25 November 2016

EZETIMIBE REVIEW

SYSTEMATIC LITERATURE REVIEW

Health Technology Assessment Team

CPHR
CENTRE FOR POPULATION HEALTH RESEARCH

DEAKIN UNIVERSITY

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Terms of reference for the post-market review of ezetimibe and associated research questions

The purpose of the Post-market Review of Ezetimibe is to review the cost-effectiveness of ezetimibe, in the context of the latest available evidence and best clinical practice.

The terms of reference (ToR) for this post-market review were, as approved by the Minister for Health, are:

- **ToR 1:** Review current utilisation of PBS-listed ezetimibe and ezetimibe combination products. Any review will consider additional data sources that may inform the current utilisation of ezetimibe.
- **ToR 2:** Review recent clinical guidelines for the treatment of hypercholesterolaemia and compare this to how ezetimibe is currently used on the Pharmaceutical Benefits Scheme (PBS);
- **ToR 3** Collate and evaluate any recent clinical studies of ezetimibe that report on long term patient relevant outcomes, and use this data to review the cost-effectiveness of ezetimibe;

ToR 1– review of utilisation of ezetimibe on the PBS

Q1: In November 2013, the PBAC expressed concern that the listing of ezetimibe with statin co-packs and combination products on the PBS may direct use away from optimal dose titration of statins. Is ezetimibe being prescribed on the PBS in accordance with the PBS restrictions for ezetimibe, which require up-titration of statins to maximally tolerated doses before initiation of treatment with ezetimibe?

ToR 2 – review of clinical guidelines on the management of hypercholesterolaemia

Q1: Are the eligibility criteria for PBS subsidy of lipid-lowering therapies (as specified in the General Statement for Lipid-Lowering Drugs [GSLLD]) consistent with Australian guidelines for primary (NVDPA-2012) and secondary (NHF-2012) prevention of cardiovascular events?

Q2: Are the Australian NVDPA guidelines consistent with international guidelines?

ToR 3 – review of clinical evidence and conduct of review of cost-effectiveness of ezetimibe

Q1: Is addition of ezetimibe (EZ) to the maximum tolerated dose of statin is associated with superior long-term outcomes of survival, quality- adjusted survival, fatal and non-fatal CVD events in comparison to placebo + maximum tolerated dose of statin?

Q2: Is addition of EZ to the maximum tolerated dose of statin associated with superior surrogate outcomes i.e., lipid endpoints (e.g. Total-C, LDL-C and HDL-C)?

Q3: Is addition of EZ to various fixed doses of statin associated with superior long-term patient outcomes or surrogate outcomes in comparison to placebo + matching dose of statin?

Q4: Is addition of EZ to statins associated with superior long-term patient outcomes or surrogate outcomes compared with up-titration of statins (either in terms of dose or potency)?

Q5: If it is established, that addition of EZ to statins is associated with superior final or surrogate outcomes, whether the listed price for EZ is justified considering the additional benefits?

Q6: Is reduction in LDL-c a valid surrogate for reduction in risk of cardiovascular (CV) events?

1.1. Background

1.1.1. Abbreviated PBS restrictions applying to ezetimibe

The key requirements for eligibility for PBS-subsidised treatment with ezetimibe are as follows:
Monotherapy

Patients must meet the criteria of the General Statement for Lipid-Lowering Drugs (GSLLD);

AND

(i) developed a clinically important product-related adverse event during treatment with a statin necessitating a reduction in the statin dose; or
(ii) a contraindication to treatment with a statin.

A clinically important product-related adverse event is defined as follows:

(i) Severe myalgia (muscle symptoms without creatine kinase elevation) which is proven to be temporally associated with statin treatment; or
(ii) Myositis (clinically important creatine kinase elevation, with or without muscle symptoms) demonstrated by results twice the upper limit of normal on a single reading or a rising pattern on consecutive measurements and which is unexplained by other causes; or
(iii) Unexplained, persistence elevations of serum transaminases (greater than 3 times the upper limit of normal) during treatment with a statin.

Combination therapy to be co-administered with HMG CoA reductase inhibitor (statin);

The treatment must be in conjunction with dietary therapy and exercise;

AND

The patient must have cholesterol levels that are inadequately controlled with an HMG CoA reductase inhibitor (statin);

AND

The patient must have one of the following conditions

- coronary heart disease (CHD); or
- diabetes mellitus; or
- peripheral vascular disease; or
- heterozygous familial hypercholesterolaemia; or
- symptomatic cerebrovascular disease; or
- a family history of coronary heart disease; or
- hypertension; or
- developed a clinically important product-related adverse event during treatment with an HMG CoA reductase inhibitor (statin) necessitating a reduction in atorvastatin dose [1]

Inadequate control with a statin is defined as follows:

[1] Applies only to 10mg atorvastatin restriction

1) where the patient falls into a category for which the General Statement for Lipid-Lowering Drugs (GSLLD) includes an initial cholesterol threshold for PBS-subsidy (i.e. a patient not in a very high risk category), a cholesterol level in excess of that threshold after at least 3 months of treatment at a maximum tolerated dose of a statin, in conjunction with dietary therapy and exercise; or
2) where the patient falls into a category for which the GSLLD allows PBS-subsidised treatment with a statin at any cholesterol level (i.e. a very high risk category patient), a cholesterol level in excess of 4 mmol/L after at least 3 months of treatment at a maximum tolerated dose of a statin, in conjunction with dietary therapy and exercise.

1.1.2 Summary of the PBAC's key positive recommendations for ezetimibe

The list of positive recommendations below includes the references to evidentiary basis (primary and supporting) for the PBAC's determinations that ezetimibe should be included on the PBS for various patient populations/indications.

June 2003

At this meeting, the PBAC recommended listing of:

- ezetimibe monotherapy for patients with homozygous sitosterolaemia[2] and
- ezetimibe in combination with satins in patients with homozygous familial hypercholesterolaemia[2] (HoFH);
- ezetimibe monotherapy in patients who are contraindicated or intolerant of statins; this listing was recommended on the basis of pricing being related to the extent of LDL cholesterol reduction with ezetimibe compared with the statins.

The evidentiary basis considered by the PBAC comprised:

- *for patients with homozygous sitosterolaemia - Protocol P02243/P02257, a trial that compared addition of ezetimibe with addition of placebo to current treatment in patients with homozygous sitosterolaemia*
- *for patients with HoFH - Protocol P01030 (Gagne 2002[1] [Circulation]), a three-arm trial that compared (i) addition of ezetimibe to background treatment with 40 mg atorvastatin or 40 mg simvastatin, (ii) addition of ezetimibe and increase in dose of statin to 80mg; and (iii) increase in statin dose to 80 mg in patients with HoFH;*
- *for patients where statins are inappropriate - two trials comparing ezetimibe monotherapy with placebo in patients with primary hypercholesterolaemia and LDL-c between 3.4 and 6.5 mmol/L (Protocol P00475 [Dujovne 2002[2]]; Protocol P00474 [Knopp 2003[3]]).*

September 2003

At this meeting, the PBAC recommended listing of:

- ezetimibe monotherapy in patients who are contraindicated or intolerant of statins; this listing was recommended on a cost-minimisation versus cholestyramine as a comparator. However, the PBAC noted that the prices of bile acid sequestrants were higher than those of the statins in terms of their ability to lower LDL cholesterol. The Pricing Authority should thus be advised that the price of these products should relate to their ability to lower LDL cholesterol levels.

The evidentiary basis considered by the PBAC was an indirect comparison of ezetimibe and cholestyramine using placebo as the common reference. Two trials comparing ezetimibe and placebo in

[2] This indication is outside the scope of the Review

patients with primary hypercholesterolaemia and LDL-c between 3.4 and 6.5 mmol/L (Dujovne 2002[2]; Knopp 2003[3]) and seven trials that included a comparison of cholestyramine versus placebo (or pravastatin) in various patient populations (Lipid Research Clinics Program Coronary Primary Prevention Trial [population: men with primary hypercholesterolaemia]; NHLBI Type II Coronary Intervention Study [population: patients with hypercholesterolaemia and coronary artery disease; Garg 1994 [population: patients with dyslipidaemia and non-insulin dependent diabetes]; Betteridge 1992 [population: patients with heterozygous familial hypercholesterolaemia {HeFH}]; Wiklund 1990 [population: familial hypercholesterolaemia; comparator: pravastatin]; Levy 1973 [population: patients with hypercholesterolaemia]; Pravastatin Multicentre Study Group II 1993 [population: patients with hypercholesterolaemia; comparator: pravastatin]) were used to conduct the indirect comparison. The endpoint upon which comparative efficacy was determined was reduction in LDL-C from the baseline.

December 2003

At this meeting, the PBAC recommended listing of:

- ezetimibe in combination with 40 mg or greater of statin in patients with coronary heart disease and/or diabetes whose cholesterol levels remain inadequately controlled after at least 3 months of treatment (i.e., cholesterol level exceed the threshold for initiation of cholesterol-lowering therapy as detailed in the qualifying criteria in the General Statement for Lipid-Lowering Drugs).

The evidentiary basis considered by the PBAC comprised:

- *three trials (P00680 Simvastatin Factorial Study [Davidson 2002[4]], P00692 Atorvastatin Factorial Study [Ballantyne 2003[5]] and P02173/P02246 Ezetimibe Add-on Study [Gagne 2002[6] {Am J Cardiol}, Simons 2004[7]] comparing ezetimibe added to fixed doses of statin vs placebo added to matching fixed doses of statin in patients with hypercholesterolemia (with no limitations on whether patients were receiving primary or secondary prevention however patients in the Ezetimibe Add-On Study were required to be at high risk of CV events);*
- *One trial Atorvastatin Filter Study Protocol P00693 (Stein 2002, 2003, 2004[8]; Vermaak 2002, 2003) comparing ezetimibe added to atorvastatin followed by up-titration of atorvastatin vs placebo added to atorvastatin followed by up-titration of atorvastatin in patients with hypercholesterolemia with no limitations on whether patients were receiving primary or secondary prevention however all patients were required to be at high risk of cardiovascular events;*

Patients in these trials were not required to be on the maximum tolerated dose of statin at baseline in any of the trials.

March 2005

At this meeting, the PBAC recommended listing of a two fixed dose combination (FDC) products for patients with coronary heart disease and/or diabetes and for patients with HoFH. One FDC contained ezetimibe 10mg + simvastatin 40 mg and the other contained ezetimibe 10mg + simvastatin 80 mg. Listing was on a cost-minimisation basis versus the components used concomitantly. The listing required that patients must be stabilised on ezetimibe before being transferred to the FDC product.

July 2005

At this meeting, the PBAC agreed to removal of the requirement that patients must be stabilised on ezetimibe before being transferred to an FDC product (i.e., permitting patients on statins to directly transfer to the FDC).

November 2005

At this meeting, the PBAC recommended listing of:

- ezetimibe in combination with 40 mg or greater of statin in patients with peripheral vascular disease (PVD) whose cholesterol levels remain inadequately controlled after at least 3 months of treatment (i.e., cholesterol level exceed the threshold for initiation of cholesterol-lowering therapy as detailed in the qualifying criteria in the general statement for lipid-lowering drugs).
- Ezetimibe in combination with statin in patients with heterozygous familial hypercholesterolaemia (HeFH).

The evidentiary basis considered by the PBAC comprised:

- *For the PVD indication*
  - *two trials previously considered at the June and December 2003 PBAC meetings (Ezetimibe Add-on Study P02173/P02246 [Gagne 2002[6], Simons 2004[7]] and Atorvastatin Filter Study Protocol P00693 [Stein 2002, 2003, 2004[8]; Vermaak 2002, 2003]*
  - *supporting evidence from the following seven studies: 1)The EASE study (Pearson 2005[9], Denke 2004), a trial which compared addition of ezetimibe or placebo to background statin therapy in patients with diabetes, metabolic syndrome or metabolic dyslipidaemia who had LDL-c levels that exceeded targets recommended by the US National Cholesterol Education Program Adult Treatment Panel III Guidelines (NCEP ATPIII); 2) Wierzbicki 2005[10], a before-and-after study investigating addition of ezetimibe to maximally tolerated doses of statins in patients with HeFH; 3) Protocol 801 (Brohet 2005[11]), a trial comparing addition of ezetimibe to addition of placebo to background therapy with simvastatin in patients with documented CHD and hypercholesterolaemia (LDL-c between 2.6 and 4.2 mmol/L); 4) Geiss 2004, 2005[12], a crossover study comparing addition of ezetimibe or placebo to background therapy with statins and apheresis in patients with severe hypercholesterolaemia and documented CHD; 5) Protocol 023 (Feldman[13] 2004), a trial comparing up-titration of atorvastatin with ezetimibe + up-titration of simvastatin in patients with high risk of CV events (CHD or equivalent risk) and hypercholesterolaemia (LDL-c >3.4 mmol/L); 6) Protocol 051 (Ballanatyne 2004[14], 2005[15]), a trial comparing addition of ezetimibe and placebo to background simvastatin therapy and to atorvastatin monotherapy in patients with high risk of CV events (due to CHD or combination of risk factors that include LDL-c at baseline); 7) Protocol 021 (Gaudiani 2004, 2005[16]), a trial comparing addition of ezetimibe to simvastatin 20 mg with up-titration of simvastatin to 40 mg in patients with thizolidinedione-treated type 2 diabetes mellitus.*
- *For the HeFH indication*
  - *a subgroup analysis of HeFH patients included in the Astorvastatin Filter Study Protocol 00693 (Stein 2002, 2003, 2004[8]; Vermaak 2002, 2003). Supporting evidence was as specified above for the PVD indication.*

The submission also requested PBS-listing of ezetimibe in combination with statin in patients with symptomatic cerebrovascular disease (CVD) but the PBAC rejected this request because the General Statement for Lipid-Lowering Drugs current at the time did not include this patient group. However, the Committee indicated that it had no objection to the inclusion of this patient group if and when the recommended changes to the General Statement occurred. On 5 September 2006, an announcement was made that the new GSLLD as recommended by the PBAC would be implemented on 1 October 2006. Consequent to these changes, the listing of ezetimibe and ezetimibe + simvastatin FDCs were changed to include patients with symptomatic cerebrovascular disease.

November 2006

At this meeting, the PBAC recommended listing of:

- Ezetimibe in combination with 40 mg or greater of statin in patients with hypertension whose cholesterol levels remain inadequately controlled
- Ezetimibe in combination with 40 mg or greater of statin in patients with a family history of coronary heart disease whose cholesterol levels remain inadequately controlled.

The evidentiary basis considered by the PBAC was a meta-analysis of results from four previously presented trials where ezetimibe was compared with placebo as add-on therapy to a fixed dose of statins (Protocol 2173/2246 (Gagne 2002[6], Simons 2004[7]); EASE study (Pearson 2005[9], Denke 2004); Protocol 801 (Brohet[11] 2005); Protocol 1030 in HoFH patients (Gagne[1] 2002) and two previously unpresented trials - Protocol 803/804 (Cruz-Fernandez 2005[17]), which compared ezetimibe and placebo as add-on therapy to stable dose of background atorvastatin (10 mg or 20 mg per day) in patients with CHD who had not achieved LDL-c target of 2.6 mmol/L; Protocol 802 (Farnier[18], 2005), which compared ezetimibe and placebo as add-on therapy to stable dose of background simvastatin (10 mg or 20 mg per day) in patients with CHD who had not achieved LDL-c target of 2.6 mmol/L.

At this meeting, the PBAC also agreed to extending the listing for ezetimibe to permit combination use in patients being treated with statins at a dose of 20 mg per day (changed from 40 mg per day). The PBAC also extended the listing for the FDC products to patients with hypertension or a family history of CHD.

At this meeting the PBAC indicated that *any future applications for extensions to the listing of ezetimibe either as monotherapy or in combination with simvastatin must be accompanied by a comparison against a therapeutic strategy where the dose of statin is increased or a switch to a more potent (on a mg per mg basis) statin is made*, eg. simvastatin 20 mg to atorvastatin 20 mg; atorvastatin 20 mg to rosuvastatin 20 mg because these strategies are increasingly being used in clinical practice and are therefore appropriate additional comparators to placebo.

July 2009

At this meeting, the PBAC recommended listing of a two additional FDC products for patients with HoFH. One FDC contained ezetimibe 10mg + simvastatin 10 mg and the other contained ezetimibe 10mg + simvastatin 20 mg. Listing was on a cost-minimisation basis versus the components used concomitantly.

November 2010

At this meeting, the PBAC recommended that the restriction for ezetimibe be amended to incorporate wording that did not specify a particular dose of a statin be attempted to achieve an appropriate lowering of cholesterol. Instead the wording should stipulate a three month trial with the maximum tolerated dose of a statin. The PBAC considered that this option would allow ezetimibe to be added as clinically appropriate while continuing to support up-titration of statins as the first line treatment of hypercholesterolaemia.

In summary, although the PBS listing of ezetimibe is for use in combination with maximally tolerated dose of statins in patients considered at high risk of CV events, the primary source of evidence considered by the PBAC was not trials investigating efficacy of ezetimibe added to maximally tolerated dose of statins. The primary source of evidence considered by the PBAC consisted of trials that involved addition of ezetimibe to various fixed doses of statin (compared to placebo added to the same fixed doses of statins) and trials that compared addition of ezetimibe to background therapy with statins to up-titration of the dose of a statin.

For the detailed history of PBS decisions on listing ezetimibe see the EXCEL spreadsheet in a separate Appendix.

2.1. Literature search methods

2.1.1. Search criteria

Randomised trials

The primary objective of the literature search was to identify all head-to-head randomised controlled trials that assess ezetimibe as monotherapy or ezetimibe co-administered with a statin therapy in the target patient population, or the population that overlaps with the target Australian population.

Search filters were set to include only randomised trials, as follows:

a) The trial included a randomisation procedure in its design (use Cochrane Highly Sensitive Search Strategies);

b) The trial assesses ezetimibe vs the relevant comparator(s);

c) The trial recruits participants with characteristics that overlap with those of the target population.

Systematic reviews and meta-analyses

Relevant systematic reviews and meta-analyses of randomised trials were identified separately.

2.1.2. Search terms

Table 2.1.1 illustrates the search terms with respect to the study design, population and intervention.

Table 2.1.1 Primary search terms used the systematic literature search

Category	Description	Search terms
Study design	Limited to RCTs (extensions of the RCTs were not necessarily excluded)	Cochrane Highly Sensitive Search Strategies for identifying randomised trials in MEDLINE
Population	Patients with hypercholesterolemia	Hypercholesterolaemia or hypercholesterolemia
Intervention	Ezetimibe monotherapy Ezetimibe in the second line treatment (i.e. used in combination with other lipid-lowering drug) (ezetimibe in the first line treatment was not necessarily excluded)	Ezetimibe, Simvastatin Drug Combination/ or Ezetimibe/ or Ezetimibe or Ezetrol/Zetia

Complete search terms used in the systematic literature search are presented in Appendix 1.

2.1.3. Search strategy

The major databases including MEDLINE, EMBASE, and Cochrane databases were searched to identify peer-reviewed publications related to ezetimibe in treating adult patients with familial or non-familial hypercholesterolemia. The search of registries of randomised trials and sponsor's PBAC submissions, commentaries was also performed. Manual search of reference lists of all relevant publications was undertaken. All searches were conducted on the 24th of May 2016 and updated in October 2016. Additional search of Clinical Trial Registry (https://clinicaltrials.gov/ct2/home) was undertaken on 1st of September 2016 to identify any registered and completed phase III or IV clinical trials involving ezetimibe for treatment of hypercholesterolaemia.

Appendix 1 lists the electronic databases searched and periods covered by the searches.

2.2. Identified relevant trials

2.2.1. Search results

Selection criteria

Of the citations returned by electronic literature search, systematic reviews and RCTs assessing clinical efficacy and economic outcomes of ezetimibe in adult patients with uncontrolled hypercholesterolemia were eligible for inclusion. Two reviewers independently screened all titles and abstracts. Full paper manuscripts of any titles/abstracts that were considered relevant by either reviewer were obtained where possible. The relevance of each paper was assessed according to the selection criteria set out below (Table 2.2.1). Any disagreement were resolved by discussion.

