c, HDL-c total cholesterol, triglycerides</li> <li>MACE</li> </ul>
America, Asia <sup>f</sup>	receiving and not receiving treatment	multicentre	Simvastatin (40mg) plus Placebo	Safety
NCT00202878		7 years		<ul> <li>Mortality, withdrawal, AE</li> </ul>
Opton and 0000175	11–10,114	DOT double	Desumentation (40, 00	Safaty
	with risk of CHD	blind	and 40mg)	<ul> <li>Mortality, withdrawal, AE,</li> </ul>
USA	LDL-c: 145–250mg/dL	Multicentre	Simvastatin (20, 40	SAE, TAE
Protocol 058	Triglycerides: ≤350mg/dL	6 weeks	or 80mg) plus ezetimibe (10mg)	
	n=2,959			
Chenot 2007 <sup>188</sup>	Acute MI	RCT, blinding NR	No drugs	Safety <ul> <li>Withdrawal, TAE</li> </ul>
Belgium	LDL-c: >90mg/dL Triglycerides: NR	Centres NR	Simvastatin (40mg)	
NR	n=60	1 week	Simvastatin (40mg) plus ezetimibe (10mg)	
Conard 2008 <sup>176</sup>	Hypercholesterolaemia with coronary artery	RCT, double- blind	Atorvastatin (40mg)	Safety <ul> <li>Mortality,</li> </ul>
Austria, Canada, Costa Rica	disease	International,	Atorvastatin (20mg)	SAE, STAE, TAE
USA	LDL-c: 100–160mg/dL Triglyceride ≤350mg/dL	multicentre	(10mg)	
Protocol 079	n=196	6 weeks		
Cruz-Fernandez 2005 <sup>177</sup>	Hypercholesterolaemia and CHD	RCT, double- blind	Atorvastatin (10 or 20mg) plus ezetimibe (10mg)	<ul> <li>Safety</li> <li>Mortality, withdrawal, AE,</li> </ul>
	LDL-c: 101–160mg/dL	International, multicentre		SAE, STAE, TAE

Study; country; trial ID	Inclusion criteria; sample size	Design; setting; follow-up	Intervention; comparator	Safety outcomes
Europe, North America <sup>g</sup>	Triglycerides: ≤350mg/dL	6 weeks	Atorvastatin (10 or 20mg) plus placebo	
Protocol 803/4	n=450			
Deharo 2014 <sup>189</sup>	ACS	RCT, open-label	Rosuvastatin (20mg)	<ul><li>Safety</li><li>Withdrawal, AE</li></ul>
France	LDL-c: ≥100mg/dL Triglycerides: NR	Single-centre	Simvastatin (40mg) plus ezetimibe	
SAFE-SE	n=128	4 weeks	(10mg)	
Farnier 2005a <sup>179</sup>	Hypercholesterolaemia with CHD	RCT, double- blind	Simvastatin (10 or 20mg) plus ezetimibe	Safety • Mortality,
Asia, Europe <sup>h</sup>	LDL-c: 100–162mg/dL	International,	(10mg)	withdrawal, AE, SAE, STAE, TAE
Protocol 802	Triglycerides: ≤354mg/dL	multicentre	Simvastatin (10 or 20mg) plus placebo	
	n=372	6 weeks		
Farnier 2009 <sup>178</sup>	Hypercholesterolaemia with high risk of CVD	RCT, double- blind	Rosuvastatin (20mg)	Safety <ul> <li>Mortality,</li> </ul>
Europe <sup>i</sup> NCT00479713	LDL-c: 100–190mg/dL Triglycerides:	International, multicentre	Simvastatin (40mg) plus ezetimibe (10mg)	Withdrawal, AE, SAE, STAE, TAE
	-330mg/dL	8 weeks		
	n=618			
Farnier 2016 <sup>149 j</sup>	Hypercholesterolaemia with high risk of CVD	RCT, double- blind	Rosuvastatin (20 or 40mg)	<ul> <li>Effectiveness</li> <li>LDL-c, HDL-c, triglycerides</li> </ul>
Australia, Europe, North America	LDL-c: >100mg/dL (high risk)	International, multicentre	Rosuvastatin (10 or 20mg) plus ezetimibe	Safety • Mortality.
NCT01730053	>70mg/dL (very high risk)	6 months	(10mg)	withdrawal, AE, SAE
	Triglycerides: ≤350mg/dL			
	n=202			
Feldman 2004 <sup>150</sup>	CHD or CHD risk equivalent	RCT, double- blind	Simvastatin (10mg)	Effectiveness <ul> <li>LDL-c, HDL-c total</li> </ul>
USA	LDL-c: ≥130mg/dL	Multicentre	Simvastatin (10, 20 or 40mg) plus	cholesterol, triglycerides
NR	Triglycerides: ≤350mg/dL	6 months	ezetimibe (10mg)	• Withdrawal, AE,
	n=710			JAE, JIAE, IAE

Study; country; trial ID	Inclusion criteria; sample size	Design; setting; follow-up	Intervention; comparator	Safety outcomes
Foody 2010 <sup>157</sup>	Hypercholesterolaemia with high risk of CHD	RCT, double- blind	Atorvastatin (10, 20 or 40mg)	<ul> <li>Safety</li> <li>Mortality, withdrawal, AE,</li> </ul>
NCT00535405	LDL-c: ≥130mg/dL Triglycerides: ≤350mg/dL	Multicentre 3 months	Simvastatin (20 or 40mg) plus ezetimibe (10mg)	SAE, STAE, TAE
	n=1289			
Gagne 2002 <sup>180</sup> NR NR	Primary hypercholesterolaemia with/without CHD LDL-c: ≥160mg/dL + 1	RCT, double- blind Multicentre	Statin plus ezetimibe (10mg) Statin plus placebo <sup>k</sup>	<ul> <li>Safety</li> <li>Mortality, withdrawal, AE, SAE, STAE</li> </ul>
	or LDL-c: ≥130mg/dL + 2 risk factors or LDL-c: ≥100mg/dL + coronary heart disease Triglycerides: NR n=769	6 weeks		
Hing Ling 2012 <sup>181</sup>	Hypercholesterolaemia	RCT, double-	Atorvastatin (40mg)	Safety
Asia, Europe, South America <sup>I</sup> NCT00782184	with high risk of CHD LDL-c: 100–160mg/dL Triglycerides: ≤400mg/dL	blind International, multicentre 6 weeks	Simvastatin (20mg) plus ezetimibe (10mg)	<ul> <li>Mortality, withdrawal, AE, SAE, TAE</li> </ul>
	n=250			
Hougaard 2017 <sup>151</sup> Denmark	ST-segment elevation MI LDL-c: NR	RCT, double- blind Single-centre	Atorvastatin (80mg) plus ezetimibe (10mg)	<ul> <li><i>Effectiveness</i></li> <li>LDL-c, HDL-c, total cholesterol</li> <li>Vascular damage</li> </ul>
NCT01385631	Triglycerides: NR n=87	12 months	Atorvastatin (80mg) plus Placebo	Safety • Withdrawal, TAE
Jackowska 2019 <sup>158</sup> Poland	Recent MI, percutaneous coronary intervention or coronary artery bypass	RCT, double- blind Single-centre	Atorvastatin (10mg) plus ezetimibe (10mg)	Effectiveness • LDL-c
NR	LDL-c : >70mg/dL Triglycerides: NR	6 months	Atorvastatin (40mg)	

Study; country; trial ID	Inclusion criteria; sample size	Design; setting; follow-up	Intervention; comparator	Safety outcomes
	n=61			
Kouvelos 2013 <sup>144</sup>	Elective vascular surgery	RCT, blinding NR	Rosuvastatin (10mg)	Effectiveness <ul> <li>LDL-c, HDL-c total</li> </ul>
Greece	LDL-c: NR	Centres NR	Rosuvastatin (10mg) plus ezetimibe	MACE
NR	Triglycerides: NR	12 months	(rong)	<ul> <li>Mortality, withdrawal, TAE</li> </ul>
	n=262			0.1.1
Landray 2006 <sup>161</sup>	Chronic kidney disease	RCT, double- blind	Simvastatin (20mg) plus ezetimibe (10mg)	<ul> <li>Mortality, withdrawal. SAE.</li> </ul>
UK	LDL-c: NR Triglycerides: NR	Multicentre	Cimunatatia (20mm)	STAE
NR	n=203	6 months	plus placebo	
Leiter 2004 <sup>182</sup>	Hypercholesterolaemia and CHD or CHD risk	RCT, double- blind	Atorvastatin (40mg) plus Ezetimibe	Safety <ul> <li>Mortality,</li> <li>withdrawal AE</li> </ul>
Canada, USA	factors with >20% CHD 10 years)	International, multicentre	(Tomg)	SAE, STAE, TAE
NCT00276484	L DI · 70-160ma/dl	6 weeks	Atorvastatin (80mg)	
	Triglycerides: ≥350mg/dL			
	n=579			
McCormack 2010 <sup>190</sup>	CVD or high-risk CVD	RCT, double- blind	Atorvastatin (40mg)	● Withdrawal, AE,
UK NCT00462748	LDL-c: 77–162mg/dL Triglycerides: <328mg/dl	Multicentre	Rosuvastatin (5 or 10mg)	SAE, TAE
	n=786	6 weeks	Simvastatin (40mg) plus ezetimibe (10mg)	
Nicholls 2017 <sup>153</sup>	ASCVD with/without diabetes	RCT, double- blind	Atorvastatin (40mg)	Effectiveness <ul> <li>LDL-c, HDL-c</li> </ul>
USA	LDL-c: ≥70ma/dL	Multicentre	Atorvastatin (80mg)	Safety Withdrawal
NCT02227784	Triglycerides: ≤400mg/dL	3 months	Atorvastatin (40mg) plus ezetimibe (10mg)	- williolawai
	n=366			
Ostad 2009 <sup>183</sup>	Coronary artery disease	RCT, double- blind	Atorvastatin (80mg)	<ul> <li>Safety</li> <li>Mortality, withdrawal</li> </ul>
Germany	LDL-c: ≥100mg/dL	Single-centre		withdrawai

Study; country; trial ID	Inclusion criteria; sample size	Design; setting; follow-up	Intervention; comparator	Safety outcomes
ISRCTN34110682	Triglycerides: NR n=58	8 weeks	Atorvastatin (10mg) plus ezetimibe (10mg)	
Patel 2006 <sup>184</sup> UK Protocol P00680	Hypercholesterolaemia and CHD LDL-c: ≥127mg/dL Triglycerides: ≤350mg/dL n=153	RCT, double- blind Multicentre 6 weeks	Simvastatin (20mg) plus ezetimibe (10mg) Simvastatin (20mg) plus placebo	Safety • Mortality, withdrawal, AE, SAE, TAE
Reckless 2008 <sup>111</sup> Asia, Europe <sup>m</sup> NCT00132717	Hospitalised for coronary event LDL-c: NR Triglycerides: ≤350mg/dL n=424	RCT, open-label International, multicentre 3 months	Double Statin dose Simvastatin (40mg) plus ezetimibe (10mg)	Effectiveness • LDL-c, HDL-c, total cholesterol, triglycerides Safety • Mortality, withdrawal, AE, SAE, STAE, TAE
Robinson 2009 <sup>185</sup> USA NCT00409773	Hypercholesterolaemia at risk of CHD with metabolic syndrome LDL-c: ≥70mg/dL with ASCVD; ≥100mg/dL without ASCVD Triglycerides: NR n=1143	RCT, double- blind Multicentre 6 weeks	Atorvastatin (10mg) Atorvastatin (20mg) Atorvastatin (40mg) Simvastatin (20mg) plus ezetimibe (10mg) Simvastatin (40mg) plus ezetimibe (10mg)	Safety • Mortality, withdrawal, AE, SAE, STAE, TAE
Roeters van Lennep 2008 <sup>154</sup> The Netherlands EASEGO	CHD with/without Type 2 diabetes LDL-c: 96–193mg/dL despite treatment Triglycerides: <350mg/dL n=367	RCT, open-label Multicentre 14 weeks	Double Statin dose Simvastatin (20mg) plus ezetimibe (10mg)	<ul> <li>Effectiveness</li> <li>LDL-c, HDL-c total cholesterol, triglycerides</li> <li>Safety</li> <li>Mortality, withdrawal, AE, SAE, TAE</li> </ul>
Settergren 2008 <sup>191</sup> Sweden NR	Coronary artery disease, dysglycemia LDL-c: NR Triglycerides: NR	RCT, double- blind Single-centre 6 weeks	Simvastatin (10mg) plus ezetimibe (10mg) Simvastatin (80mg) plus placebo	Safety • Mortality