Table 2.2.1 Selection criteria

	Inclusion criteria	Exclusion criteria
Population	*(i) Eligible for ezetimibe+statin combination treatment according to PBS restriction (both primary or secondary prevention population)*	Adults without a diagnosis of a symptomatic CVD that do not meet high risk criteria either in GSLLD or NVDPA-2012 guidelines Special subgroups of the population with homozygous sitosterolaemia or homozygous familial hypercholesterolemia
	Patients are required to have baseline cholesterol levels that are above a threshold: • where the patient falls into a category for which the GSLLD includes an initial cholesterol threshold for PBS-subsidy (i.e. a patient not in a very high risk category), a cholesterol level in excess of that threshold after at least 3 months of treatment at a maximum tolerated dose of a statin, in conjunction with dietary therapy and exercise; or • where the patient falls into a category for which the GSLLD allows PBS-subsidised treatment with a statin at any cholesterol level (i.e. a very high risk category patient), a cholesterol level in excess of 4 mmol/L after at least 3 months of treatment at a maximum tolerated dose of a statin, in conjunction with dietary therapy and exercise.	
	(ii) Eligible for treatment with ezetimibe +statin according to NVDPA guidelines (primary prevention population)	
	The PBS restricted listing of ezetimibe for patients with hypercholesterolaemia can be considered to be equivalent to	

	the criteria for lipid-lowering therapy recommended by NVPDA guidelines to patients at high and high to moderate absolute risk of a cardiovascular (CV) event over the next five years"[3]. Notably, the NVPDA guidelines recommend lipid-lowering treatment for patients considered • at high risk (i.e. ≥ 15% risk of CV event in the next 5 years as determined by the absolute risk assessment using Framingham equation or the decease -specific thresholds applicable to diabetes, chronic kidney disease, hypertension etc.); or • at moderate risk (10-15% of CV event in the next 5 years) if they meet some other criteria such as hypertension, family history of premature CVD or ethnicity.	
	(iii) Eligible for treatment with ezetimibe monotherapy Although monotherapy with ezetimibe is only permitted under the PBS for patients in whom statins are contraindicated or not tolerated, it is unlikely that trials conducted specifically in populations in whom statins are contraindicated or not tolerated have been performed. The same eligibility criteria as in ezetimibe+statin combination treatment according to PBS restriction in NVPDA guidelines apply to selecting ezetimibe monotherapy trials	
Intervention	•Ezetimibe monotherapy •Ezetimibe administered 10mg daily (orally) in combination with simvastatin (SIM) •Ezetimibe administered 10mg daily (orally) in combination with atorvastatin (ATOR) •Ezetimibe administered 10mg daily (orally) in combination with rosuvastatin (ROSUV)	Trials investigating combination use of ezetimibe and statins other than SIM, ATOR or ROSUV
Comparator	For ezetimibe monotherapy • no treatment (placebo) • cholestyramine For ezetimibe using in combination with a statin (SIM;ATOR or ROSUV) • matching statin therapy ± no treatment (placebo) • up-titration of statin therapy (either in terms of dose or in terms of potency) ± no treatment (placebo)	studies of bile acid sequestrants + statin. studies of fibrates + statin. studies of niacin + statin. studies of omega-3 fatty acids + statin studies if there was only placebo comparator (i.e. without a statin background therapy) studies (or individual arms of the trial) of pravastatin or fluvastatin as more potent statins

Final Outcomes	• Survival;
	• Quality-adjusted survival
	• Fatal cardiovascular and cerebrovascular events;
	• Non-fatal events;
	  ○ cardiovascular events;
	  ○ cerebrovascular events, and
	  ○ revascularization procedures	

Surrogate outcomes	• lipid end-points, such as Total-C, LDL-C and HDL-C;	Trials reporting only measures of atherosclerosis (e.g., carotid intimal media wall thickness, coronary artery calcification score) The factorial studies that did not report results separately for each specific strength, so only pooled data is reported and the original data could not be recovered from the previous submissions
Safety outcomes	The following safety endpoints will be considered: • adverse events (AEs) • serious adverse events (SAEs) • AEs leading to premature discontinuation of study drug	

[3] Personal communication with professor Lloyd Sansom

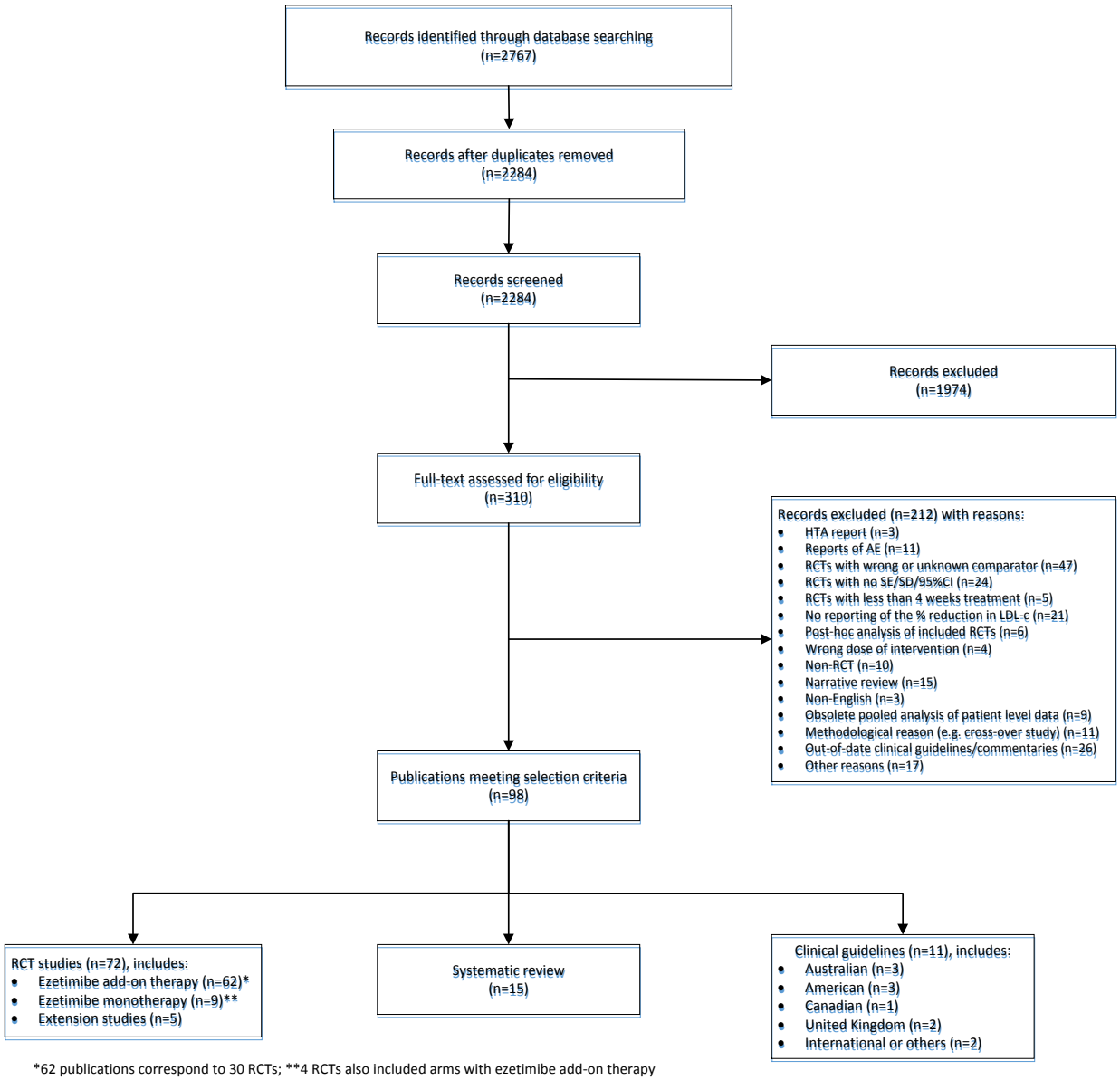
	• AEs of specific interest, including
	  ○ cancer,
	  ○ elevated liver transaminases;
	  ○ musculoskeletal events,
	  ○ newly diagnosed diabetes mellitus,
	• acute kidney injury	

Study design	• Phase III-IV randomised controlled trial (RCT) including open-label trials; • Extensions of the RCTs if they meet selection criteria for "add-on" or "up-titration" studies; • Extension of clinical trials over 24 weeks duration (to inform final patient and safety outcomes)	• non- Phase III or IV RCTs • observational study; • review articles (including reviews of cholesterol absorption inhibitors, ezetimibe data to data, new and current lipid lowering therapies, lipid management, clinical place of combination therapy, review of conference abstracts); • editorials, opinions; • published only as abstracts • available only as conference presentations; • non–English-language publications. • RCTs considered of poor quality according to the amended Cochrane quality assessment criteria (i.e. the trials that do not report the measure of variation around the endpoints are automatically considered poor quality)
Duration	Treatment of at least 4 weeks	• RCT with less than 4 weeks treatment duration
Others	-	• Biochemistry, chemistry studies; • preclinical animal studies, pharmacology studies; phase I and II pharmacokinetic and pharmacodynamics studies, clinical pharmacology, dose finding studies; • register of new chemical entities under investigational use; • industry news/drug discovery/new developments

* NVDPA = National Vascular Disease Prevention Alliance; NHF=National Heart Foundation; CHD=coronary heart disease

A PRISMA flowchart (Figure 2.2.1) presents the number of papers processed at each stage of study selection and the reasons for exclusions.

Figure 2.2.1 PRISMA flowchart



*62 publications correspond to 30 RCTs; **4 RCTs also included arms with ezetimibe add-on therapy

2.2.2. Annotated search results

The literature search identified 310 full reports that were further assessed for eligibility. 208 publications were excluded as not meeting the selection criteria, such as the wrong comparator, wrong intervention (e.g. the dose was not listed on the PBS), *post-hoc* analyses of data from the already identified RCTs etc. A number of trials were excluded because of the poor quality of reporting. An additional search of Clinical Trial Registry identified three Korean studies (NCT00166504, NCT00496730, NCT00442897) examining the ezetimibe add-on therapy. However the full-text of these trial reports were not located for further assessment of their eligibility for the systematic review. The final update was conducted in October 2016 and identified one recently published meta-analysis.

The final selection consisted of 62 publications that correspond to 30 original RCTs that met the selection criteria for clinical efficacy and safety ezetimibe co-administered with a statin. Four of these RCTs were also used in the assessment of efficacy and safety of ezetimibe monotherapy. Five open-label extension studies of the included trials were identified (Ballantyne 2004[14]; Bays 2008[19]; Masana 2005[20]; Ose 2007[21]; Strony 2008[22]) but were subsequently excluded due to inadequate reporting of the outcomes (no long-term patient outcomes and no baseline data for comparison of the surrogate outcomes). Table 2.2.4.1 in Section 2.2.4 below shows the master list of the RCTs of ezetimibe co-administered with a statin vs placebo added to a statin (equivalent to statin monotherapy).

The literature search identified 18 publications that assessed clinical efficacy and safety of ezetimibe monotherapy, including four publications that assessed ezetimibe as monotherapy in one of the arms, while ezetimibe was co-administered with a statin in other arms of these trials. Nine of the identified 18 publications met the selection criteria. Other studies were excluded because of insufficient reporting of the measure of variation around the endpoints. Table 2.2.4.1 in Section 2.2.4 below shows the master list of the RCTs of ezetimibe as monotherapy.

Table A2.1 in Appendix 2 lists the excluded published reports of the identified RCTs with reasons.

A separate systematic literature search was conducted to identify systematic reviews that assessed clinical efficacy and safety of ezetimibe monotherapy or ezetimibe co-administered with a statin therapy in treatment of hypercholesterolaemia. Systematic reviews were included if they analysed final patient outcomes and/or surrogate outcomes reported in randomised, controlled trials (RCTs) and open-label extensions that documented the final outcomes and/or adverse events.

We identified 15 publications (AHRQ 2009=Sharma 2009a[23] &Sharma 2009b[24]), AHRQ 2014[25]; Gudzune, 2014[26]; Mikhailidis 2007[27]; Mikhailidis 2011[28]; Tunceli 2010[29]; Kashani 2008[30]; Luo 2015[31]; Sando 2015[32]; Ijioma 2011[33]; HTA 2008=Ara 2008[34]; Pandor 2009[35]; Battagia 2015[36], Silverman[37]) representing 12 original systematic reviews that met the selection criteria. In addition, an independent assessment (HTA 2015) of the 2015 Merck and Co ezetimibe submission to the UK National Institute for Health and Clinical Excellence (NICE) was located on the Internet. These are described in Section 2.2.3.

2.2.3. Systematic reviews of clinical efficacy and safety of ezetimibe monotherapy and ezetimibe in combination with a statin

Table 2.2.3.1 provides the short summary of the identified systematic reviews. For more details and results of assessment of the quality of the systematic reviews refer to Appendix 3, which describes the identified systematic reviews in terms of objectives, population, selection criteria, methods and results. Assessment of the quality of identified reviews was carried out according to the criteria of the Centre for Review Dissemination (UK). Most of the identified reviews were of high or good quality. Two of the systematic reviews were assessed as poor quality (Sando 2015[32]; Ijioma 2011[33]) and excluded from further consideration.

In many instances the strength of evidence was moderate to poor due to a paucity of studies and poor quality of existing studies. In risk of bias assessment the identified trials were frequently downgraded for lack of blinding by participant and study personnel (performance bias), for not reporting the blinding of outcome assessors (detection bias), or for not accounting for losses to follow up or handling of incomplete data (attrition bias). Variance estimates for the between group differences in any outcomes over time was often not reported. In some instances, the studies did not report a mean difference or

point estimate stating only that there was no significant difference between the groups. In addition, some studies did not report an intention-to-treat analysis and others did not specify the number analysed in each arm. Studies often pooled results on adverse effects across arms, which limited the authors' ability to compare the rates of adverse events in the intervention and comparators arms or with respect to the different doses and potencies of combination and monotherapy. Given the poor quality of reporting and small number of trials some of the identified systematic reviews did not conduct meta-analyses (e.g. all AHRQ reports and subsequent publications). Where meta-analysis was conducted, substantial heterogeneity was present in most cases. The evidence base was also limited due to the short duration of most identified trials.

Only the most recent updates of the earlier work are included in the narrative description below, i.e. only results presented in the systematic review by Gudzune 2014[26] and the 2014 AHRQ report that presented an update of Sharma (2009)[23] and the 2009 AHRQ report in the population at a high risk of CVD were included. These systematic reviews included the high to medium risk population with most of the trials included in Gudzune 2014[26] systematic review specifically targeting the secondary prevention population (i.e. patients diagnosed with CHD). The AHRQ reports categorised the RCTs by the intensity of statin in the intervention and the comparator arms. The HTA 2008 and HTA 2015 reports identified the target population as patients with hypercholesterolaemia who are inadequately controlled on statin monotherapy. The primary analysis was conducted in a general population, but subgroup analyses for high risk population and a subgroup with DM was also attempted. *Unlike our review, none of the published systematic reviews categorised the trials by the first or the second line of ezetimibe therapy*.

Table 2.2.3.1 Systematic reviews identified in the systematic literature search

Systematic review/ country	Population	Relevant interventions/ comparators	End points reported and/ or meta-analysed	Main conclusion	Relevance to the present review
Sharma M, Ansari MT, Abou-Setta AM, Soares-Weiser K, Ooi TC, Sears M, et al. Systematic review: comparative effectiveness and harms of combination therapy and monotherapy for dyslipidemia. Ann Intern Med. 2009;151:622-30. Sharma M, Ansari M, Soares-Weiser K, Abou-setta A, Ooi T, Sears M, et al. Comparative Effectiveness of Lipid-Modifying Agents. AHRQ Evidence Report 09-EHC024-1. 2009. USA	High-risk patients with dyslipidaemia (defined as those with a 10 year coronary heart disease risk greater than 20%, mean baseline low-density lipoprotein levels of at least 5.0 mmol/L (≥190 milligrams/ decilitre, or both) who require an intensive lipid-lowering therapy.	Ezetimibe mg / Simvastatin mg 10/10, 10/20, 10/40, 10/80; compared to a statin administered in a higher or the matching dose to the statin in the intervention arm	All-cause mortality and vascular death; MI, acute coronary syndrome, stroke, transient ischaemic attack, and re-vascularisation procedures. SAE & AE; attainment of adenosine triphosphate and ATP-III LDL-C goals, LDL-C and HDL-C	Lower target lipid levels were more often achieved with statin– ezetimibe combination than with high-dose statin mono-therapy. Insufficient evidence that combining a statin with another agent improved final outcomes (MI, stroke, or mortality) more often than high- dose statin monotherapy	Moderately relevant to a subgroup without a diagnosed CHD (primary prevention population). Limited indication (ez+simvastatin only). Patients were not required to be at the highest tolerated dose of statin in either arm. Definition of high risk inconsistent with GSLLD criteria
Gudzune, Monroe, Sharma, et al Effectiveness of combination therapy with statin and another lipid-modifying agent compared with intensified statin monotherapy: a systematic review. Annals of Internal Medicine; 2014; 160(7) 468-76 Anne K. Monroe, Combination Therapy Versus Intensification of Statin Monotherapy: An Update AHRQ Publication No. 14-EHC013-EF February 2014 USA	Adults at moderate to high-risk of atherosclerotic CVD (defined as 10-year CHD risk ≥10% or baseline LDL-C ≥190 mg/dL (4.91 mmol/L), pre-existing ASCVD, or DM	A "moderated" combination regimen of a lower dose of a statin + non-statin lipid lowering drug compared with a higher-intensity statin monotherapy	Final outcomes: All-cause mortality, acute coronary events, cerebro-vascular events, revascularization procedures; Surrogate: LDL-C; adherence (investigator defined) and harm (SAEs, AEs withdrawals due to AEs).	Insufficient evidence to compare long-term final outcomes. The combination of ezetimibe and lower-intensity statin would lower LDL-C to the level similar to or better than those of higher intensity statin monotherapy while producing similar rates of short-term adverse events.	Moderately relevant for patients with and without the CHD diagnosis. Patients were not required to be at the highest tolerated dose of statin in either arm. Definition of high risk of CVD corresponds to ACC/AHA criteria but inconsistent with GSLLD criteria.
HTA 2008 Ara R, Tumur I, Pandor A, Duenas A, Williams R, Wilkinson A, et al. Ezetimibe for the treatment of hyper-cholesterolaemia: a systematic review and economic evaluation. Health Technology Assessment 2008;12(21) UK	Adults (age > 18 years) with primary (heterozygous familial or non-familial) hyper-cholesterolaemia whose condition is not appropriately controlled with a statin alone or in whom a statin is considered inappropriate or is not tolerated	Interventions: a) Ezetimibe monotherapy b) Ezetimibe+simvastatin; c) Ezetimibe +statin Comparators: a) placebo b) placebo + matching lipid-lowering drug c) placebo + up-titrated statin	Survival, fatal and non-fatal cardiovascular events, adverse effects of treatment and health-related quality of life (HRQoL). In the absence of clinical end points, surrogate end-point data LDL-C, total cholesterol and HDL-C were used.	Insufficient evidence to compare long-term final outcomes. Ezetimibe alone or in combination with a statin was effective in reducing LDL-C in short-term studies. When used alone, ezetimibe is less effective than statins	Moderately relevant: Population is defined in similar terms as in the present review, subgroup analysis is conducted for secondary prevention population. However, there was no requirement for the target population not being controlled on the highest tolerated dose of statin.

Pandor, A. Ara, R. M. et al Ezetimibe monotherapy for cholesterol lowering in 2,722 people: systematic review and meta-analysis of randomized controlled trials Journal of Internal Medicine, 2009, 265(5)568-80. UK	Adults (age > 18 years) with heterozygous familial and non-familial hypercholesterolaemia.	Ezetimibe monotherapy compared to placebo	Primary: survival, fatal and non-fatal cardiovascular events, AEs and health-related quality of life. Surrogate: changes in serum TC, LDL-C, HDL-C, and triglycerides	Ezetimibe mono-therapy significantly reduced LDL-C compared with placebo.Significant potentially favour-rable changes were also observed in TC, HDL-C and triglyceride levels. ezetimibe mono-therapy was well tolerated with a safety profile similar to placebo	Limited relevance: research question restricted ezetimibe monotherapy to patients intolerant to a statin, but no RCT with such a selection criterion was found.
HTA 2015 (unpublished independent assessment of the Merck and Co 2015 ezetimibe submission to NICE) UK	Adults (age > 18 years) with primary (heterozygous familial or non-familial) hyper-cholesterolaemia whose condition is not appropriately controlled with a statin alone or in whom a statin is considered inappropriate or is not tolerated	Interventions: a) Ezetimibe monotherapy b)Ezetimibe+simvastatin Comparators: a) placebo b) placebo in combination with the matching lipid-lowering drug	Survival, fatal and non-fatal cardiovascular events, adverse effects of treatment and health-related quality of life (HRQoL). In the absence of clinical end points, surrogate end-point data LDL-C, total cholesterol and HDL-C were used.	Ezetimibe monotherapy resulted in a significantly greater reduction in the LDL-C percentage change from baseline compared to placebo. Combination of ezetimibe+statin resulted in significantly greater reduction in the LDL-C percentage change from baseline and in total cholesterol compared to the matching dose of a statin alone	Moderately relevant: the target population included only patients who cannot increase their statin dose due to intolerance or contraindication. *The stated definition of the population is equivalent to the target population in the present review, however since no RCT with such a selection criterion was found, the assumption was made that all patients in add-on EZ studies are on the maximum tolerated dose of statin. Up-titration studies were excluded.*
Mikhailidis DP. Sibbring, Ballantyne G.M. Davies et al Meta-analysis of the cholesterol lowering effect of ezetimibe added to ongoing statin therapy. Current Medical Research and Opinion; 2007 Vol. 23, No. 8, 2009–2026 UK	Adults with primary hypercholesterolaemia or hyper-lipidaemia homozygous familial sitosterolaemia whose LDL-C levels were above those recommended by NCEP Adult Treatment Panel (ATP) II/III guideline criteria	Add-on studies that compared treatment with ezetimibe or placebo added to the undergoing statin therapy. Ezetimibe in combination with a statin compared with placebo+ statin (i.e. statin monotherapy)	Only the surrogate outcomes were extracted: mean % changes from baseline and in total cholesterol; LDL-C, HDL-C; Proportion of patients achieving the LDL-C goal.	A significantly greater percentage reduction in LDL-C levels was achieved in ezetimibe+statin combination vs statin mono-therapy;	Moderately relevant: Patients were not required to be at the highest tolerated dose of statin in the combination arm. NCEP ATP-III LDL-C criteria do not fully correspond to GSLLD criteria.