Study; country; trial ID	Inclusion criteria; sample size	Design; setting; follow-up	Intervention; comparator	Safety outcomes
	n=23			
Stein 2004 <sup>155</sup>	Primary HeFH with CHD or at high risk of CHD	RCT, double- blind	Atorvastatin (10mg) plus ezetimibe (10mg)	<i>Effectiveness</i> • LDL-c, HDL-c, total cholesterol,
NR	l DI -c: ≥130ma/dL	International, multicentre	Atorvastatin (20mg)	triglycerides
NR	Triglycerides: NR	14 weeks		<ul> <li>Mortality, withdrawal, AE, SAE, STAE, TAE</li> </ul>
Stojakovic 2010 <sup>159</sup>	Hypercholesterolaemia with a high-risk of CHD	RCT, single- blind	Fluvastatin (80mg)	Effectiveness • LDL-c, HDL-c, total
Germany	LDL-c: 100–160ma/dL	Single-centre	Fluvastatin (80mg) plus ezetimibe	cholesterol, triglycerides
NCT00814723	Triglycerides: NR	3 months	(10mg)	Safety • Withdrawal
	n=84			
West 2011 <sup>145</sup>	Peripheral artery disease, ABI 0.4–0.9	RCT, double- blind	Simvastatin (40mg)	Effectiveness <ul> <li>LDL-c, HDL-c, total</li> </ul>
USA	LDL-c: NR	Single-centre	Simvastatin (40mg) plus ezetimibe	triglycerides • MACE
NCT00587678	Triglycerides: NR	6 months	(10mg)	Vascular damage
	n=87			<ul> <li>Mortality, withdrawal</li> </ul>
Zieve 2010 <sup>156</sup>	Hypercholesterolaemia at high-risk of CHD	RCT, double- blind	Atorvastatin (20mg titrated to 40mg)	Effectiveness LDL-c, HDL-c, total
America and Europe n	LDL-c: 70–160mg/dL	International, multicentre	Atorvastatin (10mg)	triglycerides
NC100418834	established CHD; 100– 190mg/dL high-risk of CHD	3 months	(10mg)	<ul> <li>Safety</li> <li>Mortality,</li> <li>withdrawal AE</li> </ul>
	Triglycerides: ≤350mg/dL			SAE, STAE, TAE
	Patients ≥65 years			
	n=1053			
Zinellu 2012 <sup>160</sup>	Chronic kidney disease	RCT, double- blind	Simvastatin (40mg)	<ul> <li><i>Ettectiveness</i></li> <li>LDL-c, HDL-c, total cholesterol</li> </ul>
Italy	LDL-c: >100mg/dL Triglycerides: NR	Single-centre	Simvastatin (20mg) plus ezetimibe	triglycerides
NCT00861731		12 months	(TUMG)	
Study; country; trial ID	Inclusion criteria; sample size	Design; setting; follow-up	Intervention; comparator	Safety outcomes
-------------------------------	-------------------------------------------------------------------------------	-------------------------------------------------------------------	--------------------------------------------------------------------------------------	---------------------------------------------------------------------------------------------------------------
			Simvastatin (40mg) plus ezetimibe (10mg)	
Secondary analyses of	Cannon 2015 <sup>52</sup>	·		•
Bach 2019 <sup>163</sup>	ACS Patients stratified by age <65, 65–74 and ≥75. Also <75 and ≥75.	RCT, double- blind International, multicentre	Simvastatin (40mg) plus ezetimibe (10mg) Simvastatin (40mg)	<ul> <li>Effectiveness</li> <li>LDL-c, HDL-c, total cholesterol, triglycerides</li> <li>MACE</li> </ul>
			plus placebo	
	n=18,114	7 years		
Bohula 2017 <sup>162</sup>	ACS Patients stratified into low, intermediate and high-risk groups	RCT, double- blind International, multicentre	Simvastatin (40mg) plus ezetimibe (10mg) Simvastatin (40mg)	<ul> <li>Effectiveness</li> <li>LDL-c, HDL-c total cholesterol, triglycerides</li> <li>MACE</li> </ul>
			plus placebo	
	n=18,114	7 years		
Giugliano 2018 <sup>116</sup>	ACS Patients stratified by diabetes status n=18,114	RCT, double- blind International, multicentre 7 years	Simvastatin (40mg) plus ezetimibe (10mg) Simvastatin (40mg) plus placebo	<ul> <li><i>Effectiveness</i></li> <li>LDL-c, HDL-c total cholesterol, triglycerides</li> <li>MACE</li> </ul>

ACS = acute coronary syndrome, AE = adverse event, ASCVD = atherosclerotic cardiovascular disease, CHD = coronary heart disease, CVD = cardiovascular disease, HeFH = heterozygous familial hypercholesterolaemia, LDL-c = low density lipoprotein-cholesterol, mg = milligrams, MI = myocardial infarction, n = number of participants, NCEP-ATP = national cholesterol education adult treatment panel, NR = not reported, RCT = randomised controlled trial, SAE = serious adverse event, STAE = serious treatment-related adverse event, TAE = treatment-related adverse event.

## Notes

**a** = Estonia, France, Latvia, The Netherlands, Slovenia, Spain, Taiwan.

b = Canada, Columbia, Croatia, Denmark, Finland, Hungary, Peru, Poland, Puerto Rico, USA.

**c** = Argentina, Belgium, Bulgaria, Canada, Chile, Columbia, Croatia, Czech Republic, Denmark, Estonia, Finland, France, Germany, Hungary, Israel, Italy, Lithuania, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, the Netherlands, Turkey, United Kingdom and USA.

d = Australia, Canada, France, Germany, Italy, Mexico, Spain, UK, USA.

e = Belgium, Germany, Greece, Hungary, Israel, Norway, Portugal, Romania, Slovenia, Sweden, Switzerland and the Netherlands.

**f** = Argentina, Australia, Austria, Belgium, Brazil, Canada, Chile, Colombia, Czech Republic, Denmark, Ecuador, Estonia, Finland, France, Germany, Hong Kong, Hungary, India, Israel, Italy, Netherlands, Malaysia, NZ, Norway, Peru, Poland, Portugal, South Africa, Singapore, Switzerland, Slovakia, South Korea, Spain, Sweden, Taiwan, Turkey, Ukraine, UK and USA. **g** = Canada, Czech Republic, Germany, Greece, Hungary, Italy, Norway, Spain, the Netherlands, 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 = Australia, Canada, Germany, Italy, Mexico, Spain, UK and USA.

**k** = Statins include: Simvastatin, Atorvastatin or another Statin.

I = Costa Rica, Estonia, Guatemala, Hungary, Israel, Latvia, Malaysia, Peru, Poland, Romania and Spain.

m = Australia, Austria, Belgium, Chile, Croatia, France, Germany, Hong Kong, Italy, Jordan, Malaysia, Singapore, Switzerland, UK.

n = 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.</li>

# 15.3.3 Hyperlipidaemia without ASCVD

# Table 99 Hyperlipidaemia without ASCVD: characteristics of included RCTs assessing clinical

Study; country; trial ID	Inclusion criteria; sample size	Design; setting; follow-up	Intervention; comparator	Safety outcomes
Ansquer 2009 <sup>166</sup> Belgium, Germany, France NCT00349284	Type IIb dyslipidaemia with metabolic syndrome (NCEP–ATP III definition) LDL-c: ≥160mg/dL Triglycerides: 150– 405mg/dL n=60	RCT, double-blind International, multicentre 3 months	Ezetimibe (10mg) Fenofibrate (145mg) Fenofibrate (145mg) plus ezetimibe (10mg)	<ul> <li>Effectiveness</li> <li>LDL-c, HDL-c, total cholesterol, triglycerides</li> <li>Safety</li> <li>Mortality, withdrawal, AE, SAE, TAE</li> </ul>
Drouin-Chartier 2016 <sup>164</sup> Canada NCT01849068	Dyslipidaemia LDL-c: NR Triglycerides: 114– 620mg/dL n=25	RCT, cross-over, double blind Single-centre 3 months	Ezetimibe (10mg) Placebo	<i>Effectiveness</i> • LDL-c, HDL-c, total cholesterol, triglycerides
Farnier 2005b <sup>165</sup> NR NCT00092573	Mixed hyperlipidaemia LDL-c: 130– 220mg/dL Triglycerides: 203– 504mg/dL n=559	RCT, double-blind International, multicentre 3 months	Ezetimibe (10mg) Fenofibrate (160mg) Fenofibrate (160mg) plus ezetimibe (10mg) Placebo	<ul> <li><i>Effectiveness</i></li> <li>LDL-c, HDL-c, total cholesterol, triglycerides</li> <li><i>Safety</i></li> <li>Mortality, withdrawal, AE, SAE, STAE, TAE</li> </ul>
McKenney 2006 <sup>152</sup> NR NCT00092573	Mixed hyperlipidaemia LDL-c: 130– 220mg/dL Triglycerides: 200- 500mg/dL n=576	RCT, double-blind, extension study International, multicentre 12 months	Fenofibrate (160mg) plus ezetimibe (10 mg) Fenofibrate (160mg)	<ul> <li><i>Effectiveness</i></li> <li>LDL-c, HDL-c, total cholesterol, triglycerides</li> <li><i>Safety</i></li> <li>Mortality, withdrawal, AE, SAE, STAE, TAE</li> </ul>

# effectiveness and safety

Study; country; trial ID	Inclusion criteria; sample size	Design; setting; follow-up	Intervention; comparator	Safety outcomes
Stein 2008 <sup>125</sup>	Dyslipidaemia, muscle-related side	RCT, double-blind	Ezetimibe (10mg)	<ul><li><i>Effectiveness</i></li><li>LDL-c, HDL-c, total</li></ul>
Europe and North America <sup>a</sup>	effects from statin	International, multicentre	Fluvastatin (80mg) plus ezetimibe	cholesterol, triglycerides
NR	LDL-c: NR Triglycerides: NR	3 months	(10mg)	Safety • Withdrawal AF
	n=625		Fluvastatin (80mg)	STAE, TAE

 $\overline{AE}$  = adverse event, LDL-c = low density lipoprotein-cholesterol, mg = milligrams, n = number of participants, NR = not reported, RCT = randomised controlled trial, SAE = serious adverse event, STAE = serious treatment-related adverse event, TAE = treatment-related adverse event.

#### <u>Notes</u>

**a** = Germany, Greece, Norway, Russia, Turkey and USA.

# 15.4 Appendix D: Supplementary and Sub-group Analysis Results

# 15.4.1 Hypercholesterolaemia without ASCVD

#### Ezetimibe vs placebo

#### Number of patients achieving LDL-c goals



#### Figure 82 Forest plot indicating the risk ratio in the number of patients below 130mg/dL of LDL-

#### c for ezetimibe compared to placebo (3 months)

#### **Abbreviations**

CI = confidence interval, LDL-c = low density lipoprotein-cholesterol, mg/dL = milligrams per decilitre.

	Ezetim	ibe	Place	bo		Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl		M-H, Random, 95% Cl
Bays 2004	0	148	0	146		Not estimable		
Koren 2014	1	77	0	78	100.0%	3.04 [0.13, 73.45]		
Total (95% CI)		225		224	100.0%	3.04 [0.13, 73.45]		
Total events	1		0					
Heterogeneity: Not ap Test for overall effect:	plicable Z = 0.68 (	(P = 0.4	19)				L.01	0.1 1 10 100 Favours Placebo Favours Ezetimibe

### Figure 83 Forest plot indicating the risk ratio in the number of patients below 70mg/dL of LDL-c

#### for ezetimibe compared to placebo (3 months)

#### **Abbreviations**

CI = confidence interval, LDL-c = low density lipoprotein-cholesterol, mg/dL = milligrams per decilitre.

	Ezetim	ibe	Place	Placebo		Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl		M-H, Random, 95% Cl
Davidson 2002	15	59	7	69	25.1%	2.51 [1.10, 5.73]		_ <b>_</b>
Kerzner 2003	34	72	9	64	40.2%	3.36 [1.75, 6.45]		<b></b> ∎
Melani 2003	28	63	8	62	34.7%	3.44 [1.71, 6.96]		
Total (95% CI)		194		195	100.0%	3.15 [2.08, 4.76]		•
Total events	77		24					
Heterogeneity: Tau <sup>2</sup> =	0.00; Ch	i <sup>z</sup> = 0.3!	9, df = 2 (	P = 0.8	2); l² = 09	6		
Test for overall effect:	Z = 5.43 (	(P < 0.0	0001)				0.01	Favours Placebo Favours Ezetimibe

#### Figure 84 Forest plot indicating the risk ratio in the number of patients below NCEP-ATP goals

#### for ezetimibe compared to placebo (3 months)

#### **Abbreviations**

**CI** = confidence interval, **LDL-c** = low density lipoprotein-cholesterol, **NCEP–ATP** = National Cholesterol Education Program-Adult Treatment Panel.

# Ezetimibe vs statin

•			-	-							
	Ezetim	ibe	Stat	in		Risk Ratio		Risk	Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl		M-H, Rand	om, 95% Cl		
Bays 2004	40	147	480	606	52.9%	0.34 [0.26, 0.45]					
Goldberg 2004	31	88	283	344	47.1%	0.43 [0.32, 0.57]		-			
Total (95% CI)		235		950	100.0%	0.38 [0.31, 0.47]		•			
Total events	71		763								
Heterogeneity: Tau <sup>2</sup> = Test for overall effect: .	0.00; Chi Z = 8.72 (	i² = 1.2 (P ≺ 0.0	2, df = 1 ( )0001)	P = 0.2	7); I² = 18	%	0.01	0.1 Favours Statin	1 10 Favours Eze	timibe	100

# Number of patients achieving LDL-c goals

# Figure 85 Forest plot indicating the risk ratio in the number of patients below 130mg/dL of

## LDL-c for ezetimibe compared to statin (3 months)

#### **Abbreviations**

CI = confidence interval, LDL-c = low density lipoprotein-cholesterol, mg/dL = milligrams per decilitre.

	Ezetim	ibe	Stati	in		Risk Ratio		Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl		M-H, Random, 95% Cl	
Davidson 2002	15	59	167	261	48.3%	0.40 [0.25, 0.62]			
Melani 2003	28	63	97	203	51.7%	0.93 [0.68, 1.27]		+	
Total (95% CI) Total events	43	122	264	464	100.0%	0.62 [0.26, 1.47]		-	
Heterogeneity: Tau <sup>2</sup> = Test for overall effect:	0.36; Chi Z = 1.09 (	² = 10.: P = 0.2	22, df = 1 ?8)	(P = 0.	001); I² =	90%	0.01	0.1 1 Favours Statin Favours E	10 100 zetimibe

# Figure 86 Forest plot indicating the risk ratio in the number of patients below NCEP-ATP goals

## for ezetimibe compared to statin (3 months)

#### **Abbreviations**

**CI** = confidence interval, **LDL-c** = low density lipoprotein-cholesterol, **NCEP-ATP** = National Cholesterol Education Program-Adult Treatment Panel.