Mikhailidis DP Comparative efficacy of the addition of ezetimibe to statin vs statin titration in patients with hypercholesterolaemia: systematic review and meta-analysis. Curr Med Res Opin. 2011 Jun;27(6):1191-210 UK	Adults with primary hypercholesterolaemia or hyperlipidaemia who had not received statin therapy before (first line treatment), or whose cholesterol levels were not controlled by their existing statin monotherapy (second line treatment)	Ezetimibe in combination with a statin compared with doubling of the statin mono-therapy dose (other methods of statin up-titration were not specifically excluded). Not limited to RCTs	Only the surrogate outcomes were extracted: Proportion of patients achieving the LDL-C goal (typically 2.59 mmol/L; range 1.8–2.59 mmol/L), mean % changes from baseline in LDL-C, HDL-C and total cholesterol.	A significantly greater percentage reduction in LDL-C levels was achieved in ezetimibe+statin combination vs statin mono-therapy; Reduction in LDL-C levels attributed to add-on ezetimibe was significantly greater than that for statin dose doubling	The most relevant with respect to the intervention; statin monotherapy was up-titrated if the patients did not achieve the LDL-C goal at baseline; However, patients were not required to be at the maximally tolerated dose of statin in the combination arm
Kashani A, Sallam T, Bheemreddy S, Mann DL, Wang Y, Foody JM. Am J Cardiol. Review of side-effect profile of combination ezetimibe and statin therapy in randomized clinical trials.2008; 101(11):1606-13. USA	General population of adults (age >18 years) with hyperlipidaemia (defined uniquely within each study). Studies limited to specific patient populations were excluded.	Compare the pooled estimates of the rates of AEs in treatment with ezetimibe alone or ezetimibe in combination with a statin vs a statin monotherapy	Rates of AEs defined as myalgias, creatine kinase increases, rhabdomyolysis, transaminase increases, gastrointestinal adverse events; discontinuations because of an adverse event	Based on this systematic review, the addition of ezetimibe to statin therapy does not significantly increase the incidence of adverse events	Limited relevance Patients were not required to be at the highest tolerated dose of statin in the combination arm. Ezetimibe monotherapy was not restricted to patients intolerant to a statin; statin was a wrong comparator for EZ monotherapy in our review
Luo L, Yuan X, Huang W, et al. Safety and co-administration of ezetimibe and statins in patients with hyper-cholesterolemia: a meta-analysis. Intern Med J. 2015;45:546–557. China	Patients (age >18 years) diagnosed with hyper-cholesterolaemia, whose LDL-C levels were above NCEP ATP III guidelines.	Compare the pooled estimates of the rates of SAEs and AEs in treatment with ezetimibe– statin combination therapy vs a statin monotherapy	Rates of SAEs (defined by the RCT design); rates of AEs, treatment discontinuations due to AEs, allergic reactions or rashes, incidence of elevated ALT; AST; creatine kinase and gastrointestinal AEs.	The incidence of adverse events was similar between ezetimibe–statin combination therapy and statin monotherapy	Limited relevance Patients were not required to be at the highest tolerated dose of statin in the combination arm. NCEP ATP-III LDL-C criteria do not fully correspond to GSLLD criteria. Statin was a wrong comparator for EZ monotherapy in our review
Ijioma, N. Robinson,J.G. Lipid-lowering effects of ezetimibe and simvastatin in combination Expert Review of Cardiovascular Therapy 2011; 9(2) 131-145 USA	Poor quality review, no systematic analysis of the evidence, excluded from further considerations; see Appendix 3				
Sando Karen R. Nonstatin Therapies for Management of Dyslipidemia: A Review. Clinical	Poor quality review, no systematic analysis of the evidence, excluded from further considerations; see Appendix 3				

Therapeutics Volume 37, Issue 10, 1 October 2015, Pages 2153–2179 USA					
Battaggia A, Donzelli A, Font M, Molteni D, Galvano Clinical Efficacy and Safety of Ezetimibe on Major Cardiovascular Endpoints: Systematic Review and Meta-Analysis of Randomized Controlled Trials. PLoS ONE (2015) 10(4):e0124587. Italy	Participants were (adult?) males or females of all ages regardless of the clinical condition (*that is subgroups of patients with CVD, DM, CKD were all eligible - assessors)*	Interventions: a) Ezetimibe alone b) Ezetimibe+ another lipid-lowering drug c)Ezetimibe+simvastatin Comparators: a) placebo b) placebo in combination with the matching lipid-lowering drug c) placebo	All-cause and CV mortality; stroke; MI; cancer; SAEs that results in death, is life-threatening, or requires or prolongs hospital stay, or causes persistent or significant disability etc.	Ezetimibe±simvastatin had inconsistent effects on important final outcomes. No firm conclusions are possible, but findings indicative of damage suggest much more selective use of Ezetimibe± simvastatin.	Limited relevance; Neither the RCTs nor the meta-analysis were powered to detect the difference in final outcomes. Most of the RCTs would not meet our selection criteria
Silverman Michael G,. Ference Brian A, Im Kyungah, Wiviott, Stephen D. Giugliano, Robert P Grundy, ScottM.; Braunwald Eugene, Sabatine, Marc S. Association Between Lowering LDL-C and Cardiovascular Risk Reduction Among Different Therapeutic Interventions A Systematic Review and Meta-analysis. JAMA. 2016;316(12):1289-1297. USA	Not described. Assumed to be males or females (age >18 years) diagnosed with hyper-cholesterolaemia. Trials that enrolled study population focused on participants with significant competing risks (ie, heart failure or chronic kidney disease) were excluded	4 groups of interventions: 1) statins; 2) nonstatin therapies that lead to upregulation of LDL receptor expression;(healthy diet, bile acid sequestrants, ileal bypass surgery, SIMVA40mg+ezetimibe) 3) interventions that do not reduce LDL-C levels primarily through upregulation of LDL receptor expression (i.e, fibrates, niacin, cholesteryl ester transfer protein inhibitors) 4) PCSK9 inhibitors, which upregulate LDL-C clearance through the LDL receptor Comparators: 1) placebo; more potent statin 2) vs ezetimibe the comparator SIMVA40mg+placebo; 3) placebo or SIMVA+placebo 4) placebo	A composite end point of major vascular events, which consisted of cardiovascular death, acute MI or other acute coronary syndrome, coronary revascularization, and stroke. In some trial that was a secondary outcome. The association between the absolute amount of LDL-C reduction of an intervention (calculated as the difference in achieved LDL-C levels between the 2 treatment groups) and the hazard or risk ratio for major vascular events with that intervention was evaluated	These data suggest statins and nonstatin therapies that act through upregulation of LDL receptor expression are associated with similar cardiovascular risk reduction per decrease in LDL-C. The clinical value of adding specific nonstatin interventions to lower LDL-C to background statin therapy should be confirmed in appropriately powered clinical trials.	Fairly relevant, as the meta-analysis of the final rather than surrogate outcomes is undertaken. In comparison to the meta-analysis by Battaggia (2015), this is a higher quality meta-analysis in terms of methods and theoretical foundations. Still, most of the trials would not meet our selection criteria (except for IMPROVE IT trial, the only ezetimibe in combination with statin trial that was included in group 2 and meta-analysed alongside with surgical intervention). Most of the RCTs were not powered to detect the difference in the final outcomes. Patients in IMPROVE IT trial were not required to be on the maximum tolerated dose of statin.

Narrative description of the systematic reviews of clinical efficacy and safety of ezetimibe monotherapy and ezetimibe in combination with a statin

None of the identified systematic reviews presented conclusive evidence on the long-term risk of cardiovascular events (CVEs) in general population with hypercholesterolaemia treated with combination of statin and ezetimibe. Many of the studies included in the systematic reviews were of insufficient duration to adequately assess long-term clinical outcomes of mortality, acute coronary events, and revascularization procedures. Two systematic reviews by Battagia (2015) and by Silverman (2016) were specifically designed to meta-analyse mortality and morbidity outcomes listed in seven RCTs as clinical end points (Battagia 2015) or a composite end point of major vascular events, which consisted of cardiovascular death, acute MI or other acute coronary syndrome, coronary revascularization, and stroke (Silverman 2016). Since, in our view, meta-analysing the outcomes collected in very different populations in the RCTs with incompatible designs was not justified, results reported in these studies should be interpreted with caution. Unlike the study by Battagia (2015), the meta-analysis by Silverman (2016) had used theoretical foundations for selecting and grouping the studies into 4 intervention groups (only one was relevant to the reseach question of the present Review), so no further discussion of the results of the systematic review by Battagia (2015) is presented here. Presentation of the results of the meta-analysis reported by Silverman (2016) are limited to the intervention group defined as "nonstatin therapies that ultimately lower LDL-C predominantly by lowering intrahepatic cholesterol, thereby leading to upregulation of LDL receptor expression (i.e, diet, bile acid sequestrants, ileal bypass surgery, and ezetimibe)". The only ezetimibe RCT that met the selection criteria was IMPROVE IT trial (Cannon 2015), described in details elsewhere in the Review.

In the absence of sufficient data on the long-term patient outcomes other systematic reviews focused on the surrogate lipid-lowering outcomes. We identified five systematic analyses of surrogate outcomes in general population with hypercholesterolaemia (Mikhailidis 2007, Mikhailidis 2011, HTA 2008 (Ara 2008) HTA 2015 (unpublished), Pandor 2009); systematic analysis of surrogate outcomes in the population with high risk of cardiovascular disease (CVD) reported in Sharma 2009 (AHRQ 2009) and was further updated in Gudzune, 2014 (AHRQ 2014). Systematic analyses of surrogate outcomes in special subgroups (e.g. patients with diabetes mellitus) were attempted in HTA 2008, HTA 2015 and Gudzune (2014) but the conclusions were limited by the paucity of evidence. Two systematic reviews were specifically designed to analyse the safety outcomes of ezetimibe as monotherapy (Kashani 2008) or ezetimibe in combination with other statins using statin monotherapy as a comparator (Kashani 2008, Luo 2015). The safety profile of ezetimibe monotherapy vs placebo was also investigated in the systematic review by Pandor (2009).

Results reported in Agency for Healthcare Research and Quality (AHRQ); US Department of Health and Human Services

In 2009 the AHRQ conducted the first investigation into the benefits and harms of combination of statin and other lipid-modifying medications compared to a higher dose of statin monotherapy in the population identified as having high CHD risk (Sharma 2009). Following publication of the 2013 American College Cardiology (ACC) and American Heart Association (AHA) guidelines that introduced a new definition of the CV risk and did not recommend LDL-C thresholds as a clinical goal, the AHRQ undertook in 2014 an update of its original review aligning the definition of the target population at high-risk of atherosclerotic CVD to the recommendations of ACC/AHA. The 2014 AHRQ report compared surrogate outcomes, tolerability and safety of the combination therapy (not limited, but inclusive of ezetimibe + statin combination) with intensification of statin monotherapy.

The authors identified forty randomized trials (10,955 participants) that compared ezetimibe + statin combination with more potent statin monotherapy. Studies where comparator was a statin of the same [matching] potency as in the intervention arm were excluded. The potency of the statins was assigned as shown in Table 2.2.3.2.

Table 2.2.3.2.Different dosing of specific statins based on potency to reduce LDL-C

Potency	LDL-C reduction	Atorvastatin (mg/day)	Fluvastatin (mg/day)	Lovastatin (mg/day)	Pravastatin (mg/day)	Rosuvastatin (mg/day)	Simvastatin (mg/day)
Low potency	<30%	5	20 and/or 40	5 and/or 10 and/or 20	10 and/or 20 and/or 40	N/R	10
Mid potency	30-40%	10	80	40 and/or 80	80	2.5[a]	20
High potency	>40%	20 and/or 40 and/or 80	N/R	N/R	N/R	5 and/or 10 and/or 20 and/or 40	40 and/or 80[a]

N/R=not reported

[a]Dose not included in this review; information obtained from "FDA Advisory Committee Meeting Briefing Document NDA 21-366 for the use of CRESTOR" (www.fda.gov/ohrms/dockets/ac/03/briefing/3968b1_02_a-fda-clinical%20review.pdf).

All RCTs were categorised into the following groups:

RCTs comparing low potency statin in combination with ezetimibe to high potency statin monotherapy in general population with hyperlipidaemia (Ballantyne 2005[15]; Bays 2004[19]; Davidson 2002[4]; Goldberg 2004[38]; Ahmed 2008[43]; Araujo 2010[39]; Florentin 2011[40]; Lee 2011[44]; Lee 2012; Liberopoulos 2013; Moutzouri 2011[41]; Moutzouri 2012; Her 2010[42]) (N=13); and in population with diabetes mellitus (DM) (Rudofsky 2012) (N=1).

RCTs comparing mid potency statin in combination with ezetimibe to high potency statin monotherapy among general populations of patients with hyperlipidaemia (Ballantyne 2005[15]; Bays 2004[19]; Davidson 2002[4]; Goldberg 2004[38]; Ahmed 2008[43]; Araujo 2010[39]; Florentin 2011[40]; Lee 2011[44]; Lee 2012; Liberopoulos 2013; Moutzouri 2011[41]; Moutzouri 2012; Her 2010[42]; Ballantyne 2003[5]; Catapano 2006[45]; McKenney 2007[46]; Stein 2004[8]; Ben-Yehuda 2011[47]; Zieve 2010[48]; Foody 2010[49]; Robinson 2009[50]) (N=11); in population with pre-existing CHD (Barrios 2005[51]; Piorkowski 2007[52]; Roeters van Lennep 2008[53]; Yamazaki 2013; Bardini 2010[54]; Cho 2011[55]; Okada 2011[56]; Ostad 2009[57]; Pesaro 2012[58]; Hamdan 2011[59]; Averna 2010[60]; Matsue 2013) (N=12); and in population with DM (Constance 2007[61]; Gaudiani 2005[16]; Goldberg 2006[62]; Tomassini 2009[63]; Lee 2013[64]; Guyton 2008) (N=6).

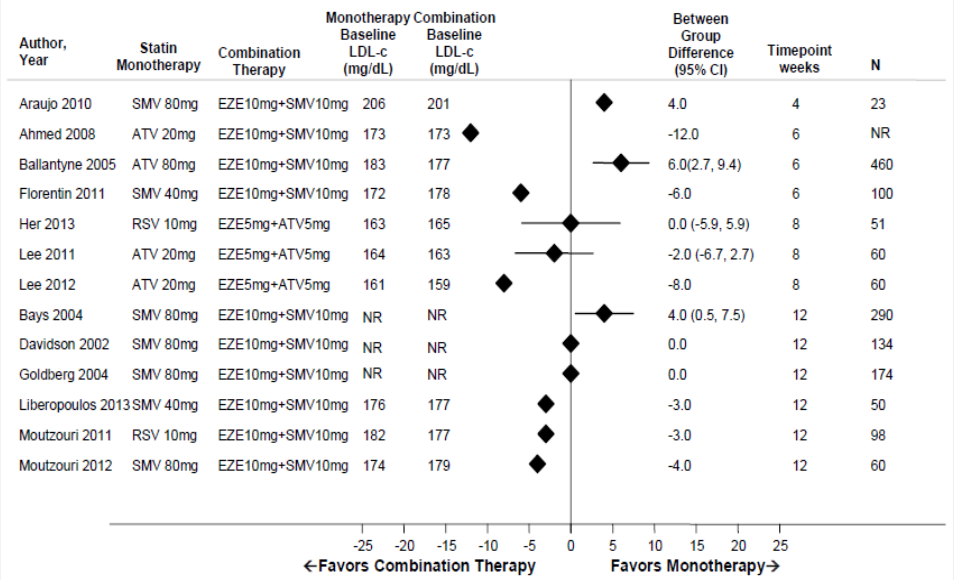
RCTs comparing low potency statin in combination with ezetimibe to mid potency statin monotherapy among general populations with hyperlipidaemia (Ballantyne 2005[15]; Bays 2004[19]; Davidson 2002[4]; Goldberg 2004[38]; Feldman[13] 2004; Kerzner 2003[65]) (N=6) and in population with DM (Kawagoe 2011[66]) (N=1).

The strength of evidence (SOE) was assigned based on the risk of bias, consistency of results, directness, and precision. Evidence for all long-term clinical outcomes (mortality, acute coronary events, cerebrovascular events, and revascularization procedures) for all combination therapy and statin intensity comparisons was insufficient. The body of evidence consisted of the analysis of the surrogate outcomes of LDL-C and HDL-C. For all comparisons, only the qualitative synthesis of data was conducted (i.e. individual mean differences with 95% CIs for individual studies grouped by combination therapy agent, statin intensity, and high-risk population). The pooled estimates of the mean difference (MD) in

reduction in the surrogate outcomes from the baseline was not calculated given the small numbers of heterogeneous trials.

The authors suggested that results from 13 trials indicate that low potency statin in combination with ezetimibe more effectively lowers LDL-C (Figure 2.2.3.1 reproduced from Figure 3 AHRQ 2014) and raises HDL-C (Figure 6, p.41, AHRQ 2014 not reproduced here) as compared to high potency statin monotherapy among general population (Strength of evidence (SOE) was low for both).

Figure 2.2.3.1 Mean difference in percent LDL change from baseline to time point comparing low potency combination therapy with ezetimibe to high potency monotherapy.

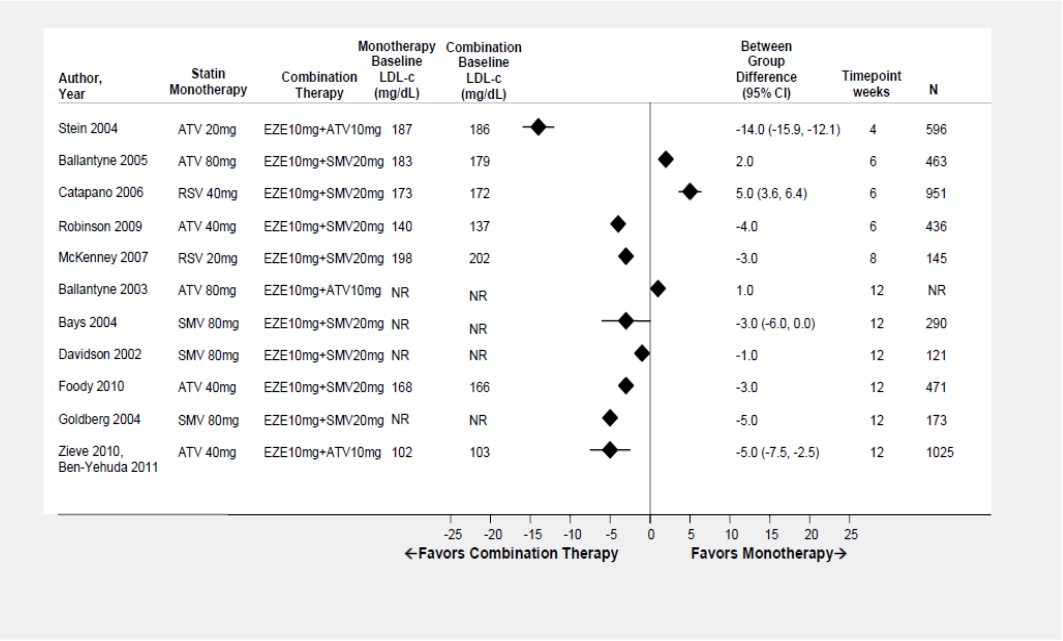


ATV = atorvastatin; SMV = simvastatin; NR = not reported
Note: For diamonds without confidence intervals, SE/SD could not be calculated.

However, the graphical presentation of the results in Figure 2.2.3.1 (reproduced from Figure 3 AHRQ 2014) suggest that this may not be the case. Taking into consideration the poor quality of some of the trials and high degree of heterogeneity preventing a meta-analysis, there is uncertainty in the clinical efficacy gain (i.e. additional reduction in LDL-C) associated with low potency statin in combination with ezetimibe vs high potency statin monotherapy.

The authors suggested that results from 11 trials indicated that mid potency statin combined with ezetimibe more effectively lowers LDL-C (Figure 2.2.3.2 reproduced from Figure 4 AHRQ 2014) and raises HDL-C (Figure 7, p.43, AHRQ 2014 not reproduced here) as compared to high potency statin monotherapy among general populations (SOE: moderate and low, respectively).

Figure 2.2.3.2 Mean difference in percent LDL change from baseline to time point comparing mid potency combination therapy with ezetimibe to high potency monotherapy.

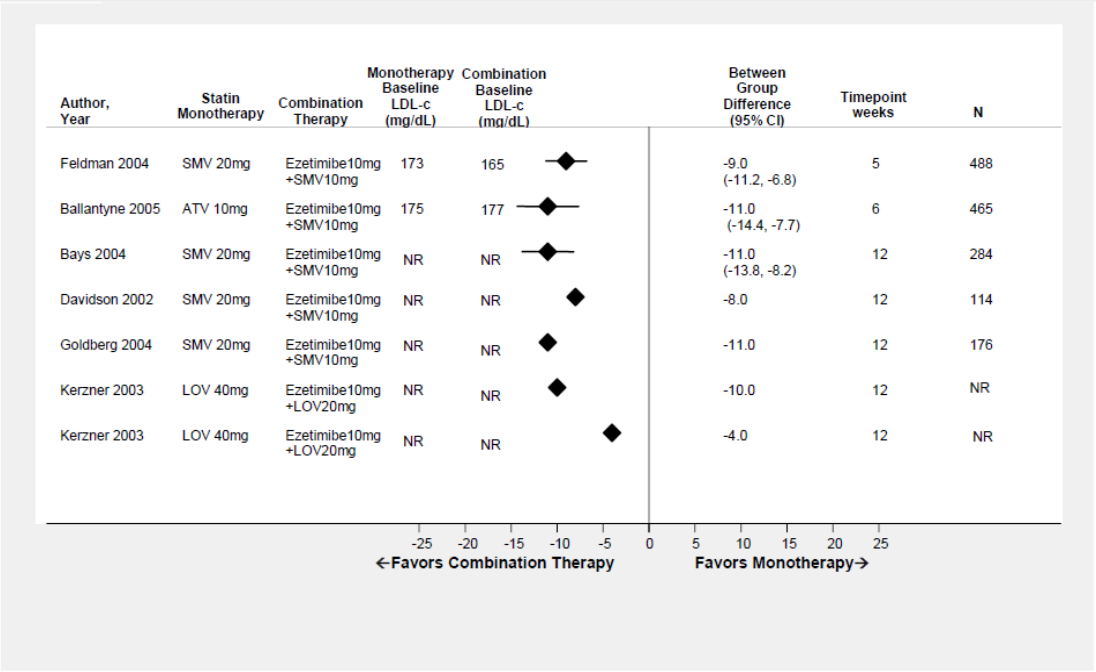


ATV = atorvastatin; NR = not reported; SMV = simvastatin
Note: For diamonds without confidence intervals, SE/SD could not be calculated.

However, as in the case of the low potency combination therapy with ezetimibe vs high potency statin the graphical presentation of the results in Figure 2.2.3.2 (reproduced from Figure 4 AHRQ 2014) is inconclusive. Taking into consideration the poor quality of some of the trials and high degree of heterogeneity preventing a meta-analysis, there is uncertainty in the clinical efficacy gain (i.e. additional reduction in LDL-C) associated with medium potency statin in combination with ezetimibe vs high potency statin monotherapy.

Results from six trials suggest that low potency statin in combination with ezetimibe more effectively lowers LDL-C (Figure 2.2.3.3 reproduced from Figure 5 AHRQ 2014) and raises HDL-C (Figure 8, p.45, AHRQ 2014 not reproduced here) as compared to mid potency statin monotherapy (SOE: moderate and low, respectively).

Figure 2.2.3.3 Mean difference in percent LDL change from baseline to time point comparing low potency combination therapy with ezetimibe to mid potency monotherapy.



ATV = atorvastatin; LOV = lovastatin; NR = not reported; RSV = rosuvastatin; SMV = simvastatin
Note: For diamonds without confidence intervals, SE/SD could not be calculated.

Graphical presentation of the results in Figure 2.2.3.3 (reproduced from Figure 5 AHRQ 2014) is more convincing suggesting that the combination of ezetimibe with a low potency statin is associated with additional 11% point reduction in LDL-C in comparison to mid-potency statin monotherapy. However, poor quality of some of the trials and high degree of heterogeneity preventing a meta-analysis are still a serious concern.

The AHRQ report also identified data on surrogate markers in special populations. Twelve trials among patients with pre-existing coronary heart disease favoured mid potency statin in combination with ezetimibe for lowering LDL-c as compared to high potency statin monotherapy (SOE: moderate). Four trials among patients with diabetes mellitus also favoured mid potency statin plus ezetimibe to a high potency statin monotherapy for lowering LDL-c and raising HDL-c (SOE: moderate for both). There was insufficient evidence to evaluate harms among the coronary heart disease and diabetes subgroups.