# Ezetimibe plus statins vs statins

### Number of patients achieving LDL-c goals

Study or Subgroup	Ezetimibe + s Events	statins Total	Statir Events	ns Total	Weight	Risk Ratio M-H, Random, 95% Cl			Risk M-H, Rand	Ratio om, 95%	CI		
Bays 2004	556	603	480	606	50.2%	1.16 [1.11, 1.22]							
Goldberg 2004	321	351	283	644	49.8%	2.08 [1.90, 2.28]				•	ł –		
Total (95% CI)		954		1250	100.0%	1.55 [0.84, 2.86]			-				
Total events	877		763										
Heterogeneity: Tau² =	= 0.19; Chi <sup>z</sup> = 13	37.56, df:	= 1 (P < 0	).00001	); <b>I</b> ² = 999	Х.		02	0.5			+	10
Test for overall effect:	Z = 1.42 (P = 0	.16)					0.1	0.2	Favours Statins	Favours	Ezetimibe	e+sta	atin

## Figure 87 Forest plot indicating the risk ratio in the number of patients below 130mg/dL of

#### LDL-c for ezetimibe plus statins compared to statins (12 months)

#### **Abbreviations**

CI = confidence interval, LDL-c = low density lipoprotein-cholesterol, mg/dL = milligrams per decilitre.

	Ezetimibe+s	tatins	Stati	ns		Risk Ratio			Risk	Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl			M-H, Rand	om, 95% Cl		
Alvarez-Sala 2008	32	37	26	39	16.3%	1.30 [1.00, 1.68]						
Ballantyne 2003	215	252	180	244	28.1%	1.16 [1.06, 1.27]				-		
Davidson 2002	207	268	167	261	26.6%	1.21 [1.08, 1.35]				-		
Masana 2005	140	253	12	53	6.7%	2.44 [1.47, 4.07]						
Melani 2003	144	204	97	203	22.3%	1.48 [1.25, 1.75]						
Total (95% CI)		1014		800	100.0%	1.32 [1.14, 1.54]				•		
Total events	738		482									
Heterogeneity: Tau <sup>2</sup> =	0.02; Chi <sup>2</sup> = 1	5.85, df=	= 4 (P = 0	i.003); I	<b>≈</b> =75%			- <del> </del> -	0.5			10
Test for overall effect:	Z = 3.69 (P = 0	0.0002)					0.1	0.2	Favours Statins	Favours Eze	etimibe+sta	atins

## Figure 88 Forest plot indicating the risk ratio in the number of patients below NCEP-ATP goals

#### for ezetimibe plus statins compared to statins (3 months)

# **Abbreviations**

**CI** = confidence interval, **LDL-c** = low density lipoprotein-cholesterol, **NCEP-ATP** = National Cholesterol Education Program-Adult Treatment Panel.

# 15.4.2 Hypercholesterolaemia with ASCVD

#### Ezetimibe plus statins vs statins

#### Number of patients achieving LDL-c goals

	Ezetimibe+s	tatins	Stati	15		Risk Ratio			Risk	Ratio			
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl			M-H, Rand	lom, 95% (	CI		
Ballantyne 2019	36	86	7	41	8.2%	2.45 [1.19, 5.03]				——	•	-	
Foody 2010	213	236	142	242	20.6%	1.54 [1.37, 1.72]							
Reckless 2008	174	204	144	199	20.7%	1.18 [1.06, 1.31]				-			
Roeters Van Lennep 2008	119	178	49	189	17.6%	2.58 [1.98, 3.35]					-		
Stein 2004	67	305	22	316	13.0%	3.16 [2.00, 4.97]					-	-	
Zieve 2010	225	516	164	509	19.9%	1.35 [1.15, 1.59]							
Total (95% CI)		1525		1496	100.0%	1.77 [1.37, 2.30]					•		
Total events	834		528										
Heterogeneity: Tau <sup>2</sup> = 0.08; C	Chi² = 56.06, d	f= 5 (P <	0.00001	); I <sup>z</sup> = 9	1%			02	0.5		1	<u> </u>	10
Test for overall effect: Z = 4.2	9 (P < 0.0001)						0.1	0.2	Favours Statins	Favours	Ezetimibe	+stati	ins

#### Figure 89 Forest plot indicating the risk ratio in the number of patients below 130mg/dL of

#### LDL-c for ezetimibe plus statins compared to statins (3 months)

## **Abbreviations**

**CI** = confidence interval, **LDL-c** = low density lipoprotein-cholesterol, **mg/dL** = milligrams per decilitre.

	Ezetimibe+s	tatins	Stati	ns		Risk Ratio			Risk	Ratio			
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl			M-H, Rand	om, 95% (	CI		
Bays 2015	36	53	18	53	12.8%	2.00 [1.32, 3.04]							
Feldman 2004	90	108	112	246	87.2%	1.83 [1.56, 2.15]					-		
Total (95% CI)	400	161	400	299	100.0%	1.85 [1.59, 2.15]				•			
l otal events	126		130										
Heterogeneity: Tau <sup>2</sup> =	$= 0.00; Chi^2 = 0.00; Chi^2 $	.16, df =	1 (P = 0.0)	69); I* =	0%		0.1	0.2	0.5	1 2		5	10
Test for overall effect:	Z = 8.05 (P < 0	J.UUUUU1)							Favours Statins	Favours	Ezetimibe	+sta	tins

#### Figure 90 Forest plot indicating the risk ratio in the number of patients below 100mg/dL of

## LDL-c for ezetimibe plus statins compared to statins (12 months)

#### **Abbreviations**

CI = confidence interval, LDL-c = low density lipoprotein-cholesterol, mg/dL = milligrams per decilitre.

	Ezetimibe+s	tatins	Stati	15		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% CI
Ballantyne 2019	9	86	0	41	5.4%	9.17 [0.55, 153.86]	
Foody 2010	143	236	83	242	25.4%	1.77 [1.44, 2.16]	+
Reckless 2008	161	204	22	199	24.0%	7.14 [4.78, 10.65]	
Roeters Van Lennep 2008	53	178	6	189	19.6%	9.38 [4.13, 21.27]	
Zieve 2010	255	516	200	509	25.6%	1.26 [1.09, 1.45]	-
Total (95% CI)		1220		1180	100.0%	3.43 [1.65, 7.14]	◆
Total events	621		311				
Heterogeneity: Tau <sup>2</sup> = 0.54; C	≿hi <b>²</b> = 96.62, dt	f=4 (P <	0.00001	); l <sup>2</sup> = 9	6%		
Test for overall effect: Z = 3.2	9 (P = 0.0010)						Favours Statins Favours Ezetimibe+statins

#### Figure 91 Forest plot indicating the risk ratio in the number of patients below 70mg/dL of LDL-

#### c for ezetimibe plus statins compared to statins (3 months)

#### **Abbreviations**

CI = confidence interval, LDL-c = low density lipoprotein-cholesterol, mg/dL = milligrams per decilitre.

Study or Subgroup	Ezetimibe+s Events	tatins Total	Statir Events	ns Total	Weight	Risk Ratio M-H, Random, 95% Cl			Risk M-H, Rand	Ratio om, 95% (	21		
Bays 2015	27	53	8	53	47.1%	3.38 [1.69, 6.74]				<u> </u>			
Farnier 2016	20	47	15	48	52.9%	1.36 [0.80, 2.33]			_		-		
Total (95% CI)		100		101	100.0%	2.09 [0.85, 5.14]			-			-	
Total events	47		23										
Heterogeneity: Tau <sup>2</sup> = Test for overall effect:	: 0.33; Chi² = 4 Z = 1.60 (P = 0	.27, df= 0.11)	1 (P = 0.0	04); I² =	77%		0.1	0.2	0.5 Favours Statins	1 2 Favours	Ezetimibe	5 +staf	10 tins

# Figure 92 Forest plot indicating the risk ratio in the number of patients below 70mg/dL of LDL-c

# for ezetimibe plus statins compared to statins (12 months)

# Abbreviations

**CI** = confidence interval, **LDL-c** = low density lipoprotein-cholesterol, **mg/dL** = milligrams per decilitre.

# 15.4.3 Sub-groups

Hypercholesterolaemia without ASCVD, ezetimibe vs placebo: effectiveness outcome in children

Table 100 Ezetimibe compared to placebo: absolute and percentage change in lipid and

Outcome	Follow-up	Ezetimibe mean ± SD n=85	Placebo mean ± SD n=42	Mean difference (95% CI)	p value			
LDL-c								
Absolute change	Baseline	229 ± 46mg/dL	222 ± 45mg/dL	7.0mg/dL (-10.5, 24.1)	NR			
	3 months	169 ± 37mg/dL	225 ± 53mg/dL	-56.0mg/dL (-72.0, -40.0)	NR			
Percentage change	3 months	-28.0 ± 14.7%	-0.95 ± 13.5%	-27.1% (-32.2, -21.9)	<0.001			
HDL-c								
Absolute change	Baseline	$50 \pm 9$ mg/dL	50 ± 12mg/dL	0.0mg/dL (-3.8, 3.8)	NR			
	3 months	51 ± 11mg/dL	51 ± 12mg/dL	0.0mg/dL (-4.2, 4.2)	NR			
Percentage change	3 months	2.0 ± 19.6%	1.0 ± 18.8	1.0% (-6.2, 8.2)	0.81			
Total cholesterol								
Absolute change	Baseline	295 ± 48mg/dL	290 ± 44mg/dL	5.0mg/dL (-12.4, 22.4)	NR			
	3 months	236 ± 39mg/dL	295 ± 55mg/dL	-59.0mg/dL (-75.8, -42.2)	NR			
Percentage change	3 months	-12.0 ± 12.2%	0.2 ± 10.3%	-11.80% (-16.5, -7.9)	<0.001			
Triglycerides <sup>a</sup>								
Absolute change	Baseline	82 ± 30mg/dL	92 ± 61mg/dL	10.0mg/dL (-25.9, 5.9)	NR			
	3 months	80 ± 40mg/dL	100 ± 64mg/dL	-20.0mg/dL (-38.4, -1.6)	NR			
Percentage change	3 months	-6.0 ± 34.3%	8.0 ± 37.7%	-14.0% (-27.2, -0.8)	0.021			

triglyceride levels in children at 3 months

## **Abbreviations**

**CI** = confidence interval, **HDL-c** = high-density lipoprotein-cholesterol, **LDL-c** = low density lipoprotein-cholesterol, **mg/dL** = milligrams per decilitre, **n** = number of patients, **NR** = not reported, **SD** = standard deviation.

<u>Notes</u> **a** = geometric mean.

Source

Kusters (2015)<sup>121</sup>

Hypercholesterolaemia without ASCVD, ezetimibe plus statin vs statin: effectiveness outcome in adolescents

# Table 101 Ezetimibe plus statins compared to statins: absolute and percentage change in lipid

Outcome	Follow up	Ezetimibe plus statins mean ± SD n=126	Statins Mean ± SD n=120	Mean difference (95% Cl)	p value
LDL-c					
Absolute	Baseline	225.63 ± 43.33	219.27 ± 43.27	6.36 (-4.52, 17.24)	0.25
change (mg/dL)	6 months	103.47 ± 40.97	134.60 ± 40.42	-31.31 (-41.36, -20.90)	<0.01
Percentage change (%)	6 months	-53.99 ± 15.82	-38.14 ± 15.66	-15.85 (-19.81, -11.89)	<0.01
HDL-c					
Absolute	Baseline	46.27 ± 9.20	45.96 ± 9.20	0.31 (-2.00, -2.62)	0.79
change (mg/dL)	6 months	47.66 ± 9.53	47.47 ± 9.53	1.70 (-0.65, -4.05)	0.87
Percentage change (%)	6 months	4.67 ± 14.26	3.68 ± 14.02	0.99 (-2.56, 4.54)	0.58
Total cholestero	1				
Absolute	Baseline	292.43 ± 45.46	285.47 ± 25.46	6.96 (-2.36, -16.28)	0.23
change (mg/dL)	6 months	167.02 ± 42.09	200.2 ± 41.51	-33.18 (-43.68, -22.68)	<0.01
Percentage change (%)	6 months	-42.45 ± 12.91	-29.25 ± 12.81	-13.20 (-16.43, 9.97)	<0.01
Triglycerides <sup>a</sup>					
Absolute	Baseline	89.0 ± 49.3	88.0 ± 38.84	NA	0.88
change (mg/dL)	6 months	71.0 ± 38.14	81.0 ± 39.07	NA	0.01
Percentage change (%)	6 months	-20.0 ± 23.76	-13.04 ± 39.00	NA	<0.01

# and triglyceride levels in adolescents at 3 months

# Abbreviations

CI = confidence interval, HDL-c = high-density lipoprotein-cholesterol, LDL-c = low density lipoprotein-cholesterol, n = number of patients, NA = not applicable, mg/dL = milligrams per decilitre, SD = standard deviation.

Notes

 $\overline{\mathbf{a}}$  = median ± SD, mean difference cannot be calculated.

Source

Van der Graff (2008)<sup>122</sup>

# Hypercholesterolaemia without ASCVD, ezetimibe plus statin vs statin: effectiveness outcomes by statin type

# Table 102 Ezetimibe plus statins compared to statin: percentage change in lipid levels by statins

Outcome	Mean difference (95% CI)					
		Γ	p v	alue	I	Γ
	Baseline	3 months	6 months	9 months	12 months	24 months
Ezetimibe plu	s simvastatin vs	simvastatin				
LDL-c	NA	-17.04%	-16.59%	-16.06%	-15.32%	-16.50%
k=9 106 107 120		(-22.02, -12.05)	(-22.17, -11.01)	(-21.71, -10.41)	(-21.10, -9.54)	(-27.61, -5.39)
122 127 128 138-140		p<0.01	p<0.01	p<0.01	p<0.001	p<0.01
HDL-c	NA	0.88%	0.63%	0.75%	1.17%	2.40%
k=9 <sup>106 107 120</sup>		(0.00, 1.77)	(-0.64, 1.91)	(-1.22, 2.72)	(-0.91, 3.26)	(-0.24, 5.04)
122 127 128 138-140		p<0.05	p>0.05	p>0.05	p>0.05	p>0.05
Total	NA	-12.04%	-11.85%	-12.88%	-12.91%	-13.40%
cholesterol		(-13.94, -10.14)	(-14.66, -9.03)	(-16.01, -9.79)	(-16.45, -9.37)	(-17.67, -9.31)
<b>k=9</b> <sup>106</sup> 107 120 122 127 128 138-140		p<0.001	p<0.001	p<0.001	p<0.001	p<0.001
Ezetimibe plu	s atorvastatin vs	atorvastatin ª	I	I	I	I
LDL-c	NA	-12.10%	-14.40%	-12.29%	-9.80%	NR
k=2 <sup>126 137</sup>		(-15.09, -9.10)	(-18.65, -10.14)	(-17.74, -6.84)	(-15.59, -4.01)	
		p<0.01	p=NR	p=NR	p<0.01	
HDL-c	NA	3.00%	NR	NR	0.90%	NR
k=2 <sup>126 137</sup>		(0.96, 5.04)			(-3.06, 4.86)	
		p<0.05			p<0.01	
Total	NA	-9.00%	NR	NR	-7.90%	NR
cholesterol		(-11.08, -6.93)			(-12.26, -3.94)	
k=2 <sup>126 137</sup>		p<0.01			p<0.01	
Ezetimibe plu	s fluvastatin vs fl	luvastatin ª				
LDL-c	NA	-14.70%	NR	NR	NR	NR
k=1 <sup>136</sup>		(-24.14, -5.26)				
		p<0.001				
HDL-c	NA	2.50%	NR	NR	NR	NR
k=1 <sup>136</sup>		(-6.79, 11.79)				
		p=NS				
Total	NA	-10.70%	NR	NR	NR	NR
cholesterol		(-17.20, -4.20)				
k=1 <sup>136</sup>		p<0.001				
Ezetimibe plu	s pravastatin vs j	oravastatin ª				
LDL-c	NA	-13.40%	NR	NR	NR	NR
k=1 <sup>133</sup>		(-16.04, -10.76)				

# type in patients with hypercholesterolaemia

Outcome		Mean difference (95% CI) p value						
		p<0.01						
HDL-c k=1 <sup>133</sup>	NA	-1.40% (-1.09, -3.89) p<0.01	NR	NR	NR	NR		
Total cholesterol k=1 <sup>133</sup>	NA	-9.90% (-12.05, -7.75) p<0.01	NR	NR	NR	NR		

CI = confidence interval, HDL-c = high density lipoprotein-cholesterol, LDL-c = low density lipoprotein-cholesterol, mg/dL = milligrams per decilitre, NA = not applicable, NR = not reported.

## <u>Notes</u>

**a** = There was only one study (per timepoint) in the sub-group so a longitudinal meta-analysis was not performed. Statistical significance was based on analysis performed in the study.

Mean difference could not be calculated for triglycerides because it was unclear whether the results were normally distributed.

# Table 103 Ezetimibe plus statins compared to statins: absolute change in lipid levels by statin

## type in patients with hypercholesterolaemia without ASCVD

Outcome		Mean difference (95% CI) p value					
	Baseline	3 months	6 months	9 months	15 months	24 months	
Ezetimibe plus simvastatin vs simvastatin							
LDL-c k=7 106 120 122 134 135 141 143	1.39mg/dL (-3.91, 6.69) p>0.05	-15.58mg/dL (-21.63, -9.52) p<0.001	NR	-31.13mg/dL (-46.31, -15.92) p<0.001	-18.70mg/dL (-32.97, -4.43) p=0.05	-51.40mg/dL (-65.52, -37.28) p<0.001	
Ezetimibe plus atorvastatin vs atorvastatin ª							
LDL-c k=1 <sup>109</sup>	4.40mg/dL (-10.44, 19.24) p=NS	-28.10mg/dL (-44.59, 11.61) p=NS	NR	NR	NR	NR	

# Abbreviations

CI = confidence interval, LDL-c = low density lipoprotein-cholesterol, mg/dL = milligrams per decilitre, NR = not reported. Notes

**a** = There was only one study in the sub-group so a longitudinal meta-analysis was not performed. Statistical significance was based on analysis performed in the study.

No study reported HDL-c, total cholesterol or triglycerides.

# Hypercholesterolaemia without ASCVD, ezetimibe vs statins and ezetimibe plus statins vs statins: safety by statin type

# Table 104 Ezetimibe compared to statins: summary of safety-related outcomes by statin type in

Intervention			Outc	omes		
vs comparator						
	All-cause mortality	Withdrawal due to adverse events	Serious adverse events	Serious treatment- related adverse events	Any adverse events	Treatment- related adverse events
Meta-analysis;	risk ratio (95% C	l); p value				
Ezetimibe vs simvastatin	0 events	0.84 (0.33, 2.09)	2.03 (0.32, 12.82)	NR	0.98 (0.88, 1.08)	0.82 (0.60, 1.13)
		p=0.70	p =0.45		p=0.65	p=0.24
Event number;	n/N	·	·	·	·	•
Ezetimibe vs	0 events	3/65 vs	NR	NR	41/65 vs	12/65 vs
atorvastatin		13/248			146/248	42/248
Ezetimibe vs	0 events	2/64 vs	NR	NR	45/64 vs	6/64 vs
pravastatin		3/205			12/205	31/205
Ezetimibe vs	NR	0 events	0 events	NR	5/8 vs	NR

# patients with hypercholesterolaemia without ASCVD

# **Abbreviations**

rosuvastatin

**CI** = confidence interval, **n** = number of patients with event, **N** = total number of patients, **NR** = not reported.

#### **Notes**

For the meta-analysis results, a risk ratio indicates direction of effect. Numbers >1 indicate risks were lower in the statin group (higher event rate in ezetimibe), numbers <1 indicate risks were lower in the ezetimibe groups(higher event rate in statin group). Studies reporting only event numbers were not meta-analysed.

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# Table 105 Ezetimibe plus statins compared to statins: summary of safety-related outcomes by

Intervention vs comparator		Outcomes						
	All-cause mortality	Withdrawal due to adverse events	Serious adverse events	Serious treatment- related adverse events	Any adverse events	Treatment- related adverse events		
Meta-analysis;	Meta-analysis; risk ratio (95% Cl); p value							
Ezetimibe plus atorvastatin vs atorvastatin	0 events	1.08 (0.64, 1.82) p=0.78	0.58 (0.17, 2.01) p=0.39	1/201 vs 2/45	1.03 (0.92, 1.16) p =0.59	1.11 (0.71, 1.75) p=0.64		
Ezetimibe plus simvastatin vs simvastatin	5/2,388 vs 1/1,738	1.17 (0.96, 1.44) p=0.12	1.23 (0.69, 2.20) p=0.48	1.16 (0.20, 6.85) p=0.87	1.02 (0.97, 1.06) p =0.50	1.11 (0.99, 1.26) p=0.08		
Event numbers	s; n/N							
Ezetimibe plus fluvastatin vs fluvastatin	NR	2/38 vs 0/44	1/38 vs 0/44	NR	25/38 vs 23/44	NR		
Ezetimibe plus pravastatin vs pravastatin	0 events	9/204 vs 3/205	NR	NR	134/204 vs 129/205	35/204 vs 31/205		
Ezetimibe plus rosuvastatin vs rosuvastatin		0/12 vs 0/12	0/12 vs 0/12	NR	11/12 vs 9/12	NR		

# statin type in patients with hypercholesterolaemia without ASCVD

## **Abbreviations**

**CI** = confidence interval, **n** = number of patients with event, **N** = total number of patients, **NR** = not reported.

#### Notes

For the meta-analysis results, a risk ratio indicates direction of effect. Numbers >1 indicate risks were lower in the statin group (higher event rate in the ezetimibe plus statin group), numbers <1 indicate risks were lower in the ezetimibe plus statin group (higher event rate in the statin group).

Studies reporting only event numbers were not meta-analysed.

# Hypercholesterolaemia with ASCVD, ezetimibe plus statins vs statin: statin type

# Table 106 Ezetimibe plus statins compared to statin: percentage change in lipid levels by statin

Outcome		Mean difference (95% Cl) p value							
	Baseline	3 months	6 months	9 months	12 months	24 months			
Ezetimibe pl	us atorvastat	in vs atorvastatin		1					
LDL-c k=5 <sup>148 151 153</sup> 155 156	NA	-16.16% (-25.89, -6.42) p<0.001	-17.60% (-39.82, 4.62) p>0.05	NR	-9.60% (-29.31, 10.11) p>0.05	NR			
HDL-c k=4 <sup>151 153 155</sup> 156	NA	2.78% (1.24, 4.31) p<0.001	NR	NR	-2.50% (-12.31, 7.31) p>0.05	NR			
Total cholesterol k=3 <sup>151 155 156</sup>	NA	-6.04% (-13.97, 1.90) p=0.14	NR	NR	-7.90% ª (-17.98, 2.18) p<0.001	NR			
Ezetimibe pl	us rosuvastat	tin vs rosuvastatin ª							
LDL-c k=1 <sup>149</sup>	NA	NR	5.30% (11.30, 21.92) p=NS	NR	NR	NR			
HDL-c k=1 <sup>149</sup>	NA	NR	3.50% (-10.10, 3.09) p=NS	NR	NR	NR			
Total cholesterol k=0	NA	NR	NR	NR	NR	NR			
Ezetimibe pl	us simvastati	n vs simvastatin ª							
LDL-c k=1 <sup>150</sup>	NA	NR	-15.00% (-17.84, -12.16) p<0.001	NR	NR	NR			
HDL-c k=1 <sup>150</sup>	NA	NR	2.90% (0.44, 5.35) p<0.05	NR	NR	NR			
Total cholesterol k=1 <sup>150</sup>	NA	NR	-11.00% (-13.93, -8.61) p<0.001	NR	NR	NR			

## type in patients with hypercholesterolaemia and ASCVD

## **Abbreviations**

**CI** = confidence interval, **HDL-c** = high density lipoprotein-cholesterol, **LDL-c** = low density lipoprotein-cholesterol, **mg/dL** = milligrams per decilitre, **NR** = not reported.

#### <u>Notes</u>

**a** = There was only one study in the sub-group, so a longitudinal meta-analysis was not performed. Statistical significance was based on analysis performed in the study.

Mean difference could not be calculated for triglycerides because it was unclear whether the results were normally distributed.

# Table 107 Ezetimibe plus statins compared to statin: absolute change in lipid levels by statin

# type in patients with hypercholesterolaemia and ASCVD

Outcome	Mean difference (95% CI) p value							
	Baseline	3 months	6 months	9 months	12 months	24 months		
Ezetimibe plu	ıs simvastatin vs	simvastatin						
LDL-c k=3 <sup>52 145 160</sup>	0.00mg/dL (-0.67, 0.67) p>0.05	-21.59mg/dL (-43.47, 0.29) p=0.10	NR	-6.17mg/dL (-24.08, 11.74) p>0.05	-16.75mg/dL (-19.25, -14.24) p<0.001	-15.00mg/dL (-44.13, 14.13) p>0.05		
HDL-c k=3 <sup>52 145 160</sup>	4.18mg/dL (-5.52, 13.87) p>0.05	NR	NR	14.83mg/dL (-5.66, 35.32) p>0.05	3.49mg/dL (-5.79, 12.96) p>0.05	2.00mg/dL (-15.35, 19.35) p>0.05		
Total cholesterol k=3 <sup>52 145 160</sup>	0.01mg/dL (-0.79, 0.81) p>0.05	-22.98mg/dL (-44.50, -1.46) p<0.05	NR	-4.70mg/dL (-22.60, 13.20) p>0.05	-19.21mg/dL (-22.37, -16.06) p<0.001	-16.00mg/dL (-49.26, 17.26) p>0.05		
Ezetimibe plu	ıs atorvastatin vs	atorvastatin ª						
LDL-c k=2 <sup>151 158</sup>	-9.09mg/dL (-23.04, 4.86) p=0.20	-10.23mg/dL (-32.53, 12.07) p=NS	NR	NR	-26.20mg/dL (-37.62, -14.78) p<0.001	NR		
HDL-c k=1 <sup>151</sup>	0.00mg/dL (-4.94, 4.94) p=0.59	NR	NR	NR	0.00mg/dL (-5.16, 5.16) p=0.48	NR		
Total cholesterol k=1 <sup>151</sup>	-15.45mg/dL (-31.14, 0.24) p=0.09	NR	NR	NR	-23.20mg/dL (-38.00, -8.40) p=0.001	NR		
Ezetimibe plu	ıs fluvastatin vs fl	luvastatin ª	•		•			
LDL-c k=1 <sup>159</sup>	10.00mg/dL (-1.21, 21.21) p=NS	-15.00mg/dL (-23.28, -6.71) p<0.001	NR	NR	NR	NR		
HDL-c k=1 <sup>159</sup>	-3.00mg/dL (-7.76, 1.76) p=NS	6.00mg/dL (-11.28, -0.71) p=0.08	NR	NR	NR	NR		
Total cholesterol k=1 <sup>159</sup>	17.00mg/dL (1.10, 32.89) p=0.047	-26.00mg/dL (-32.53, -14.47) p<0.001	NR	NR	NR	NR		
Ezetimibe plu	ıs rosuvastatin vs	rosuvastatin ª		•				
LDL-c k=1 <sup>144</sup>	5.20mg/dL (-8.45, 18.85) p=NS	NR	NR	NR	-11.30mg/dL (-19.01, -3.59) p=0.005	NR		
HDL-c k=1 <sup>144</sup>	-0.40mg/dL (-3.29, -2.50) p=NS	NR	NR	NR	0.00mg/dL (-2.40, 2.40) p=0.98	NR		

Outcome		Mean difference (95% CI) p value						
Total cholesterol	4.00mg/dL (-11.46, 19.46)	NR	NR	NR	-13.50mg/dL (-22.29, -4.70)	NR		
k=1 <sup>144</sup>	p=NS				p=0.004			

CI = confidence interval, HDL-c = high density lipoprotein-cholesterol, LDL-c = low density lipoprotein-cholesterol, mg/dL = milligrams per decilitre, NR = not reported.

# Notes

**a** = There was only one study in the sub-group so a longitudinal meta-analysis was not performed. Statistical significance was based on analysis performed in the study.

\* = described in-text as slightly higher

Mean difference could not be calculated for triglycerides because it was unclear whether the results were normally distributed.