The outcomes of reviewing the 2009 the AHRQ report suggest that there is uncertainty in the clinical efficacy gain (i.e. additional reduction in LDL-C) associated with statin in combination with ezetimibe vs statin monotherapy.

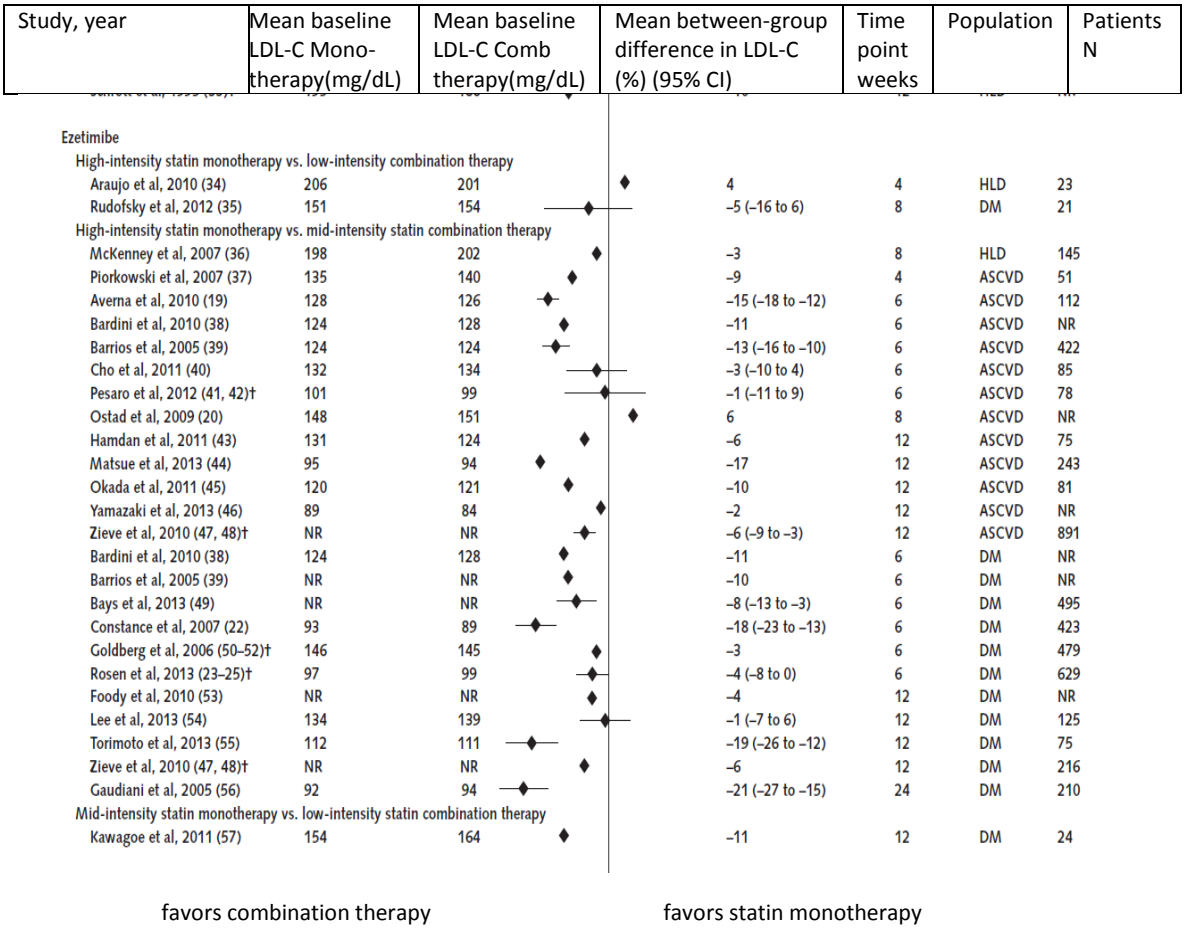
Gudzune et al. 2014[26] replicated results reported in AHRQ (2014)[25] using the data from selected trials that enrolled adult population with heterozygous familial and non-familial hypercholesterolemia at high-risk for ASCVD including those with pre-existing ASCVD (acute coronary syndromes, or a history of myocardial infarction, stable or unstable angina, coronary or other arterial revascularization, stroke, transient ischemic attack, or peripheral arterial disease presumed to be of atherosclerotic origin), baseline LDL-c ≥190 mg/dL (4.91 mmol/L) or trial inclusion criteria LDL-c ≥190 mg/dL (4.91 mmol/L), pre-existing diabetes mellitus, effectively matching the inclusion criteria to the criteria outlined in the ACC/AHA 2014 guidelines for cholesterol treatment (Stone 2013[67])

Two RCTs that met the selection criteria compared statin monotherapy and combination therapy with ezetimibe (168 participants) among primary and secondary prevention population of hyperlipidaemia patients (Araujo 2010[39]; McKenney 2007[46]). The authors identified 12 RCTs and 1 RCT subgroup analysis among patients with pre-existing ASCVD (2,702 participants). The authors identified 9 RCTs and 4 RCT subgroups analyses among patients with DM (>3493 participants). Figure 2.2.3.4 (*reproduced from Figure 2, Gudzune et al. 2014*) shows results of all trials. The authors performed no meta-analyses due to the small number of heterogeneous trials. There was insufficient evidence to evaluate LDL cholesterol, adherence, and harms for other intensity comparisons among patient groups other than those reported below.

Eleven RCTs and 1 RCT subgroup analysis compared mid-intensity statin combined with ezetimibe to high intensity statin monotherapy (2,590 participants) among patients with pre-existing ASCVD (Roeters van Lennep 2008; Ostad 2009; Averna 2010; Bardini 2010[54]; Barrios 2005; Cho 2011; Pesaro 2012; Hamdan 2011; Matsue 2013; Okada 2011; Yamazaki 2013; ; Zieve 2010; Ben-Yehuda 2011). Mid-intensity statin combined with ezetimibe decreased LDL cholesterol level 5% to 15% more than high-intensity statin monotherapy (moderate SOE).

Seven RCTs and 4 RCT subgroup analyses compared mid-intensity statin combined with ezetimibe to high-intensity statin monotherapy (>3448 participants) among patients with DM (Constance 2007; Rosen 2013a[68]; Rosen 2013b; Jimenez 2013[69]; Bardini 2010[54]; Gaudiani 2005[16]; Goldberg 2006[62]; Tomassini 2009[63]; Lee 2013[64]; Guyton 2008) Mid-intensity statin combined with ezetimibe decreased LDL cholesterol level 3% to 21% more than high-intensity statin monotherapy (moderate SOE).

Figure 2.2.3.4 Mean difference in percent LDL change from baseline to time point comparing combination therapy with ezetimibe to the higher potency monotherapy.



Graphical presentation of the results in the largest subgroup of RCTs of mid-potency statins in combination with ezetimibe vs high intensity statin monotherapy Figure 2.2.3.4 is inconclusive. Taking into consideration the poor quality of some of the trials and high degree of heterogeneity preventing a meta-analysis, there is uncertainty in the clinical efficacy gain (i.e. additional reduction in LDL-C) associated with medium potency statin in combination with ezetimibe vs high potency statin monotherapy. The conclusions of 2009 the AHRQ report do not seem to be confirmed in the subgroup of the population at high ASCVD risk. The authors noted the strength of evidence was moderate at best as most studies that reported CVE had some risk of bias, lasted less than 20 weeks and event rates were very low or no events occurred.

Given insufficient evidence to compare long-term clinical outcomes (mortality, acute coronary events, cerebrovascular events, and revascularization procedures) for all combination therapy and statin intensity comparisons the authors recommended that clinicians should consider the combination therapy especially for patients who are intolerant or unresponsive to statins, but also should counsel patients that this regimen may not result in reduced ASCVD risk.

Health Technology Assessment (HTA) reports conducted for the National Institute of health and Clinical Excellence (NICE) in UK

In 2008 NICE commissioned an independent health technology assessment (HTA) of ezetimibe (Ara et al, HTA 2008[34]). Following the publication of the Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) results, Merck and Co submitted an updated evidence of clinical and cost-effectiveness of ezetimibe. Independent assessors evaluated the company submission in December 2015 (unpublished at the time of the writing of the Review) and their conclusions contributed to therapeutical guidance TA385 that replaced TA132 (see the review of Guidelines section for details).

HTA 2008

The independent assessors evaluated clinical and cost-effectiveness of ezetimibe monotherapy and in combination with a statin in adults (over 18 years) with primary (heterozygous familial or non-familial) hypercholesterolaemia

- Whose condition is not appropriately controlled with a statin alone or
- In whom a statin is considered inappropriate or is not tolerated.

Trials in population with homozygous familial hypercholesterolaemia or homozygous sitosterolaemia were excluded. See Appendix 3 for the overview of the objectives, population, selection criteria, methods, results and quality assessment of the HTA 2008 report. For the cost-effectiveness methods and results see Section on published economic evaluations. The selection criteria limited RCTs to ≥12 weeks duration to be consistent with the requirement of licensing authorities such as the European Medicines Agency of a minimum follow-up of 3 months for trials of surrogate endpoints in lipid lowering drug therapies (EMEA 2004[70]) and to minimize tachyphylaxis effects.

A systematic literature search did not identify a published clinical outcome trial that examined the cardiovascular benefit of ezetimibe (final outcomes). Thirteen (of which five were multi-arm) phase III multi-centre RCTs (of varying methodological quality) of short-term duration (12–48 weeks) with surrogate end-point data were included.

Fixed-dose combination therapy of ezetimibe 10 mg plus a statin versus matching statin dose (for those inadequately controlled by statin) was assessed in random-effects meta-analysis using 6 RCTs (Bays 2004, Davidson 2002, Goldberg 2004, Rodney 2006[71], Melani 2003[73]). The combination of ezetimibe and statin was associated with a statistically significant reduction in LDL-C (-13.94%, 95% CI -14.90 to -12.98, p<0.00001, I^2=5.8%) and total cholesterol (-10.36%, 95% CI -11.09 to -9.63, p<0.00001, I^2=5.65%) compared with statin alone based on six trials (3,610 patients). No RCTs of ezetimibe plus statin compared to other lipid-lowering drugs were identified.

Titrated Combination therapy (for those inadequately controlled by statin): The trials compared ezetimibe plus current statin therapy versus current statin therapy titrated to the next dose (either forced or stepwise titrated). All four trials (1,800 patients) Stein 2004, Ballantyne 2004a[14], Ballantyne 2004b[72], Masana 2005[20]) found that co-administration of ezetimibe and statin was significantly more effective in reducing LDL-C (p<0.05) compared with statin alone. The studies were not eligible for meta-analysis. One study compared ezetimibe plus statin versus other lipid-lowering drugs McKenney (2007). This study found that low-moderate doses of atorvastatin/rosuvastatin plus niacin achieved similar LDL-C reductions compared with the highest doses of rosuvastatin monotherapy or ezetimibe/simvastatin.

Monotherapy (for those where a statin was inappropriate or not tolerated): All included studies compared monotherapy with placebo. A random-effects meta-analysis of all seven trials (2,577 patients) [Ballantyne 2003[5]; Bays 2004[19]; Davidson 2002[4]; Dujovne 2002[2]; Goldberg 2004[38]; Melani 2003[73]; Knopp 2003[3]] demonstrated that ezetimibe significantly reduced LDL-C levels compared with placebo (WMD -18.56, 95% CI -19.68 to -17.44, I^2=55.4%).

Pandor et al 2009. In this publication the authors of HTA 2008 updated results of the meta-analysis of the efficacy and safety of ezetimibe monotherapy (10mg/day) vs placebo reported in eight RCTs [Ballantyne 2003[5]; Bays 2004[19]; Davidson 2002[4]; Dujovne 2002[2]; Goldberg 2004; Melani 2003[73]; Kerzner 2003[65]; Knopp 2003[3]] in the same population (n=2,722). It was confirmed that ezetimibe monotherapy was associated with a statistically significant mean reduction in LDL cholesterol (from baseline to endpoint) of -18.58%, (95% CI: - 19.67 to -17.48, P < 0.00001) compared with placebo (Table 2.2.3.3). Significant (P < 0.00001) changes were also found in total cholesterol (-13.46%, 95% CI: -14.22 to -12.70), HDL cholesterol (3.00%, 95% CI: 2.06–3.94) and triglyceride levels (-8.06%, 95% CI:-10.92 to -5.20). The authors also found that ezetimibe monotherapy appeared to be well tolerated with a safety profile similar to placebo.

Table 2.2.3.5. Meta-analysis of the percentage reduction in LDL-C from the baseline reported in RCTs comparing ezetimibe monotherapy to placebo in patients with primary hypercholesterolemia

Study	Treatment duration (weeks)	Baseline LDL-C (mmol/L)	N randomised ezetimibe monotherapy	N randomised placebo	Weighted mean difference (fixed effects) 95%CI
Ballantyne 2003*	12	3.77-6.5	65	60	-24.30 (-29.5, -19.1)
Bays 2004*	12	3.77-6.5	148	146	-16.70 (-20.0, -13.4)
Davidson 2002*	12	3.77-6.5	61	70	-16.80 (-21.8, -11.8)
Dujovne 2002*	12	3.38-6.5	666	266	-17.22 (-19.2, -15.3)
Goldberg 2004*	12	3.77-6.5	89	92	-22.50 (-26.0, -19.0)
Kerzner 2003	12	3.75-6.47	72	64	-19.00 (-24.6, -13.5)
Knopp 2003	12	3.36-6.47	621	204	-18.48 (-20.5, -16.4)
Melani 2003*	12	3.8-6.5	64	65	-20.00 (-24.4, -15.6)
Total			1786	927	-18.6 (-19.7, -17.5)
Test for heterogeneity: Chi^2=13.47, df=7 (P=0.06); I^2=48%					
Test for the overall effect: Z=33.19 (P<0.00001)					

*patient-level data from these RCTs were pooled in Pearson (2009) analysis (see below)

A =atorvastatin; E =ezetimibe 10 mg/day; P =pravastatin; S =simvastatin.

Pearson et al 2009. Patient-level data from ezetimibe (n=874) and placebo (n=498) arms of six RCTs meta-analysed in HTA 2008 and Pandor (2009) were pooled in the analysis of effects of ezetimibe monotherapy on LDL-C (primary end point) and the inflammatory marker C-reactive protein (CRP) in patients with CRP ≤10 mg/L. Calculation of the least squared mean percentage change from baseline in LDL-C used an analysis-of-variance (ANOVA) with terms for treatment and protocol. Reduction in CRP by ezetimibe monotherapy was numerically greater than with placebo, but did not reach the level of statistical significance (treatment difference 6%, p =0.09). The pooled analysis of the patient-level data showed that LDL-C reduction with ezetimibe (-18.3%) was statistically significantly greater than with placebo (0.5%) (treatment differences -18.8%, p <0.001), thus confirming results of the meta-analyses reported in HTA 2008 and Pandor (2009).

HTA 2015

The HTA 2015 independent assessment of the company submission listed the same terms of reference as the HTA 2008 report, i.e. assessing clinical and cost-effectiveness of ezetimibe monotherapy and in combination with a statin in adults with primary (heterozygous familial or non-familial) hypercholesterolaemia

- whose condition is not appropriately controlled with a statin alone or
- in whom a statin is considered inappropriate or is not tolerated.

In addition, two sub-populations were considered to reflect NICE most recent recommendations in clinical guidelines CG181 (July 2014)

- primary prevention of CVD (10%-30% 10 year risk of developing CVD using QRISK2 risk assessment tool);
- secondary prevention (established CVD).

Unlike in HTA 2008 report, RCTs of ezetimibe plus current statin therapy versus current statin therapy titrated to the next dose were not considered. According to clinical practice and CG181, up-titration of a statin should be investigated before adding ezetimibe. Therefore *the target population in HTA 2015 for the intervention of ezetimibe co-administrated with a statin, included only patients who cannot increase their statin dose due to intolerance or contraindication. The stated definition of the population is equivalent to the target population in the present review.*

Subgroup analyses for three distinct patient subgroups identified only four studies in the subgroup for primary prevention in people with diabetes (Gaudiani 2005, Constance 2007, Goldberg 2006, Lee 2013) and only one each in the other two subgroups - people with CKD (Zinellu, 2012) and people with HeFH (Kastelein 2008[74]). Results of the subgroup analyses were broadly consistent with the main results (see below).

Fixed-dose combination therapy of ezetimibe 10 mg plus statin versus matching statin dose (for those inadequately controlled by statin). Thirteen studies in the company's systematic review of clinical evidence compared ezetimibe co-administered with simvastatin to matched simvastatin doses. (Bays 2004; Davidson 2002; Goldberg 2004; IMPROVE-IT 2015; Kastelein, 2008; Krysiak 2011; Krysiak 2012a; Krysiak 2012b; Krysiak 2014; Masana 2005; Rodney 2006; Shankar 2007; Zinellu 2012). A further seven studies compared co-administration of other statins and ezetimibe to matching statin doses; the

alternative statins were atorvastatin, (Ballantyne 2003); fluvastatin (Alvarez-Sala 2008[75]; Habara 2014; Kinouchi 2013; Stein 2008; Stojakovic 2010[76]) and pravastatin (Melani 2003).

Inclusion of trials of ezetimibe 10 mg plus statin versus matching statin dose into the body of evidence implicitly assumes that the maximum tolerated dose for the pertinent statin therapy is achieved in both arms at the baseline. However, it was not a selection criteria in any of the identified trials and it remained uncertain whether the population of the included trials is representative of the target population, as defined in the terms of reference for this review.

A number of studies included in the systematic review of clinical effectiveness (IMPROVE-IT 2015, Stojakovic 2010, Zinellu 2012, Clement 2014, Farnier 2005, Habara 2014, Kinouchi 2013, Stein 2008) *involve patients who do not necessarily have a diagnosis of primary hypercholesterolemia and therefore do not fulfil the stated inclusion criteria.* However it was argued by the company that these patient populations are at high risk of CVD and, prescription of ezetimibe or ezetimibe in combination with a statin reflect clinical practice. This was accepted as being reasonable. Some of the treatment regimens of these trials are shown in Table 2.2.3.6.

Table 2.2.3.6. Multicenter, double-blind, randomized, trials of ezetimibe+statin vs matching statin in patients with primary hypercholesterolemia included in HTA 2015 assessment of company submission

Study	N ezetimibe +statin	N all statin arms	Treat-ment duration (weeks)	Baseline mean LDL-C (mg/dL)	Treatment regimen (active treatment arms; Ezetimibe is administered at a dose of 10mg)
Ballantyne 2003	255	248	12	175-179	A 10,20,40, 80 mg; E+ A 10,20,40 ,80 mg
Melani 2003	204	205	12	177.6	P 10, 20 or 40 mg; E+ P 10, 20 or 40 mg;
Alvarez-Sala 2008	38	44	12	197-216	F XL 80; E+F XL 80
Habara 2014	32	31	9 months	109-123	F 30 ; E+F 30,
Kinouchi 2013	28	26	12 months	156-159	F 20 ; E+F 20,
Stein 2008	64	69	14	173-176	F XL 80; E+F XL 80
Stojakovic 2010	56	28		102-112	F 80 ; E+F 80,
Bays 2004	609	62	12	176-180	S 10,20,40, 80 mg; E+ S 10,20,40, 80 mg
Davidson 2002	263	263	12	176-181	S 10,20,40, 80 mg; E+ S 10,20,40, 80 mg
Goldberg 2004	353	349	12	NR	S 10,20,40, 80 mg; E+ S 10,20,40, 80 mg
IMPROVE-IT 2015	9,067	9,077	2.5 years min follow-up	93.8	S 40 mg; E+ S 40 mg
Kastelein, 2008	357	363	24 months	317-319	S 80 mg; E+ S 80 mg
Krysiak 2011	32	32		145-250	S 40 mg; E+ S 40 mg
Krysiak 2012a	25	25	90 days	145-250	S 40 mg; E+ S 40 mg
Krysiak 2012b	42	44	12	145-250	S 40 mg; E+ S 40 mg
Krysiak 2014	21	23		178-186	S 40 mg; E+ S 40 mg
Masana 2005	355	78	48	131-137	S 10,20,40, 80 mg; E+ S 10,20,40, 80 mg
Rodney 2006	214	123	12	175-177	S 20 mg; E+ S 20 mg
Shankar 2007	114	116	12	126-131	S 10 mg; E+ S 10 mg
Zinellu 2012	20	10		230-254	S 40 mg; E+ S 20,40 mg

S=simvastatin; P=pravastin; A=atorvastatin; F=fluvastatin;
(http://heartuk.org.uk/files/uploads/documents/huk_fs_mfsP_cholestrigly_leverlsconversion.pdf) was used to convert to mg/dL (mmol/l x 38.6).

At the baseline in the ezetimibe and statin combination trials, LDL-c values in the ezetimibe and statin groups ranged from 93.8 mg/dL (IMPROVE-IT trial) to 319 mg/dL (Kastelein, 2008). In the statin monotherapy groups, values ranged from 93.8 mg/dL (IMPROVE-IT trial) to 317.8 mg/dL (Kastelein,

2008). All the participants in the IMPROVE-IT trial had acute coronary syndrome, whilst those in the Kastelein (2008) trial had familial hypercholesterolemia.

The random-effects meta-analysis of the identified 13 trials (N=23,359, listed in Table) demonstrated that a combination of ezetimibe and a statin resulted in a statistically significant greater reduction in the LDL-C percentage change from baseline (-15.6%, 95% CI -17.1 to -14.1, p<0.0001, I^2=99.9) and in total cholesterol (-12.2%, 95% CI -12.9to -11.5, p<0.0001, I^2=99.8) compared to the matching dose of a statin alone. *There was a large degree of heterogeneity present (I^2>99) for all analyses indicating that the narrative rather than quantitative synthesis of the results would be more appropriate.*

Monotherapy (for those where a statin was inappropriate or not tolerated). The company identified 13 trials (N=3,173) that were consistent with the negotiated terms of reference. The HTA independent assessment also identified a placebo-controlled trial of ezetimibe+lovastatin (Kerzner 2003), that should have been included in meta-analysis.