# Hypercholesterolaemia with ASCVD, ezetimibe plus statins vs statin: effectiveness outcome by low, intermediate and high-risk groups

 Table 108 Ezetimibe plus statins compared to statin: MACE outcomes by risk group in patients

with hype	ercholesterolaer	nia with ASCV	/D at 7 years
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Outcome Risk groups	Ezetimibe plus statinsStatin n (%)Hazard ratio (95% CI)n (%)n (%)		Hazard ratio (95% CI)	Absolute risk reduction (95% CI)	
5P-MACE					
Overall	2,572 (32.7%)	2,742 (34.7%)	0.93 (0.89, 0.99)	NR	
Low	941 (26.4%)	943 (25.8%)	1.01 (0.93, 1.11)	-0.6% (-2.5, 1.3%)	
Intermediate	759 (33.4%)	811 (36.0%)	0.93 (0.84, 1.03)	2.6% (-0.2, 5.4%)	
High	811 (44.2%)	916 (50.8%)	0.86 (0.78, 0.94)	6.6% (3.3, 10.1) p=0.042	
3P-MACE	1		1	1	
Overall	1,718 (18.9%)	1,918 (21.1%)	0.90 (0.84, 0.96)	NR	
Low	474 (14.0%)	460 (13.1%)	1.05 (0.92, 1.19)	-0.9% (-2.5, 0.7%)	
Intermediate	424 (19.3%)	471 (21.5%)	0.89 (0.78, 1.01)	2.2% (-0.3, 4.6%)	
High	594 (33.9%)	705 (40.2%)	0.81 (0.73, 0.90)	6.3% (2.9, 9.7%) p=0.01	
Non-fatal MI	•	•	•		
Overall	977 (13.1%)	1,118 (14.8%)	0.87 (0.80, 0.95)	NR	
Low	345 (10.1%)	340 (9.7%)	1.03 (0.89, 1.20)	-0.4% (-1.8, 1.1%)	
Intermediate	276 (12.9%)	316 (14.4%)	0.87 (0.74, 1.02)	1.5% (-0.5, 3.7%)	
High	340 (20.3%)	434 (26.2%)	0.76 (0.66, 0.88)	5.9% (2.9, 9.1%) p=0.016	
lschaemic stroke	l		I		
Overall	236 (3.4%)	297 (4.1%)	0.79 (0.67, 0.94)	NR	
Low	81 (2.7%)	76 (2.3%)	1.08 (0.79, 1.48)	-0.4% (-1.1, 0.5%)	
Intermediate	60 (2.8%)	80 (3.8%)	0.75 (0.54, 1.05)	1.0% (-0.2, 2.1%)	
High	91 (6.0%)	132 (8.4%)	0.68 (0.52, 0.88)	2.4% (0.4, 4.4%) p=0.075	
Coronary revascularis	ation		·		
Overall	1871 (24.2%)	1962 (25.6%)	0.96 (0.90, 1.02)	NR	
Low	695 (19.5%)	727 (20.0%)	0.97 (0.87, 1.07)	0.5% (-1.2, 2.2%)	
Intermediate	542 (24.1%)	540 (24.8%)	1.01 (0.90, 1.14)	0.7% (-1.9, 3.2%)	
High	416 (23.7%)	481 (28.9%)	0.85 (0.75, 0.97)	5.2% (2.1, 8.3%) p=0.14	

Outcome Risk groups	Ezetimibe plus statins n (%)	Statin n (%)	Hazard ratio (95% Cl)	Absolute risk reduction (95% CI)	
Unstable angina					
Overall	148 (1.9%)	156 (2.1%)	1.06 (0.85, 1.33)	NR	
Low	54 (1.5%)	50 (1.4%)	1.09 (0.74, 1.60)	-0.1% (-0.7, 0.4%)	
Intermediate	50 (2.2%)	45 (2.1%)	1.12 (0.75, 1.67)	-0.1% (-1.0, 0.8%)	
High	48 (2.9%)	51 (3.0%)	0.94 (0.63, 1.39)	0.1% (-1.1, 1.3%)	
				p=0.80	
Cardiovascular death					
Overall	537 (6.9%)	538 (6.8%)	1.00 (0.89, 1.13)	NR	
Low	88 (2.5%)	85 (2.3%)	1.04 (0.77, 1.40)	-0.2% (-1.0, 0.5%)	
Intermediate	143 (6.3%)	138 (6.3%)	1.03 (0.82, 1.31)	0.1% (-1.3, 1.5%)	
High	295 (16.7%)	300 (16.8%)	0.99 (0.84, 1.16)	0.1% (-2.6, 2.7%)	
				p=0.93	

CI = confidence interval, MI = myocardial infarction, n = number of events.

Notes

Overall n =17,717 low risk n=8,032, intermediate risk n=5,292, high risk n=4,393.

5P MACE includes death from cardiovascular causes, major coronary event (MI, hospitalisation for unstable angina or coronary revascularisation within 30 days). 3P MACE includes cardiovascular death, non-fatal MI and ischaemic stroke. p value reflects risk group comparison (low, intermediate or high)

For the hazard ratio, numbers >1 indicate risks were lower in the statin group (higher event rate in the ezetimibe plus statin group), numbers <1 indicate risks were lower in the ezetimibe plus statin group (higher event rate in the statin group). <u>Source</u>

Overall outcomes obtained from Cannon (2015).<sup>52</sup> Low, intermediate and high risk group outcomes obtained from Bohula (2017).<sup>162</sup>

Outcome Risk groups	Pooled baseline Median (95% Cl)	Ezetimibe plus statins Median (95% Cl)	Statin Median (95% Cl)
LDL-c			
Overall	95 (79, 110)	50 (39, 62)	67 (55, 81)
Low	100 (85, 113)	51 (41, 63)	68 (56, 81)
Intermediate	94 (78, 109)	49 (38, 63)	67 (55, 80)
High	87 (73, 101)	48 (37, 61)	66 (53, 82)
HDL-c		·	
Overall	40 (33, 49)	46 (39, 55)	47 (40, 56)
Low	41 (34, 50)	48 (41, 57)	47 (40, 56)
Intermediate	39 (33, 48)	46 (40, 55)	45 (38, 55)
High	39 (32, 48)	45 (39, 54)	44 (38, 54)
Total cholest	terol		
Overall	163 (144, 181)	121 (107, 139)	142 (126, 160)
Low	167 (150, 184)	122 (108, 138)	142 (127, 159)
Intermediate	162 (143, 180)	121 (107, 140)	142 (126, 160)
High	155 (137, 174)	119 (106, 139)	142 (124, 162)
Triglyceride			
Overall	120 (85, 172)	104 (77, 143)	116 (84, 165)
Low	115 (81, 166)	98 (73, 133)	109 (79, 155)
Intermediate	124 (88, 178)	108 (80, 148)	119 (87, 172)
High	124 (89, 177)	112 (82, 157)	127 (94, 180)

# Table 109 Ezetimibe plus statins compared to statin: absolute lipid and triglyceride levels stratified by risk group in patients with hypercholesterolaemia with ASCVD at 7 years

Abbreviations

**CI** = confidence interval.

**Notes** 

p value not reported, in-text LDL-c values were described as similar. Source

Bohula (2017)<sup>162</sup>

Hypercholesterolaemia with ASCVD, ezetimibe plus statins vs statin: effectiveness outcome in older adults

# Table 110 Ezetimibe plus statins compared to statin: MACE outcomes by age group in patients

Outcome	Ezetimibe plus statins	Statin	Hazard ratio
Age groups	n/N or (%)	n/N or (%)	(95% CI)
5-MACE			
Overall	18.9%	21.1%	0.90 (0.84, 0.96)
<65 years	29.9%	30.8%	0.97 (0.90, 1.05)
65–74 years	35.1%	35.9%	0.96 (0.87, 1.06)
≥75 years	38.9%	47.6%	0.80 (0.70, 0.90)
			p=0.02
3P-MACE			
Overall	18.9%	21.1%	0.90 (0.84, 0.96)
<65 years	16.6%	17.8%	0.92 (0.83, 1.02)
65–74 years	22.4%	23.0%	0.96 (0.85, 1.09)
≥75 years	31.3%	38.0%	0.79 (0.69, 0.91)
			p=0.39
МІ			
Overall	13.1%	14.8%	0.87 (0.80, 0.95)
<65 years	12.1%	13.0%	0.93 (0.83, 1.05)
65–74 years	13.5%	15.3%	0.86 (0.74, 1.01)
≥75 years	16.4%	21.3	0.74 (0.61, 0.89)
			p=0.15
lschaemic stroke			
Overall	3.4%	4.1%	0.79 (0.67, 0.94)
<65 years	2.1%	2.8%	0.68 (0.51, 0.90)
65–74 years	4.7%	4.7%	0.99 (0.74, 1.32)
≥75 years	6.6%	8.4%	0.73 (0.53, 1.01)
			p=0.11
Cardiovascular death			
Overall	6.9%	6.8%	1.00 (0.89, 1.13)
<65 years	4.0%	3.8%	1.04 (0.85, 1.29)
65–74 years	8.1%	6.8%	1.10 (0.88, 1.37)
≥75 years	16.3%	19.1%	0.90 (0.74, 1.10)
			p=0.12

# with hypercholesterolaemia with ASCVD at 7 years

# Abbreviations

 $\label{eq:cl} \textbf{Cl} = \text{confidence interval}, \ \textbf{Ml} = \text{myocardial infarction}, \ \textbf{n} = \text{number of events}.$ 

#### **Notes**

Overall n=17,717 low risk n=8,032, intermediate risk n=5,292, high risk n=4,393. p value represents effect of age.

5P MACE includes death from cardiovascular causes, major coronary event (MI, hospitalisation for unstable angina or coronary revascularisation within 30 days). 3P MACE includes cardiovascular death, non-fatal MI and ischaemic stroke. For the hazard ratio, numbers >1 indicate risks were lower in the statin group (higher event rate in the ezetimibe plus statin group), numbers <1 indicate risks were lower in the ezetimibe plus statin group (higher event rate in the statin group). Source

Overall outcomes obtained from Cannon (2015).52 Age group outcomes obtained from Bach (2019).163

# Table 111 Ezetimibe plus statins compared to statin: absolute and percentage change in lipid

# and triglyceride levels by age group in patients with hypercholesterolaemia with

Outcome	Follow-up	Ezetimibe plus statins	Statin	
Age groups		mean ± SD	Mean ± SD	
LDL-c				
Overall	Baseline	95.00 ± 22.96mg/dL	95.00 ± 23.11mg/dL	
	12 months (absolute)	55.04 ± 76.5mg/dL	71.8 ± 76.51mg/dL	
<65 years	Baseline	82.2 ± 24.2mg/dL	83.3 ± 24.0mg/dL	
	12 months (absolute)	54.9 ± 23.1mg/dL	72.0 ± 23.6mg/dL	
	12 months (percentage)	-27.9 ± 27.8%	-11.0 ± 27.0%	
65–74 years	Baseline	79.1 ± 22.8mg/dL	79.0 ± 23.4mg/dL	
	12 months (absolute)	51.7 ± 22.0mg/dL	67.0 ± 20.8mg/dL	
	12 months (percentage)	-27.2 ± 27.7%	-12.2 ± 26.2%	
≥75 years	Baseline	77.8 ± 23.1mg/dL	78.5 ± 22.5mg/dL	
	12 months (absolute)	49.4 ± 20.5mg/dL	66.5 ± 22.3mg/dL	
	12 months (percentage)	-28.6 ± 26.2%	-11.6 ± 25.8%	
HDL-c				
Overall	Baseline	40.00 ± 11.85mg/dL	40.00 ± 11.85mg/dL	
	12 months (absolute)	48.51 ± 32.99mg/dL	47.83 ± 32.95mg/dL	
<65 years	Baseline	40.0 ± 10.9mg/dL	40.0 ± 10.6mg/dL	
	12 months (absolute)	47.2 ± 12.5mg/dL	47.0 ± 13.2mg/dL	
	12 months (percentage)	7.4 ± 9.2%	7.0 ± 9.4%	
65–74 years	Baseline	42.0 ± 10.7mg/dL	42.4 ± 11.6mg/dL	
	12 months (absolute)	50.2 ± 12.8mg/dL	49.1 ± 13.2mg/dL	
	12 months (percentage)	8.2 ± 9.3%	6.9 ± 9.0%	
≥75 years	Baseline	43.9 ± 11.1mg/dL	43.9 ± 12.1mg/dL	
	12 months (absolute)	52.2 ± 13.3mg/dL	51.0 ± 13.8mg/dL	
	12 months (percentage)	8.2 ± 9.6%	7.4 ± 9.7%	
Triglycerides				
Overall	Baseline	120.00 ± 64.44mg/dL	120.00 ± 64.44 mg/dL	
	12 months (absolute)	111.57 ± 156.83mg/dL	125.61 ± 177.58mg/dL	
<65 years	Baseline	147.9 ± 69.5mg/dL	148.7 ± 67.9mg/dL	
	12 months (absolute)	126.6 ± 78.0mg/dL	145.1 ± 97.0mg/dL	
	12 months (percentage)	-21.3 ± 79.4%	-2.3 ± 90.4%	

## ASCVD at 7 years

Outcome	Follow-up	Ezetimibe plus statins	Statin
Age groups		mean ± SD	Mean I SD
65–74 years	Baseline	135.8 ± 58.6mg/dL	134.1 ± 57.1mg/dL
	12 months (absolute)	114.8 ± 58.0mg/dL	128.6 ± 71.5mg/dL
	12 months (percentage)	-20.1 ± 58.2%	-5.2 ± 63.7%
≥75 years	Baseline	125.7 ± 51.5mg/dL	123.2 ± 50.9mg/dL
	12 months (absolute)	105.9 ± 50.3mg/dL	119.2 ± 59.4mg/dL
	12 months (percentage)	-21.5 ± 48.9%	-2.8 ± 53.6%

**CI** =confidence interval, **SD** = standard deviation.

Notes

Overall n =17,717 low risk n=8,032, intermediate risk n=5,292, high risk n=4,393. p value represents effect of age. 5P MACE includes death from cardiovascular causes, major coronary event (MI, hospitalisation for unstable angina or coronary revascularisation within 30 days). 3P MACE includes cardiovascular death, non-fatal MI and ischaemic stroke.

# <u>Source</u>

Overall outcomes obtained from Cannon (2015).<sup>52</sup> Age group outcomes obtained from Bach (2019).<sup>163</sup>

# Table 112 Ezetimibe plus statins compared to statin: percentage change in lipids and triglyceride levels in adults >65 years at 3 months (hypercholesterolaemia with ASCVD)

Outcome	Follow-up	Ezetimibe plus statins Mean ± SD	Statin Mean ± SD	p value
LDL-c				
Change from baseline <sup>157</sup>	Baseline	163 ± 29mg/dL	167 ± 34mg/dL	
	3 months	-59.1% ± NR	-39.5% ± NR	NR
Change from baseline <sup>156</sup>	Baseline	103 ± 28mg/dL	102 ± 21mg/dL	
	3 months	-23.0 ± 28.97%	-18 ± 34.53%	0.001
HDL-c				
Change from baseline <sup>157</sup>	Baseline	53 ± 13mg/dL	53 ± 13mg/dL	
	3 months	7.3% ± NR	4.6% ± NR	NR
Change from baseline <sup>156</sup>	Baseline	55 ± 14mg/dL	54 ± 12mg/dL	
	3 months	2 ± 17.38	-1 ± 17.26	<0.001
Total cholesterol			•	
Change from baseline <sup>157</sup>	Baseline	247 ± 34mg/dL	253 ± 39mg/dL	
	3 months	-41% ± NR	-27.9% ± NR	NR
Change from baseline <sup>156</sup>	Baseline	183 ± 32mg/dL	182 ± 26mg/dL	
	3 months	-14 ± 17.38%	-12 ± 17.26%	0.029
Triglycerides				
Change from baseline <sup>157</sup>	Baseline	141 ± 64mg/dL	157 ± 74mg/dL	
	3 months	-25.9% ± NR	-24.9% ± NR	NR
Change from baseline <sup>156</sup>	Baseline	113 ± 54mg/dL	117 ± 62mg/dL	
	3 months	-12 ± 28.97%	-9 ± 23.02%	0.150

Abbreviations

**mg/dL** = milligrams per decilitre, **NR** = not reported, **SD** = standard deviation.

Hypercholesterolaemia with ASCVD, ezetimibe plus statins vs statin: effectiveness outcome by diabetes status

# Table 113 Ezetimibe plus statins compared to statin: MACE outcomes by diabetes status in patients with hypercholesterolaemia with ASCVD at 7 years

Outcome	Ezetimibe plus statins n (%)	StatinHazard ration (%)(95% Cl)		p value
5P-MACE				1
Overall	2,742 (34.7%)	2,572 (32.7%)	0.94 (0.98, 0.99)	
Diabetes	824 (33.5%)	1,792 (27.2%)	0.85 (0.78, 0.94)	
No diabetes	1,748 (26.5%)	949 (38.4%)	0.98 (0.91, 1.04)	0.023
3P-MACE				
Overall	1,718 (18.9%)	1,918 (21.1%)	0.90 (0.84, 0.96)	
Diabetes	525 (21.4%)	643 (26.0%)	0.80 (0.71, 0.90)	
No diabetes	1,019 (15.4%)	1,060 (16.1%)	0.96 (0.88, 1.04)	0.016
МІ				
Overall	977 (13.1%)	1118 (14.8%)	0.87 (0.80, 0.95)	
Diabetes	317 (12.9%)	412 (16.7%)	0.76 (0.66, 0.88)	
No diabetes 660 (10.0%)		706 (10.7%) 0.93 (0.84, 1.04)		0.028
lschaemic stroke				
Overall	236 (3.4%)	297 (4.1%)	0.79 (0.67, 0.94)	
Diabetes	72 (2.9%)	117 (4.7%)	0.61 (0.46, 0.82)	
No diabetes	164 (2.5)	180 (2.7%)	0.91 (0.74, 1.13)	0.031
Coronary revascularis	ation			
Overall	1871 (24.2%)	1962 (25.6%)	0.96 (0.90, 1.02)	
Diabetes	517 (21.0%)	569 (23.0%)	0.92 (0.81, 1.03)	
No diabetes	1173 (17.8%)	1224 (18.6%)	0.80 (0.71, 0.90)	0.51
Unstable angina				
Overall	148 (1.9%)	156 (2.1%)	1.06 (0.85, 1.33)	
Diabetes	56 (2.3%)	54 (2.2%)	1.04 (0.78, 1.52)	
No diabetes	100 (1.5%)	94 (1.4%)	1.07 (0.80, 1.41)	0.941
Cardiovascular death				
Overall	537 (6.9%)	9%) 538 (6.8%) 1.00 (0.89, 1.13)		
Diabetes	225 (9.2%)	235 (9.5%)	0.96 (0.80, 1.16)	
No diabetes	312 (4.7%)	302 (4.6%)	1.03 (0.88, 1.21)	0.570

# Abbreviations

CI =confidence interval, MI = myocardial infarction, n = number of events.

#### Notes

Overall n =17,717, diabetes n=4,933 and, no diabetes n=13,202.

5P MACE= Death from cardiovascular causes, major coronary event (MI, hospitalisation for unstable angina or coronary revascularisation within 30 days), 3P MACE includes: cardiovascular death, non-fatal MI and ischaemic stroke.

p value represents interaction between treatment arm and diabetes status.

For the hazard ratio, numbers >1 indicate risks were lower in the statin group (higher event rate in the ezetimibe plus statin group), numbers <1 indicate risks were lower in the ezetimibe plus statin group (higher event rate in the statin group). <u>Source</u>

Overall outcomes obtained from Cannon (2015).<sup>52</sup> By diabetes status obtained from Giugliano (2018).<sup>116</sup>

# Table 114 Ezetimibe plus statins compared to statin: absolute and percentage change in LDL-c

levels by diabetes status in patients with hypercholesterolaemia with ASCVD at 7

Outcome Risk category	Follow-up	Ezetimibe plus statins median (95% CI)	Statin median (95% CI))
LDL-c			
Overall	Baseline	95.0mg/dL (79.0, 110.0)	95.0mg/dL (79.0, 110.2)
	12 months (absolute change)	50.0mg/dL (39.0, 62.0)	67.0mg/dL (55.0, 81.0)
	12 months (percentage change)	NR	NR
Diabetes	Baseline	89mg/dL (74, 103)	89mg/dL (74, 103)
	12 months (absolute change)	45 (NR) mg/dL	65 (NR) mg/dL
	12 months (percentage change)	-40% (NR)	- 22% (NR)
No diabetes	Baseline	97mg/dL (81, 112)	97mg/dL(81, 112)
	12 months (absolute change)	51 (NR) mg/dL	68 (NR) mg/dL
	12 months (percentage change)	-44% (NR)	-27% (NR)

years

# Abbreviations

CI = confidence interval.

### <u>Notes</u>

Overall n =17,717, diabetes n=4,933 and, no diabetes n=13,202

Significant baseline differences between diabetes and no diabetes p<0.0001, no difference at 12 months p=0.12.

Source

Giugliano (2018)116

Hypercholesterolaemia with ASCVD, ezetimibe vs statins and ezetimibe plus statins vs statin: safety by statin type

Table 115	Ezetimibe plus statins compared to statin: summary of safety-related outcomes by
	statin type in patients with hypercholesterolaemia without ASCVD

Intervention vs comparator	Outcomes Risk ratio (95% Cl); p value						
	All-cause mortality	Withdrawal due to adverse events	Serious adverse events	Serious treatment- related adverse events	Any adverse events	Treatment- related adverse events	
Ezetimibe plus simvastatin vs simvastatin	0.99 (0.92, 1.06) p=0.76	1.08 (0.83, 1.42) p=0.56	1.20 (0.58, 2.47) p=0.62	1 event in simvastatin	1.03 (0.94, 1.13) p=0.56	1.53 (1.09, 2.16) p=0.02	
Ezetimibe plus atorvastatin vs atorvastatin	2.05 (0.48, 8.65); p=0.33	1.07 (0.72, 1.59) p=0.73	1.16 (0.73, 1.85) p=0.53	0.95 (0.63, 1.42) p=0.80	1.02 (0.94, 1.10); p=0.71	0.97 (0.68, 1.40) p=0.89	
Ezetimibe plus rosuvastatin vs rosuvastatin	1.46 (0.23, 9.22) p=0.69	1.55 (0.78, 3.06) p=0.21	0.97 (0.46, 2.02) p=0.93	0.97 (0.51, 1.82) p=0.92	0.88 (0.75, 1.03) p=0.11	1.04 (0.63, 1.71) p=0.88	

# **Abbreviations**

 $\overline{CI}$  = confidence interval, **n** = number of patients with event, **N** = total number of patients, **NR** = not reported.

#### <u>Notes</u>

For the meta-analysis results, a risk ratio indicates direction of effect. For the meta-analysis results, a risk ratio indicates direction of effect. Numbers >1 indicate risks were lower in the statin group (higher event rate in the ezetimibe plus statin group), numbers <1 indicate risks were lower in the ezetimibe plus statin group (higher event rate in the statin group). Studies reporting only event numbers were not meta-analysed.

# **15.5** Appendix E: GRADE Evidence Profile Table

# Table 116 GRADE evidence profile table for ezetimibe compared placebo for hypercholesterolaemia without ASCVD at 3 months

Certainty	assessment						Number of patients Effect		nber of patients Effect		Certainty	Importance
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ezetimibe	placebo	Relative (95% Cl)	Absolute (95% CI)		
LDL-c (p	LDL-c (percentage change) (follow up: 3 months)											
13	randomised trials	serious <sup>a</sup>	serious <sup>b,c</sup>	serious <sup>d,e</sup>	not serious	none	2011	1112	-	MD 19.39% lower (21.53 lower to 17.25 lower)	⊕⊕⊖⊖ Low	IMPORTANT
LDL-c (al	bsolute chang	e) (follow u	p: 3 months)									
3	randomised trials	not serious	serious <sup>f</sup>	serious <sup>d,e</sup>	serious <sup>g</sup>	none	148	104	-	MD 46.68 mg/dL lower (53.46 lower to 39.9 lower)	⊕⊕⊖⊖ Low	IMPORTANT
Withdraw	val due to adv	erse events	(follow up: range	e 2 weeks to 3 n	nonths)							
16	randomised trials	not serious	not serious	not serious	serious <sup>h</sup>	none	82/2216 (3.7%)	41/1353 (3.0%)	RR 1.18 (0.79 to 1.76)	5 more per 1,000 (from 6 fewer to 23 more)	⊕⊕⊕⊖ MODERATE	CRITICAL

Certainty	assessment						Number of	patients	Effect		Certainty	Importance
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ezetimibe	placebo	Relative (95% Cl)	Absolute (95% Cl)		
Serious a	adverse event	(follow up:	range 2 weeks to	3 months)								
9	randomised trials	not serious	not serious	not serious	serious <sup>h</sup>	none	5/645 (0.8%)	4/652 (0.6%)	RR 0.98 (0.27 to 3.57)	0 fewer per 1,000 (from 4 fewer to 16 more)	⊕⊕⊕⊖ MODERATE	CRITICAL

**CI** = confidence interval, **MD** = mean difference, **mg/dL** = milligrams per decilitre, **RR** = risk ratio.

# <u>Notes</u>

 $\mathbf{a}$  = notable losses to follow-up,  $\mathbf{b}$  = considerable levels of heterogeneity and inconsistency,  $\mathbf{c}$  = non-overlapping confidence intervals,  $\mathbf{d}$  = surrogate for MI, vascular events, mortality,  $\mathbf{e}$  = unclear applicability of the trial population to the Swiss context,  $\mathbf{f}$  = moderate levels of heterogeneity and inconsistency,  $\mathbf{g}$  = small sample size,  $\mathbf{h}$  = 95% Confidence interval around pooled estimates includes negligible effect and appreciable benefit/harm.

Table 117	GRADE evidence profile table for	ezetimibe compared statins	for hypercholeste	rolaemia without ASCVD at 3 months
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Certainty	assessment						Number of	patients	Effect		Certainty	Importance
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ezetimibe	Statins	Relative (95% Cl)	Absolute (95% Cl)		
LDL-c (pe	ercentage cha	nge) (follov	v up: 3 months)									
5	randomised trials	serious ª	serious <sup>b,c</sup>	serious <sup>d,e</sup>	not serious	none	423	1669	-	MD 17.22% higher (11.23 higher to 23.22 higher)	⊕⊕⊖⊖ Low	IMPORTANT
LDL-c (al	osolute chang	e) (follow u	p: 3 months)				•				•	·
4	randomised trials	not serious	not serious	serious d,f	serious <sup>g</sup>	none	63	66	-	MD 10.77mg/dL higher (7.64 higher to 13.9 higher)	⊕⊕⊖⊖ Low	IMPORTANT
Withdraw	al due to adve	erse events	(follow up: range	e 2 weeks to 3 r	nonths)							
9	randomised trials	not serious <sup>h</sup>	not serious	not serious	serious <sup>i</sup>	none	20/547 (3.7%)	97/1809 (5.4%)	RR 0.95 (0.49 to 1.82)	3 fewer per 1,000 (from 27 fewer to 44 more)	⊕⊕⊕⊖ MODERATE	CRITICAL
Serious a	dverse events	s (follow up	: range 2 weeks t	to 3 months)								
4	randomised trials	not serious	not serious	not serious	serious <sup>i</sup>	none	2/310 (0.6%)	17/1246 (1.4%)	RR 0.70 (0.21 to 2.36)	4 fewer per 1,000 (from 11 fewer to 19	⊕⊕⊕⊖ MODERATE	CRITICAL

Certainty assessment							Number of patients		Effect		Certainty	Importance
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ezetimibe	Statins	Relative (95% CI)	Absolute (95% Cl)		
										more)		

**CI** = Confidence interval, **MD** = mean difference, **mg/dL** = milligrams per decilitre, **RR** = risk ratio.

#### <u>Notes</u>

 $\mathbf{a}$  = Notable losses to follow-up,  $\mathbf{b}$  = considerable levels of heterogeneity and inconsistency,  $\mathbf{c}$  = non-overlapping confidence intervals,  $\mathbf{d}$  = Surrogate for MI, vascular events, mortality,  $\mathbf{e}$  = unclear applicability of the trial population to the Swiss context,  $\mathbf{f}$  = unclear applicability of the trial population to the Swiss context,  $\mathbf{f}$  = unclear applicability of the trial population to the Swiss context,  $\mathbf{f}$  = unclear applicability of the trial population to the Swiss context,  $\mathbf{g}$  = small sample size,  $\mathbf{h}$  = there were losses to follow-up, but safety outcomes are still likely captured,  $\mathbf{i}$  = 95% Confidence interval around pooled estimates includes negligible effect and appreciable benefit/harm.