Some of the characteristics of population and treatment regimen of these trials are shown in Table 2.2.3.5

Table 2.2.3.5 Meta-analysis of the percentage reduction in LDL-c from baseline reported in RCTs comparing ezetimibe monotherapy to placebo in patients with primary hypercholesterolemia

Study	Treat-ment duration (weeks)	N Ezetimibe	N placebo	Mean Baseline LDL-C (mg/dL)	Weighted mean difference (random effects) 95%CI
Ballantyne 2003	12	65	60	175-179	-24.30 (-25.0, -23.7)
Bays 2001 arm A	12	46	52	171-177	-22.30 (-22.8, -21.8)
Bays 2001 arm B	12	77	36	171-177	-12.70 (-13.4, -12.0)
Bays 2004	12	149	148	176-180	-16.70 (-17.0, -16.2)
Davidson 2002	12	61	70	176-171	-16.80 (-17.4, -16.2)
Dujovne 2002	12	570	193	168	-17.30 (-17.4, -17.2)
Farnier 2005	6	187	64	158-162	-13.60 (-14.0, -13.2)
Goldberg 2004	12	92	93	NR	-22.50 (-22.9, -22.1)
Knopp 2003	12	622	205	164	-18.50 (-18.6, -18.4)
Krysiak 2011	90 days	33	30	175-183	-30.00 (-30.9, -29.2)
Krysiak 2012a	90 days	24	24	175-182	-29.40 (-30.5, -28.3)
Krysiak 2012b	12	43	41	179-183	-24.30 (-25.0, -23.7)
Melani 2003	12	64	65	177.6	-20.00 (-20.6, -19.5)
Total		2,033	1,081		-20.60 (-22.1, -19.1)*
Not included in the meta-analysis					
Kerzner 2003	12	72	64		
Test for heterogeneity: I^2=99.6%					
Test for the overall effect: not reported					

S=simvastatin; P=pravastin; A=atorvastatin; F=fluvastatin; L=Lovastatin

*obtained from the Figure 1 in company response to the questions raised by the independent assessors

The mean baseline LDL-c levels were balanced within individual trials but there was wide variation between trials. In the 13 ezetimibe monotherapy trials, values in the ezetimibe groups ranged from 144.1 mg/dL (Farnier 2005) to 181.3 mg/dL (Davidson 2002). In the placebo groups, values were between 130 mg/dL (Dujovne, 2002) and 179 mg/dL (Krysjak, 2012b).

Results of the random-effects meta-analysis demonstrated that ezetimibe monotherapy resulted in a significantly greater reduction in the LDL-C percentage change from baseline compared to placebo

(Mean Difference -20.6%, 95% CI -22.1 to -19.1 p<0.0001, I^2=99.6) and in the TC percentage change from baseline compared to placebo (Mean Difference -16.1%, 95% CI -17.0 to -15.1 p<0.0001, I^2=99.5).

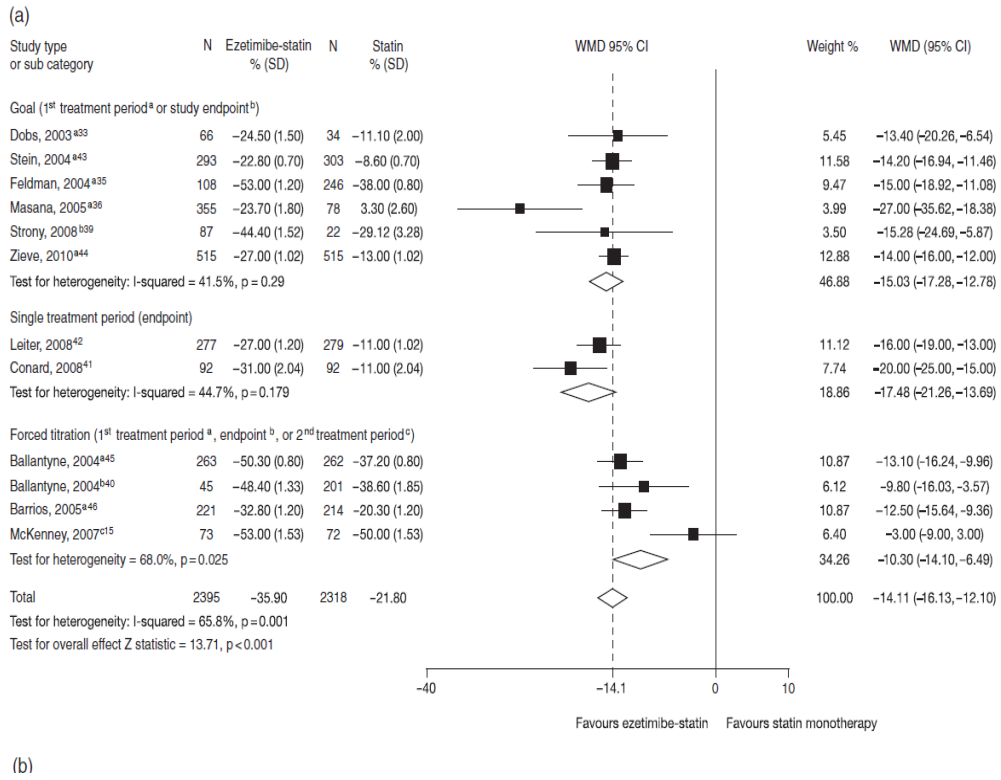
There was a large degree of heterogeneity present (I^2>99) for all analyses. This means that there were very high levels of inconsistency between the trials included in the meta-analyses (95% confidence intervals for different trials rarely overlap). *Results of this meta-analysis may not produce a reliable estimate of the true Mean Difference in LDL-C, favouring an earlier, more conservative estimate of -18.5% reduction in LDL-C from the baseline obtained from the smaller number but more heterogeneous trials (HTA 2008, Pandor 2009).*

Comparative efficacy of the addition of ezetimibe to statin vs statin titration in patients with hypercholesterolaemia (Mikhailidis, 2011)

The systematic review by Mikhailidis (2011) is an extension of the earlier systematic review comparing clinical effectiveness and safety in ezetimibe + statin combination vs matching dose of statin (with or without a placebo) Mikhailidis (2007). While the research question in Mikhailidis (2007) is similar to the research question in HTA 2015, the 2011 systematic review by Mikhailidis and colleagues replicates one of the research questions in the HTA 2008 report by further examining the comparative clinical efficacy of ezetimibe+statin combination therapy vs statin monotherapy. The objective was to compare the lipid-lowering efficacy of ezetimibe added to the background statin versus doubling the statin monotherapy dose in patients who received statin monotherapy for at least 4 weeks prior to randomisation. Doubling of a statin dose could be happening at a regular intervals, (ideally this analysis would require data for the end of each treatment period, i.e. prior to each titration point), however a single-period studies were not excluded if the statin dose was doubled in the monotherapy arm between 'run-in' and baseline (i.e. at randomisation).

The systematic review identified 13 trials suitable for meta-analyses. The aim of the analyses was to compare the difference between treatments in the percentage change in lipid levels from baseline, at the end of each treatment period, thereby comparing the effect of adding ezetimibe vs successive doubling of the statin dose. However, these data were not available for the majority of studies, therefore, two sets of statistical analyses were performed. The first set of meta-analyses (N=13) included studies reporting lipid data and dispersions around the mean for one of the treatment periods. Typically, these data were for the first treatment period (i.e. up to the first titration point; period 1) or study end in those with only a single treatment period. The result of this analysis are illustrated in Figure 2.2.3.6.

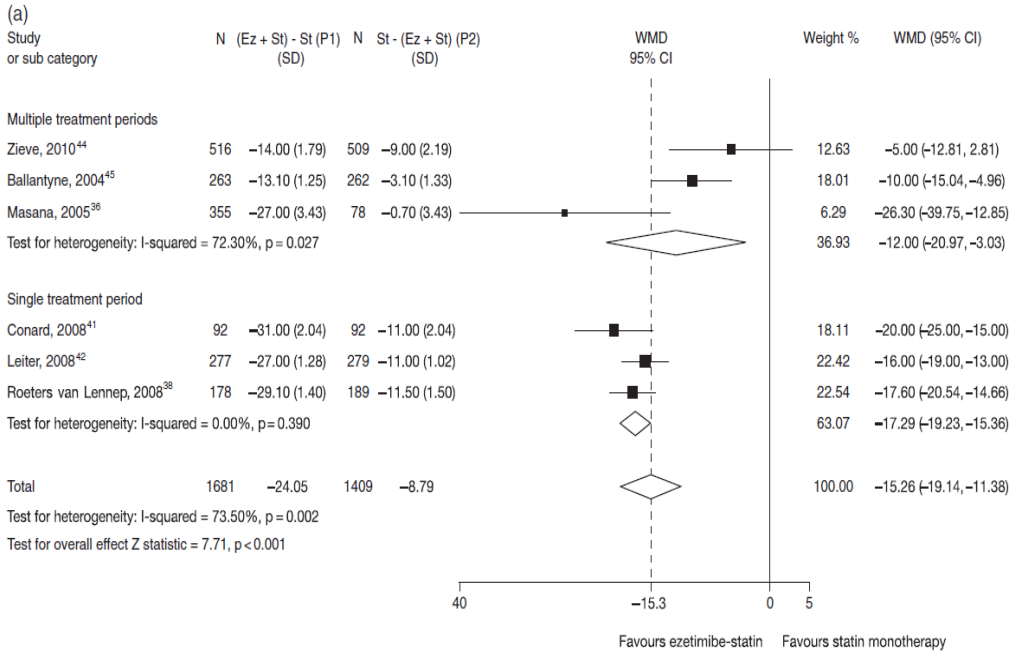
Figure 2.2.3.6 Percentage change from baseline in LDL-C in ezetimibe in combination with statin vs up-titrating statin monotherapy at the end of the first treatment period for studies with multiple treatment periods or at study endpoint for studies with a single treatment period.



In the 13 RCTs included in the first set of meta-analyses, 2396 patients received ezetimibe in combination with statin and 2318 patients received statin monotherapy. At the end of the first treatment period there was a significantly greater percentage reduction from baseline in serum LDL-C levels in patients treated with ezetimibe in combination with statin compared with those treated with statin monotherapy (Weighted Mean Difference:-14.1% [95% CI -16.1, -12.1], p<0.001). *Heterogeneity was statistically significant in all meta-analyses comparing ezetimibe + statin therapy with up-titrated statin monotherapy. It suggests that the quantitative synthesis of the outcomes may not be appropriate. Reasons for the large variations in the trial results and the confidence intervals are likely to relate to a) variation in the populations, where secondary, primary prevention and mixed prevention populations were lumped together; b) interventions that involved statins of different potencies in terms of intensity and dose; c) interventions that were administered as the first line in some RCTs and the second line in others.*

A further set of meta-analyses (N=6) was conducted to compare period 1 data for the ezetimibe–statin combination therapy arm with the data after the first titration point, and up to the second titration point (i.e. period 2), for the statin monotherapy arm. A limitation of the first set of analyses is that in the period compared, the statin monotherapy dose in three studies had not been up-titrated by that point; furthermore, in nine studies, the statin dose was up-titrated in both arms, which did not allow a comparison of ezetimibe addition and statin monotherapy up-titration. Therefore, the second set of analyses was conducted to compare the incremental reduction in lipid levels (or increase in HDL-C levels) with addition of ezetimibe vs doubling the dose of statin monotherapy. The result of this analysis are illustrated in Figure 2.2.3.7.

Figure 2.2.3.7. Percentage change from baseline in LDL-C in ezetimibe in combination with statin vs doubling statin monotherapy.



In the six RCTs included in the second set of meta-analyses, 1681 patients received ezetimibe in combination with statin and 1409 patients received statin monotherapy. The reduction in LDL-C levels attributed to the addition of ezetimibe during the first treatment period was greater than the reduction in LDL-C levels with doubling the dose of statin monotherapy during the second treatment period and the difference between treatment arms was significant (Weighted Mean Difference: -15.3% [95% CI -19.1, -11.4], p<0.001). Degree of heterogeneity was larger than in the first set of meta-analyses and statistically significant.

Despite of the evident uncertainties, the authors concluded that ezetimibe in combination with statin is associated with a significantly greater reduction in LDL-C levels than increasing the statin monotherapy dose, thereby enabling more patients to achieve LDL-C goal, specified in most studies as 2.59 mmol/L (range 1.8–2.59 mmol/L).

The aim of the analyses in the systematic review by Mikhailidis (2011) was to compare the effect of adding ezetimibe vs successive doubling of the statin dose. With respect to the research question of the present Review, this is the more relevant approach that, still short of the population who were on the maximally tolerated dose of statin prior to receiving ezetimibe, may better approximates the clinical practice that would be consistent with meeting the PBS restrictions. Still the analysis utilised only the surrogate outcomes and, the degree of heterogeneity between the trials was large suggesting that the outcomes were inappropriately aggregated using a quantitative technique and the resulting WMD should be interpreted with caution.

Association between lowering LDL-C and cardiovascular risk reduction among different therapeutic interventions. A Systematic Review and Meta-analysis (Silverman, 2016)

The most recent meta-analysis (Silverman 2016) aimed at evaluation of the association between lowering LDL-C and relative cardiovascular risk reduction across different statin and non-statin therapies. The association between the absolute amount of LDL-C reduction of an intervention (calculated as the difference in achieved LDL-C levels between the 2 treatment groups) and the hazard or risk ratio for major vascular events with that intervention was evaluated. Summary effect estimates (which are presented as relative risk (RR) with 95% CIs, P values, and R^2 values (a measure of the proportion of between-study variability accounted for by the variable) were obtained with meta-regression analyses using random-effects models.

Only one of the intervention groups involving non-statin therapies that ultimately lower LDL-C predominantly by lowering intrahepatic cholesterol, thereby leading to upregulation of LDL receptor expression (i.e., diet, bile acid sequestrants, ileal bypass surgery, and ezetimibe) was relevant to the research question of the present review. A single ezetimibe RCT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial IMPROVE IT, Cannon 2015, also described below) that reported cardiovascular outcomes as primary endpoint met the inclusion criteria for this meta-analysis (see Table 2.2.3.1 above). For this intervention group an association between the achieved LDL-C level and the estimated 5-year rate of major coronary events (coronary death or MI) was evaluated using random-effects meta-regression analysis of the data from each group (experimental and control). There were eight trials of established non-statin therapies that ultimately act predominantly via upregulation of LDL receptor expression (4 diet trials, 2 trials of bile acid sequestrants, 1 trial of ileal bypass surgery, and (IMPROVE IT trial). In IMPROVE-IT trial in patients receiving background statin therapy the RR reduction for major vascular events was 6.4% (95% CI, 1%-11%), with an absolute risk reduction of 2% over 7 years. The relatively small magnitude of the observed effect reflects the low starting LDL-C level by design that yielded a small absolute between-group difference, and is similar to what was predicted from the Cholesterol Treatment Trialists' meta-regression of statin trials and confirmed in the meta-regression in this recent meta-analysis.

In these eight trials of established non-statin therapies it was found that each 1-mmol/L reduction in LDL-C was associated with an RR of 0.75 (95%CI, 0.66-0.86; P = .002). *The between-group difference comparing RR reduction in major vascular events in this particular non-statin therapy with statin therapy was not statistically significant (P =0.72).* There was a significant association between the observed absolute achieved LDL-C and the 5-year rates of major coronary events (coronary death or MI, n = 11 301) in the intervention and control groups among the trials of statins and established non-statin therapies that ultimately act predominantly via upregulation of LDL receptor expression. This association was seen in primary prevention trials (1.5% lower event rate [95%CI, 0.5%-2.6%] per 1-mmol/L lower LDL-C; P = .008) and secondary prevention trials (4.6% lower event rate [95%CI, 2.9%-6.4%] per 1-mmol/L lower LDL-C; P < .001). Baseline LDL-C was not a significant variable in either of these models. Surprisingly, despite of the evident incompatibility of the interventions aggregated into one group (e.g. diet is a "zero line" therapy, preceding the first line with a statin and the second line with ezetimibe, with ileal surgery being an intervention in the class of it own), no significant heterogeneity was observed in meta-analysis of this 8 trials.

In this meta-regression analysis, the use of statin and non-statin therapies that act via upregulation of LDL receptor expression to reduce LDL-C were associated with similar RRs of major vascular events per change in LDL-C. Lower achieved LDL-C levels were associated with lower rates of major coronary events.

Safety profile of ezetimibe in combination with a statin vs statin monotherapy

Literature search identified two systematic reviews that specifically aimed at assessing the risk of adverse events in ezetimibe in combination with a statin versus a statin monotherapy (Kushani 2008; Luo 2015). Kushani (2008) identified 18 fairly large (>100 patients) RCTs that reported AEs and Luo (2015) identified 20 RCT without any restrictions on the sample size. However Luo (2015) used the latest NCEP ATP III criteria for the LDL-C threshold level, that produced two sets of trials that only partially overlap (10 RCTs were included in both).

Kushani (2008) reported results aggregated by the type of AE, and within this subgroup, by the type of statin. Luo (2015) reported the total numbers and proportions of AEs by the type of a statin as well as the grand total. Luo (2015) also reported the total number and proportions of serious AEs but no definition of a serious AE was produced; some selected categories of AEs were also pooled across the studies and analysed in total and by the type of a statin. In addition to AEs, both systematic reviews evaluated discontinuations of study drug because of any adverse event. Comparability of the definitions of the AEs in two systematic reviews is difficult to establish as they are frequently lacking in Luo (2015) (Table X.X).

Table 2.2.3.8. Definitions of AEs in Kushani (2008) and Luo (2015)

Adverse events (AE)	Definitions in studies identified by Kushani (2008)	Definitions in studies identified by in Luo (2015)
Myalgias	Myalgias; musculoskeletal AE; or myalgia/muscle pain	Not defined, not extracted as a separate AE.
Creatine Kinase (CK) increases	≥3 times the upper limit of normal (ULN); ≥5 times the ULN; or myopathy	(CK) >10 × ULN
Rhabdomyolysis	CK increases ≥10 times the ULN	
Hepatotoxicity	Increase of serum alanine aminotransferase or aspartate aminotransferase of ≥3 times the ULN; or Increase of serum alanine aminotransferase or aspartate aminotransferase of ≥3 times the ULN on 2 consecutive visits;	alanine aminotransferase (ALT) ≥3 × ULN, aspartate aminotransferase (AST) ≥3 × ULN
Gastrointestinal AE	gastrointestinal adverse effects in general; abdominal pain	Not defined
Allergic reactions or rashes	Not defined or calculated	Not defined
Serious AEs	Not defined or calculated	Calculated but not defined

Ezetimibe monotherapy vs a statin (Kushani 2008)

Although the primary objective of this systematic review was to assess the risk of adverse events in combination ezetimibe+statin versus a statin monotherapy, the results of ezetimibe monotherapy vs a placebo were also reported in some of the identified RCTs and were analysed by the authors in the same way as the main results. The review identified six RCTs (Ballantyne 2003[5]; Kerzner, 2003[65]; Melani

2003; Davidson 2002[4]; Bays 2004[19] and Goldberg 2004[38]) that reported AE with respect to the ezetimibe monotherapy arm and a statin arm (that included atorvastatin, lovastatin, pravastatin and simvastatin). The incidence of myalgias was lower with ezetimibe monotherapy versus statin monotherapy, this difference did not reach statistical significance with RR calculations (RR=0.32, 95% CI 0.06 to 1.66). This lack of significance persisted in subgroup analysis of all simvastatin studies (RR=0.48, 95% CI 0.06 to 3.71). CK increases were not significantly higher with ezetimibe monotherapy versus statin monotherapy (RR=3.20, 95% CI 0.20 to 50.50). Rhabdomyolysis did not occur significantly more often with ezetimibe monotherapy versus statin monotherapy (RR=0.97, 95% CI 0.20 to 4.60). The incidence of transaminase increases, did not reach statistical significance when comparing ezetimibe monotherapy with statin monotherapy (RR=0.74, 95% CI 0.19 to 2.88). Gastrointestinal symptoms did not occur significantly more often with ezetimibe monotherapy versus statin monotherapy (RR=1.14, 95% CI 0.62 to 2.10). Discontinuations because of any adverse event was not significantly higher with ezetimibe monotherapy versus statin monotherapy (RR=1.04, 95% CI 0.61 to 1.78).

Ezetimibe combination with a statin vs a statin (Kushani 2008).

Myalgias, reported by 7 studies including 3,185 patients (39% of total studies in this systematic review), were not more common with ezetimibe plus statin combination therapy (RR=0.86, 95% CI 0.60 to 1.24) compared with statin monotherapy. CK increases, reported by 7 trials including 5,611 patients were not significantly higher with combination therapy versus statin monotherapy (RR=0.84, 95% CI 0.10 to 6.81). Rhabdomyolysis, reported in all 18 studies (100% of included studies) including 14,471 patients, did not occur more frequently in patients treated with combination therapy compared with statin monotherapy (RR=0.67, 95% CI 0.27 to 1.70). The incidence of transaminase increases, reported in 18 studies (100% of included studies) including 14,471 patients, did not reach statistical significance when comparing combination therapy with statin monotherapy (RR=1.55, 95% CI 0.99 to 2.44), although the lower boundary of the confidence interval was approaching the level of statistical significance. Gastrointestinal symptoms were the end point with the highest incidence and were reported by 7 studies (39% of total studies) that included 3,891 patients. Overall, 6.7% of 1,978 patients receiving ezetimibe experienced gastrointestinal symptoms versus 6.4% of 1,725 patients receiving statins alone. However, this was not significantly higher with combination therapy compared with statin monotherapy (RR=1.07, 95% CI 0.82 to 1.38). Discontinuations because of any adverse event were reported by 17 studies (94% of total studies) and included 12,569 patients. This end point was not higher with combination therapy vs statin monotherapy (RR=1.08, 95% CI 0.89 to 1.31).

Authors stated that the observed rates of AEs are consistent with smaller single-site studies. In premarketing clinical trials, the incidence of myalgias was reported as <2% with ezetimibe monotherapy and 3.2% to 4.5% with ezetimibe-statin combination therapy (Smith 2003[77]). Patient information and previous studies reported a 1.3% to 1.4% incidence of hepatotoxicity and a 0.1% to 0.2% incidence of rhabdomyolysis with combination therapy (Davidson, 2004[78]). In addition, reports indicated a 2.8% to 3.7% rate of adverse gastrointestinal events with combination therapy (Miocromedex(R) Healthcare Series. Vol 127. Thompson Healthcare, 2004). Although their meta-analysis found a higher rate of gastrointestinal adverse events (6.7%), this did not reach statistical significance in comparison to statin therapy. In a pooled analysis of 1,861 patients, Davidson (2004) found a slightly higher rate of hepatotoxicity with ezetimibe-statin combination therapy versus statin monotherapy (1.4% vs 0.4%; p=0.03). In Kushani (2008) analysis that included 13,978 patients for comparison, this difference did not reach statistical significance (0.8% vs 0.6% respectively).

Based on results of the analyses, Kushani (2008) concluded that the addition of ezetimibe to statin therapy does not significantly increase the incidence of adverse events.

Ezetimibe combination with a statin vs a statin (Luo 2015)

Out of 20 identified RCTs, total adverse events were reported in 16 studies, with 1,165 events occurring in 3,856 patients (30%) treated with ezetimibe and statins, compared with 1,198 events in 4,171 patients (29%) treated with statins alone. There was no statistically significant difference in the two arms (OR=0.95 95% CI 0.85 to1.06; P = 0.34, I^2=0). Serious adverse events were reported in 13 studies, with 76 events occurring in 3,997 patients (2%) treated with ezetimibe and statins, compared with 69 events in 4,301 patients (1.6%) treated with statins alone. This end point was not higher with combination therapy compared with statin monotherapy (OR=1.04 95% CI, 0.75 to 1.45; P = 0.81; I^2 = 0%),

Eighteen studies were assessed in terms of treatment discontinuation, 169 of 4818 patients (3.5%) discontinued treatment with ezetimibe and statins and 148 of 5142 patients (2.9%) discontinued statins alone. There was no significant difference between combination therapy and statin monotherapy (OR=1.15 95% CI, 0. 92 to 1.44; P = 0.22; I^2 = 0%).

Nine studies were assessed for gastrointestinal adverse events. A total of 123 events occurred in 2446 patients (5%) treated with ezetimibe and statins, compared with 122 events in 2957 patients (4%) treated with statins alone. There was no significant difference between combination therapy and statin monotherapy (OR=1.26 95% CI, 0.97 to 1.63; P = 0.08; I^2 = 24%). Six trials reported allergic reactions or rashes. Seventeen events occurred in 1903 patients (0.9%) treated with ezetimibe and statins, compared with 31 events in 2391 patients (1.3%) treated with statins alone. There was no significant difference between the groups (OR=0.76 95% CI, 0.41 to 1.35; P = 0.33; I^2 = 0%). CK>10 × ULN, was reported in 11 studies. Eleven events occurred in 5579 patients (0.2%) treated with ezetimibe and statins, compared with 10 events in 5850 patients (0.2%) treated with statins alone. There was no significant difference between the groups (OR=1.07 95% CI, 0.51 to 2.23; P =0.86; I^2 = 0%).

The incidence of ALT >3 × ULN was reported in 11 studies and did not reach statistical significance when compared between the combination therapy and statin monotherapy groups (OR= 1.01 95% CI, 0.58 to 1.77; P = 0.96; I^2 =0%). Seven trials reported the proportion of patients with AST >3 × ULN. A total of 17 events occurred in 3864 patients (0.4%) treated with ezetimibe and statins, compared with 16 events in 4335 patients (0.4%) treated with statins alone. There was no significant difference between the groups (OR=1.21 95% CI, 0.61 to 2.39; P = 0.58; I^2 = 35%).

Consistent with the conclusion of Kushani (2008), Luo (2015) also concluded that the incidence of adverse effects with co-administration of ezetimibe and statins did not differ significantly from those with statin monotherapy. The systematic reviews Kushani (2008) and Luo (2015) do not restrict the population to patients with statin intolerance or contraindication. Therefore the applicability of their conclusions to the research question of the review is uncertain.

Summary of the systematic reviews

Table 2.2.3.9 shows a check list of the identified systematic reviews.

Table 2.2.3.9. A check list of the identified systematic reviews

Number of original reviews identified	**15**
Excluded	
Poor quality Duplicate More recent update	3 (Ijioma 2011, Sandro 2015, Battagia 2015) 1 (Sharma 2009b=AHRQ 2009 full report) 2 (AHRQ 2009; Mikhailidis 2007)
Systematic reviews of “add-on” EZ+statin	HTA-2008; HTA 2015 (both general population);

trials vs matching dose of statin	
Systematic reviews of trials in EZ+statin vs up-titrated dose of statin	HTA-2008; Mikhailidis 2011 (both general population);
Systematic reviews of trials in EZ+statin vs more powerful statin	AHRQ 2014; Gudzune 2014 (secondary prevention population);
Systematic review of trials in EZ monotherapy vs placebo	Pandor 2009 (general population without intolerance or contraindications to statin)
Systematic reviews of AE reported in trials of EZ+statin vs statin	Kushani 2008; Luo 2015
Systematic review of final outcomes (e.g. MI)	Silverman 2016

Clinical effectiveness of ezetimibe as monotherapy or in combination with a statin was evaluated using a surrogate outcomes in all but two systematic reviews, of which one was of poor methodological quality (Battagia 2015) and was excluded from further consideration in favour of the more recent and higher quality systematic review by Silverman (2016).

In this meta-regression analysis, the use of statin and non-statin therapies (including ezetimibe) that act via upregulation of LDL receptor expression to reduce LDL-C were associated with similar RRs of major vascular events per change in LDL-C. Lower achieved LDL-C levels were associated with lower rates of major coronary events (e.g. as in IMPROVE IT trial). The between-group difference comparing RR reduction in major vascular events in non-statin therapy with statin therapy was not statistically significant (P =0.72).

The authors of the remaining systematic reviews that used surrogate outcomes as endpoints indicated that

a) ezetimibe monotherapy resulted in a significantly greater reduction in the LDL-C percentage change from baseline compared to placebo and a similar safety profile;
b) ezetimibe + statin combination therapy (ezetimibe "add-on" study) resulted in a greater reduction in LDL-C levels than the matching dose of statin monotherapy;
c) ezetimibe + statin combination therapy resulted in a greater reduction in LDL-C levels than up-titrating statin monotherapy (either in terms of potency or dose);
d) the incidence of adverse effects with co-administration of ezetimibe and statins did not differ significantly from those with statin monotherapy

The Review identified a number of concerns that generate uncertainty in the reported results of the systematic reviews:

- *The meta-analysed results of ezetimibe in combination with statin ("add-on" trials) have limited applicability to the research questions of the present Review. It could not be reasonably assumed that the population in trials of ezetimibe 10 mg plus statin versus matching statin dose were administered a maximum tolerated dose of statin at the baseline. It was not a selection criterion in any of the identified trials and it remained uncertain whether the population is representative of the target population, as defined in the terms of reference for this Review.*
- *The claim that treatment with ezetimibe + statin therapy resulted in a greater reduction in LDL-C levels than up-titrating statin monotherapy is not generalizable across all combinations as there is likely to be equi-effective statin doses of the more potent statins. For example, two large trials (Ballantyne 2005, Bays 2004) found ATOR 80 (maximum dose) to be significantly more effective in lowering LDL-than EZ 10 +SIM 10*.
- *Heterogeneity was statistically significant in all meta-analyses comparing ezetimibe + statin therapy with a statin monotherapy. It suggests that the quantitative synthesis of the outcomes may not be appropriate. Reasons for the large variations in the trial results and the confidence intervals are likely to relate to a) variation in the populations, where secondary, primary prevention and mixed prevention populations were lumped together; b) interventions that*

involved statins of different potencies in terms of intensity and dose; c) interventions that were administered as the first line in some RCTs and the second line in others.

2.2.4 Master list of identified trials that formed the evidence basis for the review

The primary objective of the literature search was to identify the studies that evaluated the effect of ezetimibe as monotherapy or in combination with a statin on final patient outcomes of survival; quality-adjusted survival; fatal cardiovascular and cerebrovascular events and non-fatal cardiovascular and cerebrovascular events.

Table 2.2.4.1 lists the studies that reported the final patient outcomes and the reasons for inclusion/exclusion.

Table 2.2.4.1 RCTs of ezetimibe in combination with a statin that report final patient outcomes

Trial	Population	Intervention/ Comparator	Included/ Excluded (reason)
IMPROVE-IT Cannon 2015	Acute coronary syndrome	SIM+EZ vs SIM +PBO	Included
ENHANCE Kastelein 2008	HeFH	SIM+EZ vs SIM +PBO	Included for LDL-c outcomes only[#]
SEAS Rossebø 2008	Aortic stenosis	SIM+EZ vs PBO	Excluded (wrong comparator)
SHARP 2001 Baigent 2011, Haynes 2014	CKD	SIM+EZ vs PBO	Excluded (wrong comparator)
ARBITER 6-HALTS Taylor 2009	CHD or high risk of CHD	Statin+EZ vs Statin+ X niacin	Excluded (wrong comparator)
SANDS Howard 2008	American Indians with DM & no prior CVD events	SIM+EZ vs SIM +PBO	Excluded[#]; results may not be generalizable to Australian population

[#]The trial was not powered to detect a statistically significant difference in patient outcomes;
HeFH= heterozegous familial hypercholesterolaemia; CKD= chronic kidney disease; DM=diabetes mellitus

The 24 month ENHANCE trial (Kastelein 2008) did not include morbidity or mortality as primary or secondary outcomes and was not powered to detect a statistically significant difference in final patient outcomes. Investigator-reported cardiovascular events were observed in 7 patients in the simvastatin group (including 1 death from a cardiovascular cause, 2 nonfatal myocardial infarctions, 1 nonfatal stroke, and 5 coronary revascularization procedures) and in 10 patients in the combined-therapy group (including 2 deaths from cardiovascular causes, 3 nonfatal myocardial infarctions, 1 nonfatal stroke, and 6 coronary revascularizations).

Patients diagnosed with kidney disease were considered within the scope of the review. However the large SHARP trial (Baigent 2011[79]; Haynes 2014[80]) of ezetimibe in combination with simvastatin in patients with chronic kidney disease did not meet the selection criteria because of the comparator (placebo) was out of scope of the review. The literature search identified two other publications (Zinellu 2012a; Zinellu 2012b) of the RCTs of ezetimibe in combination with statin in population with chronic kidney disease with and without hypercholesterolemia. However, the outcomes of percentage reduction in lipid endpoints were not reported separately for every arm of the trial that used different doses of simvastatin. These publications were excluded on the basis of insufficient reporting.

No published report of the RCTs that would meet selection criteria of ezetimibe in combination with maximum tolerated statin dose in the target population (Table 2.2.1 Selection criteria) was identified. **Therefore, there was insufficient evidence to address the first two research questions that related to ToR1, namely** whether addition of ezetimibe to the maximum tolerated dose of statin is associated with superior patient long-term or surrogate outcomes in comparison to placebo + maximum tolerated dose of statin **(Q1 and Q2).**

IMPROVE-IT (Cannon 2015)[81] was the only RCT designed to assess the long-term patient outcomes that met the selection criteria. It assessed clinical efficacy and safety of ezetimibe + simvastatin vs placebo + simvastatin in the secondary prevention population who had been hospitalized for an acute coronary syndrome within the preceding 10 days. A few issues associated with applicability of results from IMPROVE-IT to the target population were identified: firstly, the IMPROVE-IT patient population would not met PBS restriction criteria for ezetimibe (the baseline LDL-C was set at 1.3 to 2.43 mmol/L); secondly, at the time of enrolment only 34% of patients were being treated with a statin; for other patients ezetimibe in combination with simvastatin was prescribed as the first-line treatment. Also, as in all other identified trials, there was no evidence that patients who had been treated with statins prior to randomisation were at their maximum tolerated dose. Therefore, IMPROVE-IT RCT enrolled the population that did not meet the PBS eligibility criteria for subsidised prescription of ezetimibe. However, in the absence of any better evidence on the long-term outcomes in the population with hypocholesterolaemia the outcomes of IMPROVE-IT trial were extracted and described alongside other evidence included in the analysis of clinical effectiveness to inform **ToR1: Q3** (see Section 2.5. below). The long-term outcomes of IMPROVE-IT trial were used in the modelled economic evaluation presented by the sponsor for the ezetimibe review. Their approach to incorporating these outcomes into the updated version of the model are reviewed in a separate document assessing the quality and applicability of published economic evaluations and modelled economic evaluations previously considered by PBAC.

The remaining **questions Q4-Q6** within the **ToR1 scope** are addressed with the evidence extracted from 30 identified RCTs of ezetimibe in combination with statin as the first or second line therapy that met the selection criteria for the review**.**

The master lists of all included trials of ezetimibe in combination with a statin that meet the selection criteria are shown in Table 2.2.4.2. The RCTs (N=12) that were not considered by the PBS previously are marked with an asterisk (*****).

Table 2.2.4.2 Reports of the RCTs of ezetimibe in combination with a statin

Trial	Reports
Up-titrating dose of statin + ezetimibe vs up-titrating dose of statin	
Cannon 2015* IMPROVE-IT	Cannon CP, Blazing MA, Giugliano RP, McCagg A, White JA, Theroux P, et al. Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes. N Engl J Med. 2015;372(25):2387-97.
P025 Ballantyne 2004	Ballantyne CM, Blazing MA, King TR, Brady WE, Palmisano J. Efficacy and safety of ezetimibe co-administered with simvastatin compared with atorvastatin in adults with hypercholesterolemia. American Journal of Cardiology. 2004;93(12):1487-94. o Ballantyne et al. 2004, Atherosclerosis 5(Suppl. 1) p105-105; o Ballantyne et al. 2004, Journal of the American College of Cardiology 43 (5, Suppl. A) 480A-481A)
P693 Stein 2004	Stein E, Stender S, Mata P, Sager P, Ponsonnet D, Melani L, et al. Achieving lipoprotein goals in patients at high risk with severe hypercholesterolemia: Efficacy and safety of ezetimibe co-administered with atorvastatin. American Heart Journal. 2004;148(3):447-55. o Stein et al. 2002, Atherosclerosis 3(2) p211; o Stein et al. 2003, J. Am. Coll. Cardiol. 41 (6, Suppl. A) 255A-255A; o Vermaak et al. 2003, J. Am. Coll. Cardiol. 41 (6, Suppl. A) 255A-255A; o Vermaak et al. 2002, Atherosclerosis 3(2) p230-231

Trial	Reports
McKenney 2007 COMPELL	McKenney JM, Jones PH, Bays HE, Knopp RH, Kashyap ML, Ruoff GE, et al. Comparative effects on lipid levels of combination therapy with a statin and extended-release niacin or ezetimibe versus a statin alone (the COMPELL study). Atherosclerosis. 2007;192(2):432-7.
Fixed dose of statin + ezetimibe vs up-titrating statin either in terms of dose or in terms of potency	
P090 Leiter 2008	Leiter LA, Bays H, Conard S, Bird S, Rubino J, Hanson ME, et al. Efficacy and safety of ezetimibe added on to atorvastatin (40 mg) compared with uptitration of atorvastatin (to 80 mg) in hypercholesterolemic patients at high risk of coronary heart disease. American Journal of Cardiology. 2008;102(11):1495-501. PubMed PMID: 19026303.
Teramoto 2012*	Teramoto T, Sawada T, Iwamoto K, Daida H. Clinical Efficacy and Tolerability of Ezetimibe in Combination With Atorvastatin in Japanese Patients With Hypercholesterolemia-Ezetimibe Phase IV Randomized Controlled Trial in Patients With Hypercholesterolemia. Current Therapeutic Research, Clinical & Experimental. 2012;73(1-2):16-40.
P079 Conard 2008	Conard SE, Bays HE, Leiter LA, Bird SR, Rubino J, Lowe RS, et al. Efficacy and safety of ezetimibe added on to atorvastatin (20 mg) versus uptitration of atorvastatin (to 40 mg) in hypercholesterolemic patients at moderately high risk for coronary heart disease. American Journal of Cardiology. 2008;102(11):1489-94.
Pesaro 2013*	Pesaro AE, Serrano CV, Jr., Fernandes JL, Cavalcanti AB, Campos AH, Martins HS, et al. Pleiotropic effects of ezetimibe/simvastatin vs. high dose simvastatin. International Journal of Cardiology. 2012;158(3):400-4. PubMed PMID: 21334753. o Pesaro AE, Serrano CV, Jr., Katz M, Marti L, Fernandes JL, Parra PR, et al. Increasing doses of simvastatin versus combined ezetimibe/simvastatin: effect on circulating endothelial progenitor cells. Journal of Cardiovascular Pharmacology & Therapeutics. 2013;18(5):447-52. PubMed PMID: 23739650.
P021 Gaudiani 2005	Gaudiani LM, Lewin A, Meneghini L, Perevozskaya I, Plotkin D, Mitchel Y, et al. Efficacy and safety of ezetimibe co-administered with simvastatin in thiazolidinedione-treated type 2 diabetic patients. Diabetes, Obesity and Metabolism. 2005;7(1):88-97. o Gaudiani et al. 2004, Journal of the American College of Cardiology 43(5, Suppl A) 479A-479A;
P700 Dobs 2003	Trial Report (Preliminary Summary) – Protocol 700: A phase III double-blind efficacy and safety study of SCH 58235 (10 mg) in addition to simvastatin in subjects with coronary heart disease or multiple risk factors and with primary hypercholesterolemia not controlled by a starting dose (20 mg) of simvastatin. February 2002. o Dobs AS, Guyton JR, McClusky D, Ponsonnet D, Melani L, Lebeaut A, et al. Coadministration of ezetimibe with simvastatin. Journal of the American College of Cardiology. 2003;41(6):227.
Zieve 2010*	Zieve F, Wenger NK, Ben-Yehuda O, Constance C, Bird S, Lee R, et al. Safety and Efficacy of Ezetimibe Added to Atorvastatin Versus Up Titration of Atorvastatin to 40 mg in Patients >= 65 Years of Age (from the ZETia in the ELDerly [ZETELD] Study). American Journal of Cardiology. 2010;105(5):656-63.
P809 Farnier 2009	Farnier M, Averna M, Missault L, Vaverkova H, Viigimaa M, Massaad R, et al. Lipid-altering efficacy of ezetimibe/simvastatin 10/20 mg compared with rosuvastatin 10 mg in high-risk hypercholesterolaemic patients inadequately controlled with prior statin monotherapy – The IN-CROSS study. International Journal of Clinical Practice. 2009;63(4):547-59.
P058 Catapano 2006	Catapano AL, Davidson MH, Ballantyne CM, Brady WE, Gazzara RA, Tomassini JE, et al. Lipid-altering efficacy of the ezetimibe/simvastatin single tablet versus rosuvastatin in hypercholesterolemic patients. Current Medical Research & Opinion. 2006;22(10):2041-53. o Abate et al. 2006, J. Am. Geriatric Society 54(4, Suppl.) S163-S163;
P077 Goldberg 2006	Goldberg RB, Guyton JR, Mazzone T, Weinstock RS, Polis A, Edwards P, et al. Ezetimibe/simvastatin vs atorvastatin in patients with type 2 diabetes mellitus and hypercholesterolemia: the VYTAL study.[Erratum appears in Mayo Clin Proc. 2007 Mar;82(3):387]. Mayo Clinic Proceedings. 2006;81(12):1579-88.; o Guyton JR, Goldberg RB, Mazzone T, Weinstock RS, Polis A, Rosenberg E, et al. Lipoprotein and apolipoprotein ratios in the VYTAL trial of ezetimibe/simvastatin compared with atorvastatin in type 2 diabetes. Journal of Clinical Lipidology. 2008;2(1):19-24.; o Weinstock RS, Goldberg RB, Guyton JR, Mazzone T, Polis A, Tomassini JE, et al. Effect of ezetimibe/simvastatin vs atorvastatin on lowering levels of LDL-C and non-HDL-C, ApoB, and hs-CRP in patients with type 2 diabetes. Journal of Clinical Lipidology. 2008;2(1):25-35.

Trial	Reports
Lee 2013*	Lee JH, Kang HJ, Kim HS, Sohn DW, Oh BH, Park YB. Effects of Ezetimibe/Simvastatin 10/20 mg vs. Atorvastatin 20 mg on Apolipoprotein B/Apolipoprotein A1 in Korean Patients with Type 2 Diabetes Mellitus: Results of a Randomized Controlled Trial. Am J Cardiovasc Drug. 2013;13(5):343-51.
Cho 2011*	Cho YK, Hur SH, Han CD, Park HS, Yoon HJ, Kim H, et al. Comparison of Ezetimibe/Simvastatin 10/20 mg Versus Atorvastatin 20 mg in Achieving a Target Low Density Lipoprotein-Cholesterol Goal for Patients With Very High Risk. Korean Circ J. 2011;41(3):149-53
Protocol 051 Ballantyne 2005 VYVA study	Ballantyne CM, Abate N, Yuan Z, King TR, Palmisano J. Dose-comparison study of the combination of ezetimibe and simvastatin (Vytorin) versus atorvastatin in patients with hypercholesterolemia: the Vytorin Versus Atorvastatin (VYVA) study.[Erratum appears in Am Heart J. 2005 May;149(5):882]. American Heart Journal. 2005;149(3):464-73. o Ballantyne et al. 2005, Journal of the American College of Cardiology 45 (3, Suppl. A) 423A-423A; o Ballantyne et al. 2005, Diabetes 54 (Suppl. 1) A235-A235; o Ballantyne et al. 2004, XV International Symposium on Drugs Affecting Lipid Metabolism, p124; o Abate et al. 2005, Diabetologia 48 (Suppl. 1) A392-A393
P807 Constance 2007	Constance C, Westphal S, Chung N, Lund M, Sisk CM, Johnson-Levonas AO, et al. Efficacy of ezetimibe/simvastatin 10/20 and 10/40 mg compared with atorvastatin 20 mg in patients with type 2 diabetes mellitus. Diabetes Obes Metab. 2007;9(4):575-84.
P806 Barrios 2005	Barrios V, Amabile N, Paganelli F, Chen JW, Allen C, Johnson-Levonas AO, et al. Lipid-altering efficacy of switching from atorvastatin 10 mg/day to ezetimibe/simvastatin 10/20 mg/day compared to doubling the dose of atorvastatin in hypercholesterolaemic patients with atherosclerosis or coronary heart disease. International Journal of Clinical Practice. 2005;59(12):1377-86.
Garcia 2016*	Garcia MMO, Varela CG, Silva PF, Lima PRP, Góes PM, Rodrigues MG, et al. Endothelial effect of statin therapy at a high dose versus low dose associated with ezetimibe. Arquivos Brasileiros de Cardiologia. 2016;106(4):279-88.
Ostad 2009*	Ostad MA, Eggeling S, Tschentscher P, Schwedhelm E, Böger R, Wenzel P, et al. Flow-mediated dilation in patients with coronary artery disease is enhanced by high dose atorvastatin compared to combined low dose atorvastatin and ezetimibe: Results of the CEZAR study. Atherosclerosis. 2009;205(1):227-32.
McCormack 2010	McCormack T, Harvey P, Gaunt R, Allgar V, Chipperfield R, Robinson P, et al. Incremental cholesterol reduction with ezetimibe/simvastatin, atorvastatin and rosuvastatin in UK General Practice (IN-PRACTICE): randomised controlled trial of achievement of Joint British Societies (JBS-2) cholesterol targets. Int J Clin Pract. 2010;64(8):1052-61
Fixed dose of statin + ezetimibe vs matching fixed dose of statin	
P692 Ballantyne 2003	Ballantyne CM, Houri J, Notarbartolo A, Melani L, Lipka LJ, Suresh R, et al. Effect of ezetimibe coadministered with atorvastatin in 628 patients with primary hypercholesterolemia: A prospective, randomized, double-blind trial. Circulation. 2003;107(19):2409-15. o Ballantyne et al. 2002, J. Am. Coll. Cardiol. 39(9, Suppl. B) 135B-135B; o Ballantyne et al. 2002, J. Am. Coll. Cardiol. 39 (9, Suppl. B) 227A-227A

P038
Bays 2004
	Bays HE, Ose L, Fraser N, Tribble DL, Quinto K, Reyes R, et al. A multicenter, randomized, double-blind, placebo-controlled, factorial design study to evaluate the lipid-altering efficacy and safety profile of the ezetimibe/simvastatin tablet compared with ezetimibe and simvastatin monotherapy in patients with primary hypercholesterolemia. Clinical Therapeutics. 2004;26(11):1758-73. Bays et al. 2004, J Am Coll Cardiol 43 445A-446A;
	o Ose et al. 2004, Atherosclerosis 5(Suppl. 1) p140-140;
	o Ose et al. 2004, Atherosclerosis 5(Suppl. 1) p140-141;
	o Feldman et al. 2005, J. Am. Coll. Cardiol. 45(3, Suppl. A) 392A-392A

Chirinos 2010*	Chirinos JA, Williams MM, Bregman DB, Ashfaq H, Khayyam U, Iqbal N. Efficacy of cholesterol uptake inhibition added to statin therapy among subjects following a low-carbohydrate diet: A randomized controlled trial. American Heart Journal. 2010;159(5):918.e1-.e6.
Protocol P680 Davidson 2002	Davidson MH, McGarry T, Bettis R, Melani L, Lipka LJ, LeBeaut AP, et al. Ezetimibe coadministered with simvastatin in patients with primary hypercholesterolemia. Journal of the American College of Cardiology. 2002;40(12):2125-34. o Sager PT, Melani L, Lipka L, Strony J, Yang B, Suresh R, et al. Effect of coadministration of ezetimibe and simvastatin on high-sensitivity C-reactive protein. American Journal of Cardiology. 2003;92(12):1414-8. o Sager et al. 2004, Atherosclerosis 5 (Suppl. 1) p148-148; o Davidson et al. 2002, J. Am. Coll. Cardiol. 39(9, Suppl. B) 135B-135B; Davidson et al. 2002, J.