Table 118	GRADE evidence profile table for	ezetimibe plus statins co	mpared statins for hyperch	nolesterolaemia without ASCVD at 3 to 24 months
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Certainty	assessment						Number of	patients	Effect		Certainty	Importance
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ezetimibe plus statins	Statins	Relative (95% Cl)	Absolute (95% CI)		
3P-MACE	E (follow up: 24	4 months)										
1	randomised trials	serious <sup>a</sup>	not serious	serious <sup>b</sup>	serious c,d	none	Ezetimibe p 6 events vs	lus statins vs s 4 events	statins		⊕⊕⊖⊖ Low	CRITICAL
Cardiova	scular death (	follow up: 2	4 months)	•	•							
1	randomised trials	serious <sup>a</sup>	not serious	serious <sup>b</sup>	serious <sup>d</sup>	none	Ezetimibe p 2/357 (0.5%	lus statins vs s b) vs 1/363 (0.2		⊕⊕⊖⊖ Low	CRITICAL	
Hospitali	sed for unstal	ole angina -	not reported									
NR												
Coronary	/ revascularisa	ation (follow	/ up: 24 months)									
1	randomised trials	serious <sup>a</sup>	not serious	serious <sup>b</sup>	serious <sup>c,d</sup>	none	Ezetimibe p 6 events vs	lus statins vs s 5 events	statins		⊕⊕⊖⊖ Low	CRITICAL
LDL-c (p	ercentage cha	nge) (follow	up: range 3 to 2	4 months)								
17	randomised trials	serious <sup>e</sup>	serious <sup>f.g</sup>	serious <sup>b,h</sup>	not serious <sup>i</sup>	none	3 months MD -16.14% (95% CI -19.67, -12.60%); p<0.01 12 months MD -14.24% (95% CI -18.91, -9.57%); p<0.01			⊕⊕⊖⊖ Low	IMPORTANT	
LDL-c (al	LDL-c (absolute change) (follow up: range 3 to 24 months)								•	•		
13	randomised trials	serious <sup>e</sup>	serious <sup>f.g</sup>	serious <sup>b,h</sup>	not serious <sup>i</sup>	none	3months MD -16.72m 15 months MD -14.24m	ng/dL (95% CI ng/dL (95% CI	-22.34, -11.11 -32.59, -4.81);	%); p<0.01 ; p<0.01	⊕⊕⊖⊖ Low	IMPORTANT

Certainty	assessment						Number of	patients	Effect		Certainty	Importance
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ezetimibe plus statins	Statins	Relative (95% CI)	Absolute (95% Cl)		
Withdraw	val due to adv	erse event (	follow up: range	2 to 24 months	)							
21	randomised trials	not serious <sup>j</sup>	serious <sup>g</sup>	not serious	not serious	none	248/4271 (5.8%)	143/3484 (4.1%)	RR 1.18 (0.95 to 1.45)	7 more per 1,000 (from 2 fewer to 18 more)	⊕⊕⊕⊖ MODERATE	CRITICAL
Serious a	adverse event	(follow up:	range 2 weeks to	12 months)								
12	randomised trials	not serious <sup>j</sup>	serious <sup>g,k</sup>	not serious	not serious	none	132/3151 (4.2%)	49/2365 (2.1%)	RR 1.08 (0.66 to 1.77)	2 more per 1,000 (from 7 fewer to 16 more)	⊕⊕⊕⊖ MODERATE	CRITICAL

CI = confidence interval, **3P-MACE** = 3-point major adverse cardiac event, **MD** = mean difference, **mg/dL** = milligrams per decilitre, **RR** = risk ratio.

<u>Notes</u>

 $\mathbf{a}$  = Losses to follow-up, important considering low event number,  $\mathbf{b}$  = unclear applicability of the trial population to the Swiss context,  $\mathbf{c}$  = not reported whether number of patients or events, cannot calculate risk,  $\mathbf{d}$  = outcomes derived from one study,  $\mathbf{e}$  = notable losses to follow-up,  $\mathbf{f}$  = considerable levels of heterogeneity and inconsistency,  $\mathbf{g}$  = non-overlapping confidence intervals,  $\mathbf{h}$  = surrogate for MI, vascular events, mortality,  $\mathbf{i}$  = later timepoints informed by one study,  $\mathbf{j}$  = losses to follow-up, event likely still captured appropriately,  $\mathbf{k}$  = moderate levels of heterogeneity and inconsistency.

Certainty	assessment						Number of p	atients	Effect		Certainty	Importance
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ezetimibe plus statins	Statins	Relative (95% CI)	Absolute (95% Cl)		
3P-MACE	E (follow up: 7	years)										
1	randomised trials	serious ª	not serious	serious <sup>b</sup>	not serious °	none	1718/9067 (18.9%)	1918/9077 (21.1%)	HR 0.90 (0.84 to 0.96)	19 fewer per 1,000 (from 31 fewer to 8 fewer)	⊕⊕⊖⊖ Low	CRITICAL
Cardiova	scular death (	follow up:	7 years)									
1	randomised trials	serious ª	not serious	serious <sup>b</sup>	not serious c	none	537/9067 (5.9%)	538/9077 (5.9%)	HR 1.00 (0.89 to 1.13)	0 fewer per 1,000 (from 6 fewer to 7 more)	⊕⊕⊖⊖ Low	CRITICAL
Hospitali	ised for unstat	ole angina	(follow up: 7 yea	rs)								
1	randomised trials	serious ª	not serious	serious <sup>b</sup>	not serious °	none	156/9067 (1.7%)	148/9077 (1.6%)	HR 1.06 (0.85 to 1.33)	1 more per 1,000 (from 2 fewer to 5 more)	⊕⊕⊖⊖ Low	CRITICAL
Coronary	/ revascularisa	ation (follo	w up: 7 years)									
1	randomised trials	serious ª	not serious	serious <sup>b</sup>	not serious °	none	1690/9067 (18.6%)	1793/9077 (19.8%)	HR 0.95 (0.89 to 1.01)	9 fewer per 1,000 (from 20 fewer to 2 more)	⊕⊕⊖⊖ Low	CRITICAL
LDL-c (p	ercentage cha	nge) (follo	w up: range 3 to	12 months)								
12	randomised trials	serious ª	serious <sup>d,e</sup>	serious <sup>f</sup>	not serious	none	3 months					IMPORTANT

# Table 119 GRADE evidence profile table for ezetimibe plus statins compared statins for hypercholesterolaemia with ASCVD at 3 to 24 months

Certainty	assessment						Number of pa	atients	Effect		Certainty	Importance
							MD -13.41%	(95% CI -19.26	, -7.56); p<0	.01		
							12 months					
							MD -9.60% (§	95% CI -27.33,	9			
LDL-c (al	LDL-c (absolute change) (follow up: range 3 to 24 months)											
9	randomised serious serious <sup>d,e</sup> serious <sup>f</sup> not serious none 3 months								$\oplus \oplus \bigcirc \bigcirc$	IMPORTANT		
	trials	а			g		-17.22mg/dL	(95% CI -24.23	LOW			
							12 months					
							-16.82mg/dL (95% CI -22.51, -11.12mg/dL); p<0.01					
Withdraw	val due to adve	erse event	s (follow up: rang	ge 1 to 30 mont	hs)		1				•	
30	randomised trials	not serious	not serious	serious <sup>f</sup>	not serious	none	1199/16828 (7.1%)	1151/17199 (6.7%)	RR 1.05 (0.97 to 1.13)	3 more per 1,000 (from 2 fewer to 9 more)	⊕⊕⊕⊖ MODERATE	CRITICAL
Serious a	adverse events	s (follow u	p: range 6 weeks	to 6 months)								
29	randomised trials	not serious	not serious	serious <sup>f</sup>	not serious	none	228/7047 (3.2%)	198/7468 (2.7%)	RR 1.20 (1.00 to 1.44)	5 more per 1,000 (from 0 fewer to 12 more)	⊕⊕⊕⊖ MODERATE	CRITICAL

CI = confidence interval, **3P-MACE** = 3-point major adverse cardiac event, **MD** = mean difference, **mg/dL** = milligrams per decilitre, **RR** = risk ratio.

# <u>Notes</u>

 $\overline{\mathbf{a}}$  = Notable losses to follow-up,  $\mathbf{b}$  = results reflective of one study in patients with ACS. Unclear how reflective they are of all ASCVD patients in Switzerland  $\mathbf{c}$  = results representative of Cannon (2015) trial,  $\mathbf{d}$  = considerable levels of heterogeneity and inconsistency within the model,  $\mathbf{e}$  = non-overlapping confidence intervals,  $\mathbf{f}$  = highly heterogeneous population. Unclear how reflective they are of ASCVD patients in Switzerland,  $\mathbf{g}$  = later timepoints informed by one study.
### Table 120 GRADE evidence profile table for Ezetimibe compared placebo for hyperlipidaemia without ASCVD at 3 months

Certainty	assessment						Number of	patients	Effect		Certainty	Importance
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ezetimibe	Placebo	Relative (95% Cl)	Absolute (95% CI)		
LDL-c (p	LDL-c (percentage change) (follow up: 3 months)											
1	randomised trials	not serious	serious <sup>a</sup>	serious <sup>b,c</sup>	serious <sup>d</sup>	none	Ezetimibe v: -13.4 ± 17.0	s placebo I% vs 0.2 ± 16	6.2%; p=NR		⊕⊕⊖⊖ LOW	IMPORTANT
LDL-c (a	LDL-c (absolute change) (follow up: 3 months)											
1	randomised trials	serious <sup>e</sup>	serious <sup>a</sup>	serious <sup>c,f</sup>	serious <sup>d</sup>	none	Ezetimibe vs placebo $102.1 \pm 21.3$ mg/dL vs $133.0 \pm 41.0$ mg/dL; p<0.0001				⊕OOO VERY LOW	IMPORTANT
Withdrav	val due to adve	erse events	(follow up: 3 mo	nths)			p 0.0001					
2	randomised trials	not serious	not serious <sup>g</sup>	not serious	serious <sup>f,h</sup>	none	4/212 (1.9%)	0/89 (0.0%)	RR 3.16 (0.17 to 59.57)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	⊕⊕⊕⊖ MODERATE	CRITICAL
Serious a	adverse event											
1	randomised trials	not serious	not serious	not serious	serious <sup>h</sup>	none	Ezetimibe vs 4/187 (2.1%	s placebo ) vs 0/64 (0.09	%)		⊕⊕⊕⊖ MODERATE	CRITICAL

#### Abbreviations

**CI** = confidence interval, **mg/dL** = milligrams per decilitre, **NR** = not reported, **RR** = risk ratio.

#### <u>Notes</u>

 $\mathbf{a} = \mathbf{O}$ verlapping standard deviations,  $\mathbf{b}$  = surrogate for MI, vascular events, mortality,  $\mathbf{c}$  = unclear applicability of the trial population to the Swiss context,  $\mathbf{d}$  = one study, small sample size,  $\mathbf{e}$  = notable losses to follow-up,  $\mathbf{f} = 95\%$  confidence interval around pooled estimates includes negligible effect and appreciable benefit/harm,  $\mathbf{g}$  = unclear as heterogeneity could not be calculated,  $\mathbf{h}$  = small sample size, low number of events.

#### Table 121 GRADE evidence profile table for Ezetimibe compared statins for hyperlipidaemia without ASCVD at 3 months

Certainty	assessment						Impact	Certainty	Importance			
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations						
LDL-c (p	LDL-c (percentage change) (follow up: 3 months)											
1	randomised trials	serious ª	serious <sup>b</sup>	serious <sup>c,d</sup>	serious <sup>e</sup>	none	Ezetimibe vs statins -15.6 ± NR -32.8 ± NR; p<0.0001	⊕⊕⊖⊖ LOW	Important			
LDL-c (a	LDL-c (absolute change) (follow up: 3 months)											
1	randomised trials	serious ª	not serious	serious <sup>c,d</sup>	serious <sup>e</sup>	none	Ezetimibe vs statins 161.5 ± 18.6mg/dL vs 114.5 ± 21.7mg/dL; p =NR	⊕⊕⊖⊖ LOW	Important			
Withdrav	val due to adve	erse event	(follow up: 3 mor	nths)								
1	randomised trials	not serious	not serious	not serious	serious <sup>e</sup>	none	Ezetimibe vs statins 8/66 (12.1%) vs 8/69 (11.6%)	⊕⊕⊕⊖ MODERATE	CRITICAL			
Serious a	adverse event	(follow up	: 3 months)									
1	randomised trials	not serious	not serious	not serious	serious <sup>e</sup>	none	Ezetimibe vs statins 0/66 (0.0%) vs 0/69 (0.0%)	⊕⊕⊕⊖ MODERATE	CRITICAL			

#### Abbreviations

**CI** = confidence interval, **mg/dL** = milligrams per decilitre, **NR** = not reported, **RR** = risk ratio.

#### <u>Notes</u>

**a** = Notable losses to follow-up, **b** = measures of variance not reported, **c** = surrogate for MI, vascular events, mortality, **d** = unclear applicability of the trial population to the Swiss context, **e** = one study, small sample size.