Trial	Reports
	Am. Coll. Cardiol. 39(9, Suppl. A) 226A-226A; o Sager et al. 2003, Eur. Heart J. 24 (Abstract Suppl.) p690-690; o Sager et al. 2003, J. Am. Coll. Cardiology 41 (6, Suppl. A) 316A-317A
P005 Goldberg 2004	Goldberg AC, Sapre A, Liu J, Capece R, Mitchel YB. Efficacy and Safety of Ezetimibe Coadministered with Simvastatin in Patients with Primary Hypercholesterolemia: A Randomized, Double-Blind, Placebo-Controlled Trial. Mayo Clinic Proceedings. 2004;79(5):620-9 o Goldberg et al. 2004, J Am Coll Cardiol 43 480A-480A;
Kastelein 2008*	Kastelein JJ, Akdim F, Stroes ES, Zwinderman AH, Bots ML, Stalenhoef AF, et al. Simvastatin with or without ezetimibe in familial hypercholesterolemia. N Engl J Med. 2008;358(14):1431-43. Epub 2008/04/01
Shankar 2007*	Shankar PK, Bhat R, Prabhu M, Reddy BP, Reddy MS, Reddy M. Efficacy and tolerability of fixed-dose combination of simvastatin plus ezetimibe in patients with primary hypercholesterolemia: Results of a multicentric trial from India. Journal of Clinical Lipidology. 2007;1(4):264-70
P023 Feldman 2004	Feldman T, Koren M, Insull Jr W, McKenney J, Schrott H, Lewin A, et al. Treatment of high-risk patients with ezetimibe plus simvastatin co-administration versus simvastatin alone to attain National Cholesterol Education Program Adult Treatment Panel III Low-Density lipoprotein cholesterol goals. American Journal of Cardiology. 2004;93(12):1481-6. o Feldman et al. 2004, Atherosclerosis 5(Suppl. 1) p118-118; o McKenney et al. 2004, Diabetologia 47(Suppl. 1) A409-409

The master list of all included trials of ezetimibe as a monotherapy that meet the selection criteria are shown in Table 2.2.4.3. Some of these trials are also included in Table 2.2.4.2. The list of ezetimibe monotherapy studies includes nine trials, eight of which were included in the comprehensive meta-analysis by Pandor (2009)[35]. We have identified one additional study by Farnier (2009)[82], that was not published at the time of writing the systematic review by Pandor (2009)[35].

Table 2.2.4.3 Reports of the RCTs of ezetimibe as a monotherapy

Trial	Reports
P692 Ballantyne 2003	Ballantyne CM, Houri J, Notarbartolo A, Melani L, Lipka LJ, Suresh R, et al. Effect of ezetimibe coadministered with atorvastatin in 628 patients with primary hypercholesterolemia: A prospective, randomized, double-blind trial. Circulation. 2003;107(19):2409-15. o Ballantyne et al. 2002, J. Am. Coll. Cardiol. 39(9, Suppl. B) 135B-135B; o Ballantyne et al. 2002, J. Am. Coll. Cardiol. 39 (9, Suppl. B) 227A-227A
P005 Goldberg 2004	Goldberg AC, Sapre A, Liu J, Capece R, Mitchel YB. Efficacy and Safety of Ezetimibe Coadministered with Simvastatin in Patients with Primary Hypercholesterolemia: A Randomized, Double-Blind, Placebo-Controlled Trial. Mayo Clinic Proceedings. 2004;79(5):620-9 o Goldberg et al. 2004, J Am Coll Cardiol 43 480A-480A;

P038
Bays 2004
	Bays HE, Ose L, Fraser N, Tribble DL, Quinto K, Reyes R, et al. A multicenter, randomized, double-blind, placebo-controlled, factorial design study to evaluate the lipid-altering efficacy and safety profile of the ezetimibe/simvastatin tablet compared with ezetimibe and simvastatin monotherapy in patients with primary hypercholesterolemia. Clinical Therapeutics. 2004;26(11):1758-73. Bays et al. 2004, J Am Coll Cardiol 43 445A-446A;
	o Ose et al. 2004, Atherosclerosis 5(Suppl. 1) p140-140;
	o Ose et al. 2004, Atherosclerosis 5(Suppl. 1) p140-141;
	o Feldman et al. 2005, J. Am. Coll. Cardiol. 45(3, Suppl. A) 392A-392A

Protocol P680 Davidson 2002	Davidson MH, McGarry T, Bettis R, Melani L, Lipka LJ, LeBeaut AP, et al. Ezetimibe coadministered with simvastatin in patients with primary hypercholesterolemia. Journal of the American College of Cardiology. 2002;40(12):2125-34. o Sager PT, Melani L, Lipka L, Strony J, Yang B, Suresh R, et al. Effect of coadministration of ezetimibe and simvastatin on high-sensitivity C-reactive protein. American Journal of Cardiology. 2003;92(12):1414-8. o Sager et al. 2004, Atherosclerosis 5 (Suppl. 1) p148-148; o Davidson et al. 2002, J. Am. Coll. Cardiol. 39(9, Suppl. B) 135B-135B; Davidson et al. 2002, J. Am. Coll. Cardiol. 39(9, Suppl. A) 226A-226A; o Sager et al. 2003, Eur. Heart J. 24 (Abstract Suppl.) p690-690; o Sager et al. 2003, J. Am. Coll. Cardiology 41 (6, Suppl. A) 316A-317A
Protocol 809	Farnier M, Averna M, Missault L, Vaverkova H, Viigimaa M, Massaad R, et al. Lipid-altering efficacy of

Trial	Reports
Farnier 2009	ezetimibe/simvastatin 10/20 mg compared with rosuvastatin 10 mg in high-risk hypercholesterolaemic patients inadequately controlled with prior statin monotherapy – The IN-CROSS study. International Journal of Clinical Practice. 2009;63(4):547-59.
Protocol 475 Dujovne 2002	Dujovne CA, Ettinger MP, McNeer JF, Lipka LJ, LeBeaut AP, Suresh R, et al. Efficacy and safety of a potent new selective cholesterol absorption inhibitor, ezetimibe, in patients with primary hypercholesterolemia.[Erratum appears in Am J Cardiol. 2003 Jun 1;91(11):1399]. American Journal of Cardiology. 2002;90(10):1092-7.
Protocol 474 Knopp 2003	Knopp RH, Gitter H, Truitt T, Bays H, Manion CV, Lipka LJ, et al. Effects of ezetimibe, a new cholesterol absorption inhibitor, on plasma lipids in patients with primary hypercholesterolemia. European Heart Journal. 2003;24(8):729-41.
Kerzner 2003	Kerzner B, Corbelli J, Sharp S et al. Efficacy and safety of ezetimibe coadministered with lovastatin in primary hypercholesterolemia. Am J Cardiol 2003; 91: 418–24.
Melani 2003	Melani L, Mills R, Hassman D et al. Efficacy and safety of ezetimibe coadministered with pravastatin in patients with primary hypercholesterolemia: a prospective, randomized, double-blind trial. Eur Heart J 2003; 24: 717–28

2.2.5. Approach taken to assess ezetimibe in combination with statins or as a monotherapy

No RCT was identified that would assess ezetimibe in the target population with inadequately controlled hypercholesterolemia managed with the maximum tolerated dose of statin (if statin is not contraindicated). Patients enrolled in ezetimibe monotherapy trials were not required to demonstrate intolerance to statin or have some contraindications. Therefore the best available evidence for this review consists of the RCTs that employed one of the following designs:

- Ezetimibe as a monotherapy compared to placebo (no treatment) (N=9)[4].
- Up-titration of a dose of statin added to ezetimibe vs up-titration of statin in the comparator arm (N=4)[5].
- Addition of ezetimibe to the fixed dose of statin (background therapy) vs up-titration of a statin in the control arm (either in terms of dose or in terms of potency) (N=19)
- Addition of ezetimibe to the various fixed dose of statin compared to placebo added to the same fixed dose of statin (N=8)

Note: Some of the trials fall into more than one category.

[4] Another study by Farnier 2005 did not report statistical estimates of the variation around the end points and was excluded from the meta-analysis, but was retained for the assessment of safety of ezetimibe monotherapy vs placebo

[5] IMROVE-IT trial falls into this category but did not report statistical estimates of the variation around the surrogate outcomes that were subsequently excluded from the systematic overview of the LDL-C and HDL-C results.

2.3. Trial design and execution

2.3.1. Appraisal of evidence

Appraisal of the quality of the evidence was conducted alongside the following dimensions which is based on the Cochrane Handbook for Systematic Reviews of Intervention:

- study design (randomisation, concealment of allocation) to assess the risk of selection bias;
- blinding of participants and personnel to the knowledge of the allocated interventions (to assess the risk of performance bias)
- blinding of the outcome assessor (to assess the risk of detection bias)
- adequate description of the flow of the patients
- incomplete outcome data (to assess the risk of attrition bias)
- selective/ incomplete and inconsistent reporting of outcomes (to assess the risk of reporting bias)
- basis for data analysis (ITT, per-protocol, or as treated)

Table 2.3.1 summarises the methodological quality of RCTs in ezetimibe as monotherapy.

Table 2.3.1: Methodological quality of included studies in ezetimibe as monotherapy

	Concealment of randomisation	Blinding of participant	Blinding of investigator	Blinding of outcome assessor	Basis of analysis is ITT	Consistent, comprehensive reporting of primary outcomes	Level of evidence	Risk of Bias‡	Appropriate comparison	Overall quality of study
P692 Ballantyne 2003	√	√	√	√	√	×	II	A	C1	Q1
P005 Goldberg 2004	√	√	√	√	√*	√	II	A	C1	Q1
P038 Bays 2004	√	√	√	√	√*	√	II	A	C1	Q1
P680 Davidson 2002	√	√	?	√	√	√	II	A	C1	Q1
Farnier 2005	√	√	√	?	√*	√	II	B	C1	Q2
P474 Dujovne 2002	?	√	?	×	√	√	II	B	C1	Q2
P475 Knopp 2003	√	√	√	×	√	√	II	A	C1	Q2
Kerzner 2003	?	√	?	×	√	√	II	B	C1	Q2
Melani 2003	√	√	√	√	√	√	II	A	C1	Q1

*modified ITT;

Table 2.3.2 summarises the methodological quality of RCTs in ezetimibe in combination with statin.

Table 2.3.2: Methodological quality of included studies

	Concealment of randomisation	Blinding of participant	Blinding of investigator	Blinding of outcome assessor	Basis of analysis is ITT	Consistent, comprehensive reporting of primary outcomes	Level of evidence	Risk of Bias‡	Appropriate comparison	Overall quality of study
up-titrating dose of statin + ezetimibe vs up-titrating dose of statin										
P025 Ballantyne 2004	√	√	√	√	√	√	II	B	C1	Q2
P693 Stein 2004	√	√	√	√	×	√	II	B	C1	Q2
McKenney 2007**	√	×	×	×	×	√	II	B	C1	Q3
Cannon 2015 IMPROVE-IT	√	√	√	√	√	√	II	A	C1	Q1
fixed statin dose+ ezetimibe vs up-titrating statin either in terms of dose or in terms of potency										
Leiter 2008	√	√	√	√	×§	√	II	B	C1	Q2
Teramoto 2012**§	√	×	×	×	√	√	II	B	C1	Q2
P079 Conard 2008	√	√	√	√	√	√	II	B	C1	Q2
Pesaro 2013	√	√	√	√	√	√	II	A	C1	Q1
P021 Gaudiani 2005	√	√	√	√	√	√	II	B	C1	Q2
P700 Dobs 2003	√	√	√	√	√	×	II	B	C1	Q2^
Zieve 2010	√	√	√	√	×‖	√	II	B	C1	Q2
Farnier 2009	√	√	√	√	×§	√	II	B	C1	Q2
P058 Catapano 2006	√	√	√	√	√*	√	II	A	C1	Q1
P077Goldberg 2006 VYTAL	√	√	√	?	√*	√	II	A	C1	Q1
Lee 2013**	√	×	×	×	×§	√	II	B	C1	Q2
Cho 2011**	√	×	×	×	×§	√	II	B	C1	Q2
P051 Ballantyne 2005	√	√	√	√	√*	√	II	A	C1	Q1
P807 Constance 2007	√	√	√	×	×	×	II	B	C1	Q3
P806 Barrios 2005	√	√	√	?	√	×	II	A	C1	Q1
Garcia 2016	√	√	√	√	×‖	√	II	B	C1	Q2
Ostad 2009	?	√	√	?	√*	√	II	B	C1	Q2
McCormack 2010	√	√	√	√	√*	√	II	B	C1	Q2

fixed dose of statin +ezetimibe vs matching fixed dose of statin										
P692 Ballantyne 2003	√	√	√	√	√	×	II	A	C1	Q2
P038 Bays 2004	√	√	√	√	√	√	II	A	C1	Q1
Chirinos 2010	√	√	√	√	√	√	II	A	C1	Q1
P680 Davidson 2002	√	√	?	√	√*	√	II	A	C1	Q2
P005 Goldberg 2004	√	√	√	√	√*	√	II	A	C1	Q1
Kastelein 2008 ENHANCE	√	√	√	√	√	√	II	A	C1	Q1
Shankar 2007	√	√	√	√	√	√	II	A	C1	Q1
P023 Feldman 2004	√	√	√	?	√*	√	II	A	C1	Q1

*modified ITT; **open-label study §full analysis set population: randomised patients who used one dose of study medication and had a baseline value and at least one post-baseline value; ^Based on CSR; ‖ similar to modified ITT patients have one baseline measurement and at least an 'on-treatment' measurement.

Most of the identified RCTs used a secure randomisation procedure; all but four open-label trials (McKenney 2007, Teramoto 2012; Lee 2013 and Cho 2011) were double-blinded with the investigators and the participants being unaware of the treatment assignment. Fourteen trials employed an intent-to-treat (ITT) statistical analysis for the primary outcome, while other trials used a modified ITT analysis whereby only patients who had at least one dose of assigned medication and one post-baseline measure were included in the primary analyses. The overall risk of bias was considered low or very low and the overall quality seems to be high for the double-blinded RCTs with points taking off primarily for insufficient reporting that either impeded the statistical analysis or affected our ability to assess the methodological quality of the trial.

Our selection of the trials has a higher overall rating of quality than the trials included in the systematic reviews presented in section 2.2.3. This is because, with meta-analysis being an ultimate goal of a systematic review, the studies that did not report the measure of variation around the point estimates were excluded on the basis of insufficient reporting that was frequently associated with the poorer overall quality of the study.

Table 2.3.3 shows the patient flow through the trials.

Table 2.3.3 Flow of participants through the trials

Trial ID	Intervention arm	No. randomised	Did not receive intervention	Lost to follow- up	Discontinued	Analysed
up-titrating dose of statin + ezetimibe vs up-titrating dose of statin						
P025 Ballantyne 2004	EZ+ATOR	201	0	NA	18(9%)	201(100%)
	PBO+ ATOR	45	0	NA	3(7%)	45(100%)
McKenney 2007	EZ+SIM	72	NA	NA	5 (6.5%)	72 (93.5%)
	ROSUV	73	NA	NA	3 (3.9%)	73 (96.1%)
Stein 2004	EZ+ATOR	305	0	3(0.9%)	27(9%)	293(96%)
	PBO+ ATOR	316	0	1(0.3%)	26(8%)	303(96%)
Cannon 2015 IMPROVE-IT	EZ+SIM	9067	216(2%)	1008(11%)	2199 (25%)	9067 (100%)
	PBO+SIM	9077	222(2%)	1018(11%)	2217(24%)	9077(100%)
fixed statin dose+ ezetimibe vs up-titrating statin either in terms of dose or in terms of potency						

Trial ID	Intervention arm	No. randomised	Did not receive intervention	Lost to follow- up	Discontinued	Analysed
Leiter 2008	EZ+ATOR	288	NA	1(0.3%)	9(3.1%)	277 (96.2%)
	PBO+ ATOR	291	NA	1(0.3%)	13(4.5%)	279 (95.9%)
Teramoto 2012	EZ+ATOR	47	NA	NA	4 (8.5%)	47 (100%)
	PBO+ ATOR	46	NA	NA	1 (2.2%)	46 (100%)
	PBO+ ROSUV	32	NA	NA	0	32 (100%)
P079 Conard 2008	EZ+ ATOR	98	NA	2 (2%)	6 (6%)	92 (94%)
	PBO+ ATOR	98	NA	2 (2%)	7 (7%)	92 (94%)
Pesaro 2013	EZ+SIM	37	NA	NA	NA	37 (100%)
	PBO+ SIM	31	NA	NA	NA	31 (100%)
P021 Gaudiani 2005	EZ+SIM	104	NA	2(2%)	11 (11%)	103 (99%)
	PBO+ SIM	110	NA	3(3)	21 (20%)	107 (97%)
P700 Dobs 2003	EZ+SIM	34	34 (100%)	0	3 (9%)	34 (100%)
	PBO+ SIM	66	66 (100%)	1 (2%)	9 (14%)	66 (100%)
Zieve 2010	EZ+ATOR	526	NA	0	23 (4.4%)	516 (98.1%)
	PBO+ ATOR	527	NA	1 (0.2%)	20 (3.8%)	509 (96.6%)
Farnier 2009	EZ+SIM	314	NA	0	13 (4.1%)	300 (95.5%)
	ROSUV	304	NA	1 (0.3%)	9 (3.0%)	293 (96.4%)
P058 Catapano 2006	EZ+SIM (all)	1478	NA	11 (1%)	68 (4.6%)	1427 (96.5%)
	PBO+ ROSUV (all)	1481	NA	10 (1%)	76 (5.1%)	1428 (96.4%)
P077Goldberg 2006 VYTAL	EZ+SIM (all)	494	0	4(0.8%)	22(4.5%)	480 (97.2%)
	PBO+ATOR (all)	735	3 (0.4%)	0	22 (3.0%)	718 (97.7%)
Lee 2013	EZ+SIMV	66	1(1.5%)	0	3 (4.5%)	62 (93.9%)
	PBO+ATOR	66	0	0	3 (4.5%)	63 (95.5%)
Cho 2011	EZ+SIMV	42	NA	7 (8%)	11 (13%)	36 (85.7%)
	ATOR	43	NA			38 (88.4%)
P051 Ballantyne 2005	EZ+SIM (all)	951	3 (0.3%)	4 (0.4%)	32 (3.4%)	923 (97.1%)
	PBO+ATOR (all)	951	4 (0.4%)	1 (0.1%)	23 (2.4%)	927 (97.5%)
P807 Constance 2007	EZ+SIM (all)	442	3 (1%)	NA	13 (2%)	442 (100%)
	PBO+ ATOR	219	1 (0.5%)	NA		219 (100%)
P806 Barrios 2005	EZ+SIM	221	NA	0 (0.0)	7 (3.2)	215 (97.2%)
	PBO+ ATOR	214	NA	0 (0.0)	9 (4.2)	207 (96.7%)
Garcia 2016	EZ+SIM	16	0	0	0	16 (100%)
	SIM	16	0	0	0	16 (100%)
Ostad 2009	EZ+ATOR	28	NA	NA	4 (14%)	24(86%)
	PBO+ATOR	29	NA	NA	5 (17%)	24(83%)
McCormack 2010	EZ+SIM	261	2 (0.8%)	4 (1.5%)	12 (4.6%)	255 (97.7%)
	ATOR	263	3 (1.1%)	1 (0.4%)	11 (4.2%)	259 (98.5%)
	ROSU	262	1 (0.4%)	3 (1.1%)	11 (4.2%)	258 (98.5%)
fixed dose of statin +ezetimibe vs matching fixed statin dose						
P692 Ballantyne 2003	EZ+ATOR (all)	255	NA	1 (0.4%)	23 (9%)	255 (100%)
	PBO+ATOR (all)	248	NA	2 (0.8%)	19 (8%)	248 (100%)
P038 Bays 2004	EZ+SIM (all)	609	5 (1%)	1 (0.2%)	1 (0.2%)	604 (99%)
	PBO+SIM (all)	622	10 (2%)	2 (0.3%)	2 (0.3%)	612 (98%)
Chirinos 2010	EZ+SIMV	28	NA	NA	4 (14.3%)	28 (100%)
	SIM	30	NA	NA	4 (13.3%)	30 (100%)
P680 Davidson 2002	EZ+SIM (all)	274	NA	1 (0.4%)	35 (13%)	274 (100%)
	PBO+SIM (all)	263	NA	3 (1.1%)	26 (10%)	263 (100%)
P023 Feldman 2004	EZ+SIM (all)	457	NA	7 (3.4%)	60(13.1%)	444 (97%)
	PBO+SIM	253	NA	5 (1.9%)	34(13.4%)	246 (97%)
P005 Goldberg 2004	EZ+SIM (all)	353	NA	3 (0.8%)	30 (8%)	352 (99%)
	PBO+SIM (all)	349	NA	3 (0.9%)	27 (7.7%)	345 (98.9%)
Kastelein 2008	EZ+SIM	357	1 (0.3%)	2 (0.6%)	41 (11.5%)	357 (100%)
	PBO+SIM	363	2 (0.6%)	2 (0.6%)	64 (17.6%)	363 (100%)
Shankar 2007	EZ+SIM	114	NA	2 (1%)	7 (3%)	114 (100%)
	SIM	116	NA			116 (100%)
P023 Feldman 2004	SIM 20	253	NA	5 (1.9%)	34 (13.4%)	246 (97%)
	EZ+SIM10	251	NA	6 (2.4%)	38 (15.1%)	242 (96%)
	EZ+SIM 20	109	NA	0 (0%)	8 (7.3%)	108 (99%)
	EZ +SIM 40	97	NA	1 (1%)	14 (14.4%)	96 (99%)

For some trials, the patient flow information was available only for the combined arms. All large trials (N>100) included of a high proportion (>95%) of the randomised patients in the analysis. The analysis set from the small size trials could be as low as 83% (Ostad 2009), although many of the smaller size trials maintained an ITT principle. The rate of discontinuation, where reported, ranged from 0.2% (Bays, 2004) to 25% (Cannon 2015, the 7 year IMPROVE-IT trial) and 27% (Stein 2004, 14 week trial).