#### Table 122 GRADE evidence profile table for Ezetimibe compared fenofibrate for hyperlipidaemia without ASCVD at 3 months

Certainty	assessment						Number of p	patients	Effect		Certainty	Importance
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ezetimibe	Fenofibrate	Relative (95% CI)	Absolute (95% CI)		
LDL-c (pe	LDL-c (percentage change) (follow up: 3 months)											
2	randomised trials	not serious	serious <sup>a,b</sup>	serious <sup>c,d</sup>	not serious	none	229	237	-	MD 9.72% lower (27.85 lower to 8.41 higher)	⊕⊕⊖⊖ LOW	IMPORTANT
Withdraw	al due to adve	erse events	s (follow up: 3 mo	onths)								
2	randomised trials	not serious	not serious	not serious	serious <sup>e,f</sup>	none	5/247 (2.4%)	11/249 (4.4%)	RR 0.46 (0.16 to 1.30)	20 fewer per 1,000 (from 7 fewer to 57 more)	⊕⊕⊕⊖ MODERATE	CRITICAL
Serious a	dverse events	s (follow up	o: 3 months)									
2	randomised trials	not serious	not serious	not serious	serious <sup>e,f</sup>	none	4/247 (1.6%)	1/249 (0.4%)	RR 4.40 (0.46 to 35.83)	14 more per 1,000 (from 2 fewer to 140 more)	⊕⊕⊕⊖ MODERATE	CRITICAL

#### **Abbreviations**

**CI** = confidence interval, **MD** = mean difference, **mg/dL** = milligrams per decilitre, **RR** = risk ratio.

<u>Notes</u>

**a** = Considerable levels of heterogeneity and inconsistency, **b** = non-overlapping confidence intervals, **c** = surrogate for MI, vascular events, mortality, **d** = unclear applicability of the trial population to the Swiss context, **e** = small event number for sample size, **f** = 95% confidence interval around pooled estimates includes negligible effect and appreciable benefit/harm.

Table 123	GRADE evidence profile table for ezetimib	e plus statins compared statins	s for hyperlipidaemia without ASCVD at 3 months
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Certainty	assessment						Number of pat	ients	Effect		Certainty	Importance
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ezetimibe plus statins	Statins	Relative (95% CI)	Absolute (95% Cl)		
LDL-c (pe	ercentage cha	nge) (follov	v up: 3 months)				-				•	
1	randomised	serious	serious <sup>b</sup>	serious c,d	serious <sup>e</sup>	none	Ezetimibe plus	statins vs statin	s		$\oplus \oplus \bigcirc \bigcirc$	IMPORTANT
	trials	а					-46.1 ± NR vs -	-32.8 ± NR; p=N		LOW		
LDL-c (al	LDL-c (absolute change) (follow up: 3 months)											
1	randomised	serious	serious <sup>f</sup>	serious c,d	serious <sup>e</sup>	none	Ezetimibe plus	statins vs statin	s		$\oplus \oplus \bigcirc \bigcirc$	IMPORTANT
	trials	а					89.7 ± 19.6mg/	/dL vs 114.5 ± 2	1.7mg/dL; p	=NR	LOW	
Withdraw	al due to adve	erse events	(follow up: 3 mo	onths)								•
1	randomised	not	not serious	not serious	serious e	none	Ezetimibe plus	statins vs statin	S		$\oplus \oplus \oplus \bigcirc$	CRITICAL
	trials	serious					5/64 (7.8%) vs	5/64 (7.8%) vs 8/69 (11.6%)			MODERATE	
Adverse	events (follow	up: 3 mon	ths)				•				•	•
1	randomised	not	not serious	not serious	serious e	none	Ezetimibe plus statins vs statins				$\oplus \oplus \oplus \bigcirc$	CRITICAL
	trials	serious					0/64 (0.0%) vs	0/69 (0.0%)			MODERATE	

#### **Abbreviations**

**CI** = confidence interval, **mg/dL** = milligrams per decilitre, **NR** = not reported, **RR** = risk ratio.

## <u>Notes</u>

**a** = Notable losses to follow-up, **b** = measures of variance not reported, **c** = surrogate for MI, vascular events, mortality, **d** = unclear applicability of the trial population to the Swiss context, **e** = one study, small sample size, **f** = overlapping standard deviations.

Certainty	assessment						Number of p	oatients	Effect		Certainty	Importance
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ezetimibe plus fenofibrate	Fenofibrate	Relative (95% CI)	Absolute (95% Cl)		
LDL-c (p	ercentage cha	nge) (follow	up: range 3 to 1	2 months)								
3	randomised trials	serious <sup>a</sup>	serious <sup>b,c</sup>	serious <sup>d,e</sup>	not serious	none	3 months (m MD -19.94% 12 months ( MD -13.40 (s	eta-analysis) (95% CI -31.80 1 study) 95% CI -16.06, -	), -8.09%); p= -10.74%); p<	=0.001 0.001	⊕⊕⊖⊖ LOW	IMPORTANT
Withdrav	val due to adve	erse event (	follow up: range	3 to 12 months)								
3	randomised trials	serious <sup>a</sup>	not serious	not serious	serious <sup>f</sup>	none	23/585 (3.9%)	25/485 (5.2%)	RR 0.74 (0.43 to 1.30)	13 fewer per 1,000 (from 29 fewer to 15 more)	⊕⊕○○ LOW	CRITICAL
Serious a	adverse event	(follow up:	range 3 to 12 mo	nths)	•	•	•	·				
3	randomised trials	serious <sup>a</sup>	not serious	not serious	serious <sup>f</sup>	none	30/585 (5.1%)	15/485 (3.1%)	RR 1.71 (0.64 to 4.53)	22 more per 1,000 (from 11 fewer to 109 more)	⊕⊕○○ LOW	CRITICAL

### Table 124 GRADE evidence profile table for ezetimibe plus fenofibrate compared fenofibrate for hyperlipidaemia without ASCVD at 3 to 12 months

Abbreviations

CI = confidence interval, MD = mean difference, mg/dL = milligrams per decilitre, NR = not reported, RR = risk ratio.

<u>Notes</u>

 $\mathbf{a}$  = Notable losses to follow-up,  $\mathbf{b}$  = considerable levels of heterogeneity and inconsistency,  $\mathbf{c}$  = non-overlapping confidence intervals,  $\mathbf{d}$  = surrogate for MI, vascular events, mortality,  $\mathbf{e}$  = unclear applicability of the trial population to the Swiss context,  $\mathbf{f}$  = 95% confidence interval around pooled estimates includes negligible effect and appreciable benefit/harm.

# 15.6 Appendix F: Ongoing Clinical Trials

Trial registry ID	Indication; Target sample size	Design	Intervention	Comparator	Primary outcomes	Status
EU Clinical Tri	als Register		•	•		
2011-001055- 36	Diabetes, dyslipidaemia n=28	RCT, double- blind, multicentre	Simvastatin Atorvastatin Rosuvastatin Ezetimibe	Fluvastatin Pravastatin	Cost- effectiveness in prescribing leads, determined by initial LDL-c	Ongoing
2016-004556- 30	Patients with primary hypercholeste rolaemia n=1,316	RCT, double- blind, multi centre	Rosuvastatin (10mg) plus ezetimibe (10mg) Rosuvastatin (20mg) plus ezetimibe (10mg) Rosuvastatin (40mg) plus ezetimibe (10mg)	Rosuvastatin (10mg) Rosuvastatin (20mg) Rosuvastatin (40mg)	Change in LDL-c	Ongoing
2009-013622- 17	Suspected stable coronary artery disease candidates to PCI n=1,080	RCT, double- blind, multi centre	Ezetimibe (10mg) Atorvastatin (40mg)	Rosuvastatin (40mg)	Reduction in MI	Ongoing
2008-000824- 20	Type 2 diabetes mellitus n=16	RCT, double- blind, single centre	Simvastatin (10mg) plus ezetimibe (10mg)	Simvastatin (20mg)	vLDL and chylomicron concentration	Ongoing
2019-001912- 50	Patients with coronary artery disease n=120	RCT, open label, multicentre	Ezetimibe (10mg)	Rosuvastatin (40mg) Atorvastatin (40mg)	Coronary plaque size	Ongoing
2004-000959- 42	Hypercholeste rolemia high risk patients: coronary artery disease or diabetes n=553	RT, open label, multicentre	Atorvastatin (10mg) plus Ezetimibe (10mg)	Atorvastatin (20mg) Rosuvastatin (10mg)	Change in LDL-c	Ongoing
Clinicaltrials.g	ov					
NCT0316998 5	Coronary artery disease	RCT, single- blind, single centre	Rosuvastatin (10mg) plus	Rosuvastatin (20mg)	Change in percent	Recruiting

# Table 125 Ongoing clinical trials fitting the inclusion criteria

Trial registry ID	Indication; Target sample size	Design	Intervention	Comparator	Primary outcomes	Status
	n=280		ezetimibe (10mg)		atheroma volume (PAV)	
NCT0304466 5	Cardiovascula r disease n=3,780	RCT, open- label, single centre	Rosuvastatin (10mg) plus ezetimibe (10mg)	Rosuvastatin (20mg)	MACE	Recruiting
NCT0377105 3	CHD n=240	RCT, double- blind, single Centre	Simvastatin (40mg) plus Ezetimibe (10mg)	Simvastatin (40mg)	Change in plaque size	Recruiting
NCT0359741 2	ASCVD Type 2 diabetes mellitus n=244	RCT, Open Label, Single centre	Rosuvastatin (10mg) plus ezetimibe (10mg)	Rosuvastatin (20mg)	Change in LDL-c	Recruiting
NCT0340355 6	ASCVD Type 2 Diabetes n=140	RCT, Open Label, Multi- centre	Rosuvastatin (10mg) plus ezetimibe (10mg)	Rosuvastatin (20mg)	Change in LDL-c	Recruiting
NCT0376842 7	Hypercholeste rolemia n=450	RCT, double- blind, single centre	Atorvastatin (10mg) plus ezetimibe (10mg) Atorvastatin (20mg) plus ezetimibe (10mg)	Atorvastatin (10mg) Atorvastatin (20mg)	Change in LDL-c	Recruiting
NCT0351088 4	Hypercholeste rolaemia n=150	RCT, triple- blind, multi centre	Ezetimibe (mg)	Rosuvastatin (mg NR) Atorvastatin (mg NR) Simvastatin (mg NR) Pravastatin (mg NR) Lovastatin (mg NR) Fluvastatin (mg NR) Fluvastatin (mg NR) Cholestyramin e (mg NR) Nicotinic acid Fenofibrate Omega-3 fatty acids Placebo Alirocumab	Change in LDL-c	Ongoing

Trial registry ID	Indication; Target sample size	Design	Intervention	Comparator	Primary outcomes	Status
				SAR236553 (REGN727)		
NCT0399323 6	Stroke n=584	RCT, open label, multicentre	Rosuvastatin (NR) plus ezetimibe (10mg)	Rosuvastatin (20mg)	Change in LDL-c	Recruiting
NCT0439765 3	Hypercholeste rolemia, chronic kidney disease n=50	RCT, quadruple- blind, single centre	Ezetimibe (mg NR)	PCSK9 (140mg) Placebo	Change in LDL-c	Recruiting
NCT0449985 9	MI, statin adverse reaction n=3,548	RCT, open label, multicentre	Rosuvastatin (5mg) plus ezetimibe (10mg)	Rosuvastatin (20mg)	MACE	Not yet recruiting
NCT0443353 3	Hyperlipidaem ia, left ventricular diastolic dysfunction n=200	RCT, open label, single centre	Rosuvastatin (10mg) plus ezetimibe (10mg)	Rosuvastatin (20mg)	Change in LDL-c	Not yet Recruiting
NCT0394786 6	Hypercholeste rolemia or hyperlipidaem ias n=2,000	Observational Study, multicentre	Simvastatin (NR) plus ezetimibe (NR)	NR	Change in LDL-c	Not yet Recruiting
NCT0364878 8	Mixed dyslipidaemia n=600	Observation study	Rosuvastatin (NR) plus ezetimibe (NR)	NA	Safety	Not yet Recruiting
NCT0335502 7	ASCVD n=60	RCT, open label, single centre	Ezetimibe (10mg)	Atorvastatin (40mg) Atorvastatin (80mg) Rosuvastatin (20mg) Rosuvastatin (40mg) Simvastatin (80mg) Alirocumab (150mg/ml)	Vascular inflammation	Ongoing
NCT0354377 4	Hypercholeste rolemia Chronic kidney disease n=30	RCT, open label, single centre	Simvastatin (20mg) plus ezetimibe (10mg) Simvastatin (40mg) plus	Simvastatin (40mg)	Change in LDL-c	Recruiting

Trial registry ID	Indication; Target sample size	Design	Intervention	Comparator	Primary outcomes	Status
			ezetimibe (10mg)			
NCT0393329 3	Homozygous familial hypercholeste rolemia n=59	RCT, quadruple- blind, multicentre	Ezetimibe (NR)	Statins (NR)	Change in LDL-c, AE	Recruiting
NCT0435843 2	Hypercholeste rolemia n=260	RCT, triple- blind, centre single	Statins (NR) plus ezetimibe (NR) Ezetimibe (NR)	Statins (NR) Placebos AK102	Change in LDL-c	Not yet Recruiting
NCT0417379 3	Heterozygous familial hypercholeste rolemia n=168	RCT, triple- blind, multicentre	Statins (NR) plus ezetimibe (NR) Ezetimibe (NR)	Statins (NR) Placebos AK102	Change in LDL-c	Not yet Recruiting
NCT0417340 3	Hypercholeste rolemia n=200	NR, open label, single centre	Statins (NR) plus ezetimibe (NR) Ezetimibe (NR)	Statins (mg NR) AK102 (450mg) AK102 (300mg) AK102 (150mg)	Change in LDL-c	Not yet Recruiting

#### Abbreviations

AE = adverse events, ASCVD = atherosclerotic cardiovascular disease, CHD = coronary heart disease, HDL-c = high density lipoprotein, LDL-c = low density lipoprotein-cholesterol, MACE = major adverse cardiac event, MI = myocardial infarction, n = number of patients, NA = not applicable, NR = not reported, PCI = percutaneous coronary intervention, RCT = randomised controlled trial.

## <u>Notes</u>

**a** = dyslipidaemia not defined.