2.4. Trial characteristics

Table A4.1 in Appendix 4 shows a brief description of each of the 30 trials, inclusion and exclusion criteria and assessment of the degree of each trial population overlapping with the target population for the review.

Tables 2.4.1- 2.4.2 show characteristics of the identified trials that formed the evidence basis for the report. The RCTs were grouped according to the study design. The following characteristics of the RCTs are also included in the tables: the type of the prevention population (primary or secondary); the line of ezetimibe therapy (the first-line treatment assigned to statin-naïve or patients who undertook a wash-out period or the second-line therapy with ezetimibe added to a background statin). Min and max LDL-C values reflect the selection criteria, if reported. The equivalent to the mean 5 year risk of a CV event (as recommended by the NVDPA-2012) was not reported in any of the RCTs; the trials that included the risk assessment based on epidemiological evidence (e.g. formulae derived from Framingham Heart Study Anderson 1991, D'Agostino 2000) aligned the selection criteria with the American guidelines, that use the combination of conditions known to predict CHD and the thresholds (in %) for a 10 year CHD risk using the Framingham risk equation and the Pooled Cohort Equations at the later stage. Tables 2.4.1-2.4.2 identify the studies that assessed patients using the risk equations. Other included trials specifically targeted the population identified as "high", "medium" or "low" risk based (explicitly or implicitly) on the NCEP ATP III criteria that combine cholesterol level with clinical conditions and other factors known to increase the risk of CHD, but do not utilise a risk assessment algorithm based on a mathematical formula.

Primary or secondary endpoints in all RCTs included the mean percentage change from baseline in LDL-cholesterol and other surrogate outcomes identified for the review: total cholesterol (TC) and high density lipoprotein cholesterol (HDL-C). Other lipid parameters such as the ratio of TC:HDL-C and the median change from baseline in triglycerides (TG) were also reported in some of the identified trials but were outside the scope of the review.

Table 2.4.1 Characteristics of trials of ezetimibe in combination with a statin

Trial	Design	Duration of follow-up	N	Patient population						Interventions	Outcomes	
				1°, 2° or mixed	Age (SD, range)	Min LDL-c at baseline	Max LDL-c at baseline	Other	CV risk at baseline		Change in LDL-c	Reduction in CV endpoints
up-titrating dose of statin + ezetimibe vs up-titrating dose of statin												
P025 Ballantyne 2004	MC, R, DB	24 weeks	263 263 262	3º	59.4±10.62 59.9±10.88 60.8±9.99	3.36-4.91	NR	1st line treatment	10-20%^ (10-year risk)	EZ 10+SIM 10 EZ 10+SIM 20 PBO + ATOR 10	At week 6 At week 12 At week 18 At week 24	Not assessed
McKenney 2007	MC, R, OL, P	12 weeks	72 73	3º	59±10 59±11	3.4-4.9	NR	1st line treatment	NR	EZ 10+SIM 20 ROSUV 10	At week 8 At week 12	Not assessed
P693 Stein 2004	MC, R, DB	14 weeks	305 316	3º	53.0(18-82) 51.6(18-80)	3.36	NR	2nd line treatment	NR	EZ 10+ATOR 10 PBO + ATOR 20	At week 14	Not assessed
Cannon 2015 IMPROVE-IT	MC, R, P, DB	2.5 years	9077 9067	2º (ACS within past 10 days)	63.6±9.8 63.6±9.7	1.3	2.6	1st & 2nd line treatment	*High*	PBO + SIM 40* EZ 10+SIM 40*	At year 1 At year 7	At year 7
fixed dose of statin + ezetimibe vs up-titrating statin either in terms of dose or in terms of potency												
P090 Leiter 2008	MC, R, DB, P	6 weeks	288 291	1º	61±10 62±9	1.81	4.14	2nd line treatment	High >20% (10 year)	EZ 10+ATOR 40 PBO + ATOR 80	At week 6	Not assessed
Teramoto 2012	MC, R, OL, P	12 weeks	47 46 32	1º	62.7±11.4 59.3±11.8 61.1±12.0	2.59	NR	1st line treatment	NR	EZ 10+ATOR 10 ATOR 20 ROSUV 2.5	At week 12	Not assessed
P079 Conard 2008	MC, R, P, DB	6 weeks	98 98	1º	56±10 58±10	2.59	4.14	2nd line treatment	Moderately high risk	EZ 10+ ATOR 20 PBO + ATOR 40	At week 6	Not assessed
Pesaro 2013	R, DB	6 weeks	37 31	2º(CHD)	64.5±9 61.8±10	1.81	NR	2nd line treatment	NR	EZ 10+SIM 20 PBO + SIM 80	At week 6	Not assessed
P021 Gaudiani 2005	MC, R, DB, P	24 weeks	110 104	3º	58.3(37-78) 57.8(35-80)	2.6	NR	2nd line treatment	NR	PBO + SIM 40 EZ 10+SIM 20	At week 24	Not assessed

P700 Dobs 2003	R, DB	4 weeks	66 34	3º	NR NR	3.36	NR	1st line treatment	*High*	EZ 10+SIM 20 PBO + SIM 40	At week 4	Not assessed
P112 Zieve 2010	MC, R, P, DB	12 weeks	526 527	3º	71±5 71±5	1.81-2.59	4.14-4.91	2nd line treatment	High >20% (10-year)	EZ 10+ATOR 10 PBO + ATOR 20	At week 12	Not assessed
Farnier 2009	MC, R, P, DB,	6 weeks	314 304	3º	63.2±9.8 63.1±10	2.59	4.92	2nd line treatment	High >20% (10-year)	EZ 10+SIM 20 PBO + ROSUV 10	At week 6	Not assessed
Catapano 2006	MC, R, P,DB,	6 weeks	492 492 495 493 494 493	1º	55.6±10.3 54.9±10.4 55.8±10.4 56.2±10.4 55.4±10.6 55.9±10.0	3.75	6.47	1st line treatment	NR	PBO + ROSUV 10 EZ 10+SIM 20 PBO + ROSUV 20 EZ 10+SIM 40 PBO + ROSUV 40 EZ 10+SIM 80	At week 6	Not assessed
P077 Goldberg 2006	MC, R, P DB	6 weeks	245 247 245 247 245	3º	59.1±10.1 59.8±10.3 60.1±10.6 58.7±10.2 59.9±10.4	2.59	NR	1st line treatment	NR	PBO + ATOR 10 EZ 10+SIM 20 PBO + ATOR 20 EZ 10+SIM 40 PBO + ATOR 40	At week 6	Not assessed
Lee et al 2013	R, OL, P	12 weeks	66 66	1º	64.2±7.7 65.0±7.6	2.59	NR	1st line treatment	NR	ATOR 20 EZ 10+SIM 20	At week 12	Not assessed
Cho 2011	R, OL	6 weeks	42 43	2º (CHD)	60.5±9.5 62.6±9.7	2.59	6.47	1st line treatment	Very high risk	EZ 10+ SIM 20 ATOR 20	At week 6	Not assessed
P051 Ballantyne 2005	MC, R, P, DB	6 weeks	951 951	3º	59.0±10.6 58.5±10.2	3.36-4.91	NR	1st line treatment	>10%^ (10-year)	EZ 10+SIM (10,20,40,80) PBO + ATOR (10,20,40,80)	At week 6	Not assessed
P807 Constance 2007	MC, R, DB, P	6 weeks	220 222 219	3º	62.1(28-86) 62.4(35-84) 61.7(29-82)	NR	NR	2nd line treatment	NR	EZ 10+ SIM 20 EZ 10+ SIM 40 PBO + ATOR 20	At week 6	Not assessed
P806 Barrios 2005	MC, R, P, DB,	6 weeks	221 214	2º (CHD)	63.5±9.6 63.4±10.2	2.5	4.2	2nd line treatment	NR	EZ 10+SIM 20 PBO + ATOR 20	At week 6	Not assessed
Garcia 2016	R, DB	8 weeks	14 16 16	1º	40±12 41±8.6 48±8.1	2.59	NR	1st line treatment	NR	PBO PBO + SIM 80 EZ 10+ SIM 10	At week 4 At week 8	Not assessed

Ostad 2009	R, DB	8 weeks	24 25	2º (CHD)	66±9 64±10	2.6	NR	1st line treatment	NR	PBO + ATOR 80 EZ 10+ATOR 10	At week 8	Not assessed
McCormack 2010	MC, R, P, DB,	6 weeks	261 263 262	3º	64.7±8.7 64.2±8.4 63.9±8.6	2.0	4.2	2nd line treatment	>20% (10-year)	EZ 10+SIM 40 ATOR 40 ROSU 5/10	At week 6	Not assessed
fixed dose of statin + ezetimibe vs matching fixed dose of statin												
P692 Ballantyne 2003	R, P, DB,	12 weeks	60 65 248 255	1°	56.9±12.1 56.7±11.7 57.8±11.7 58.7±11.4	3.75	6.47	1st line treatment	NR	PBO EZ 10 PBO + ATOR (10,20,40,80) EZ 10+ATOR (10,20,40,80)	At Week 12	Not assessed
P038 Bays 2004	MC, R, DB,	12 weeks	148 149 622 609	1º	560. ±10.8 55.5±11.0 54.9±11.2 56.4±10.6	3.75	6.47	1st line treatment	NR	PBO EZ 10 PBO + SIM (10,20,40,80) EZ10+SIM (10,20,40,80)	At week 12	Not assessed
Chirinos 2010	R,P, DB	8 weeks	30 28	1º	58.8±7.2 56.4±10.9	3.36	4.91	1st line treatment	NR	PBO + SIM 20 EZ 10+ SIM 20	At week 8	Not assessed
P680 Davidson 2002	MC, R, DB	12 weeks	70 61 263 274	1º	58.8(25-84) 60.3(34-84) 56.4(25-87) 57.6(27-87)	3.75	6.47	1st line treatment	NR	PBO EZ 10 PBO + SIM (10,20,40,80) EZ 10+ SIM (10,20,40,80)	At week 12	Not assessed
P005 Goldberg 2004	MC, R, DB	12 weeks	93 92 349 353	1º	≥18	3.75	6.47	1st line treatment	NR	PBO EZ 10 PBO + SIM (10,20,40,80) EZ 10+ SIM (10,20,40,80)	At week 12	Not assessed
Kastelein 2008	MC, R, DB	24 months	363 357	1º	45.7±10.0 46.1±9.0	5.43	NR	1st line treatment	NR	PBO + SIM 80 EZ 10+SIM 80	At month 6 At month 12 At month 18 At month 24	Not assessed
Shankar 2007	MC, R, DB,P	12 weeks	116 114	1º	51.54±10.1 52.19±12.2	3.1-3.5	NR	1st line treatment	NR	PBO + SIM 10 EZ 10+SIM 10	At week 12	Not assessed
P023 Feldman$ 2004	MC, R, P	23 weeks	253 251 109 97	3º	62.1±9.7 61.3±10.2 64.0±9.8 61.7±9.8	3.36	NR	1st line treatment	High >20% (10-year)	SIM 20 EZ 10+SIM 10 EZ 10+SIM 20 EZ 10+SIM 40	At week 5	Not assessed

1° = primary prevention population; 2° = secondary prevention population; 3° = "mixed" prevention population (both primary and secondary); ^ one of the risk assessment criterion, patients above and below 10% risk were selected. Min = minimum; Max = maximum; CV risk = risk of major cardiovascular events; MC=multi-centre; R=randomised; P= parallel group; CO = cross-over; DB=double blind; OL = open-label; EZ 10 = ezetimibe 10 mg/day; SIM 10 = simvastatin 10 mg/day; SIM 20 = simvastatin 20mg/day; PBO = placebo; NR = not reported (& cannot be estimated)

* For patients in either study group who had LDL cholesterol levels higher than 2.0 mmol/L on two consecutive measurements, the simvastatin dose was increased to 80 mg in a double-blind manner. In June 2011, in accordance with Food and Drug Administration guidance for limiting new prescriptions of 80 mg of simvastatin, patients were no longer eligible for an increased dose of simvastatin to 80 mg, and any patient who had been receiving the 80-mg dose for less than 1 year had the dose reduced to 40 mg. If an LDL cholesterol measurement on the new regimen was confirmed to be higher than 2.6 mmol/L, the study drug could be discontinued and more potent therapy initiated. *Italicised font indicates "estimated during the evaluation" based on the characteristics of the patients (e.g., patients who have had ACS in the past 10 days would be considered to have a very high risk of a major CV event in the next 5 years)*

$Design of the trial included a dose-response up-titration of statins every 6 weeks. However the only reported results relate to the first observation after the randomisation. For the purposes of this review this trial contributed to two sets of analsyses corresponding to "add-on" matching dose of statin and up-titarting (doubling dose of the same stain) design trial design.

Table 2.4.2 Characteristics of trials of ezetimibe as monotherapy (only the studies or the relevant arms within the study that are not included in Table 2.4.1)

Trial	Design	Duration of follow-up	N	Patient population						Interventions	Outcomes	
				1°, 2° or mixed	Age (SD, range)	Min LDL-c at baseline	Max LDL-c at baseline	Other	Mean 5-year CV risk at baseline		Change in LDL-c	Reduction in CV endpoints
P475 Dujovne 2002	MC, R, DB	12 weeks	666	1°	57.9(18-85)	3.36	6.47	1st line treatment	NR	EZ 10	At week 12	Not assessed
			226		58.1(30-85)					PBO		
P474 Knopp 2003	MC, R, DB	12 weeks	622	1°	58.3(20-86)	3.36	6.47	1st line treatment	NR	EZ 10	At week 12	Not assessed
			205		57.6(24-79)					PBO		
Farnier 2005	MC, R, DB, P	12 weeks	187	1°	53.5+9.2	3.4	5.7	1st line treatment	High <20% (10-year)	EZ 10	At week 12	Not assessed
			64		54.5+10.8					PBO		
Kerzner 2003	MC, R, DB,P	12 weeks	64	1°	58±12	3.75	6.47	1st line treatment	NR	PBO	At week 12	Not assessed
			72		55±11					EZ 10		
Melani 2003	MC, DB R, P	12 weeks	65	1°	53.4 (32-76)	3.8	6.5	1st line treatment	NR	PBO	At week 12	Not assessed
			64		52.0 (26-75)					EZ 10		

1° = primary prevention population; 2° = secondary prevention population; 3° = "mixed" prevention population (both primary and secondary); ^ one of the risk assessment criterion, patients above and below 10% risk were selected. Min = minimum; Max = maximum; CV risk = risk of major cardiovascular events; MC=multi-centre; R=randomised; P= parallel group; CO = cross-over; DB=double blind; OL = open-label;

The trials that form the evidentiary basis for the review fall into different categories depending on the outcomes (final or surrogate); the design ("up-titration" or "add-on"); whether ezetimibe treatment was administered as primary or secondary therapy and the enrolled population, that varied in terms of the primary, secondary or mixed prevention population and the degree of a CHD risk.

Table 2.4.3 shows the number of trials by design, primary, secondary or mixed prevention population and the line of therapy in RCTs (N=30) that were included into analysis of the surrogate outcomes.

Table 2.4.3 Number of trials by design and the enrolled population

	Primary prevention population (N=13)		**Secondary prevention population (N=4)**		**Mixed prevention population (N=14)**	
Line of therapy	**first**	**second**	**first**	**second**	**first**	**second**
Design of the trial						
Up-titrating statin dose+ ezetimibe vs up-titrating statin dose IMPROVE-IT					2 both primary and secondary	1
Fixed dose of statin +ezetimibe vs up-titrating of statin in terms of dose or potency	4	2	2	2	4	5
Fixed dose statin +ezetimibe vs matching fixed dose of statin	7				1*	

*the study by Feldman (2004) contributed to both "up-titrating" and "matching dose" designs for the mixed prevention 1st line treatment population

Nearly half of the trials (N=13) targeted the population for primary prevention of CHD. In majority of these RCTs (N=11) ezetimibe in combination with statin was administered as the first line treatment requiring that the patients who received lipid-lowering drugs at the screening phase would undergo a wash-out period of 4 to 9 weeks. Only 2 of the RCTs in the primary prevention population (N=740) administered ezetimibe + statin as the second line treatment (Conard 2008, Constance 2007). All the RCTs that up-titrated statin in both arms enrolled patients from both primary and secondary prevention categories but only one of these trials administered ezetimibe + statin as the second line treatment (Stein 2004, N=621). Two trials that used either a higher dose or a more potent statin in the control arm and enrolled secondary prevention population (N=503) used ezetimibe + statin as the second line treatment (Barrios 2005, Pesaro 2013). In addition, five trials that used either a higher dose or a more potent statin in the control arm and enrolled mixed prevention population (N=2775) administered ezetimibe + statin as the second line treatment (Constance 2007, Zieve 2010, Gaudiani 2005, Farnier 2009, McCormack 2010).

The duration of active therapy in the included trials ranged from 4 weeks (Dobs 2003) to 7 years (Cannon 2015) and followed (depending on whether the ezetimibe was the first or second line therapy) either a statin or placebo "run-in" period up to 12 week duration (McCormack 2010). The size of the trials varied substantially. A few recently conducted small size RCTs (N<150) that met the selection criteria were conducted in the countries with ethnic diversity that differs from the USA or European

countries (Lee 2013 and Cho 2013 - South Korea; Pesaro 2013 and Garcia 2016 – Brazil); enrolled a special subgroup of the population with hypercholesterolaemia (Chirinos 2010 studied the population of overweight or obese patients; Lee 2013 and Cho 2013 - South Korea enrolled only diabetic patients, Garcia 2016 enrolled only females) or were designed to measure non-lipid outcomes as a primary outcome (Ostad 2009, Pesaro 2013). The second line ezetimibe trial by Pesaro (2013) became the smallest study (N=68) in this category after the earlier study by Dobs (2003) (N=100). The largest study, IMPROVE-IT (Cannon, 2015) randomised 18,144 patients, with 25% of them discontinuing treatment over the 7 year duration.

2.4.1. Participants

The inclusion exclusion criteria of the selected RCTs are presented in Table A4.1 Appendix 4. The populations in the identified trials were fairly comparable in terms of age (mean ages ranging from 52-66 years across 27 of the 30 trials). The exceptions included the trial by Kastelein (2008) in the subgroup of the population with heterozygous familial hypercholesterolaemia (HeFH) with mean age of 46 years; and the female-only trial by Garcia (2016) with mean age across the arms of 40 to 48 years; and the trial by Zieve (2010) with one of the selection criteria of patients' age > 65 years that resulted in the mean age of 71 years old. In the selected trials the patient populations varied across the high risk categories and the specific high risk subgroups. These included primary prevention patients with hypercholesterolemia and no more than 2 other risk factors (low risk category), secondary prevention patients with hypercholesterolemia and atherosclerosis and/or CHD (high risk category), patients with CHD and/or type 2 diabetes (medium to high risk category), and patients with heterozygous familial hypercholesterolemia. The criteria for assigning a high risk category to the different populations in the trials also differed with some trials using the formalised risk assessment tool, others using the combination of risk factors as suggested by the guidelines. In the second line therapy the eligibility criteria for the patients to enter the randomised phase was an "inadequate lipid control", typically aligned with the in LDL-C goals specified in the National Cholesterol Education Program (NCEP) Adult Treatment Panel II (in the later RCTs – NCEP-III) for patients at the different level of CHD risk.

Design of 18 RCT trials in the first line ezetimibe treatment required a wash-out period for up to 12 weeks (six weeks for statins, bile acid sequestrants and nicotinic acid and 8-12 weeks for fibrates) before randomisation and initiating the study therapy. There was insufficient information on patient's pre-treatment history (e.g. dose of statin and duration of treatment) to establish whether the recruited patients were inadequately controlled with the most recent dose of the statin and whether it was the maximum/most potent dose of the last prescribed statin.

Other RCTs (N=11) in patients with hypercholesterolaemia were designed to assess addition of ezetimibe as a second line therapy to the ongoing or newly initiated statin treatment and included a run-in period of at least 4 weeks and up to 10 weeks (Stein 2004). The McCormack (2010) trial was the only one where the duration of the run-in period (on simvastatin 40 mg) was 12 weeks, which together with the evidence of insufficient lipid control of LDL-C> 2 mmol/L at the end of this period would bring the population closest to the PBS restrictions, albeit it remained unknown whether simvastatin 40 mg is the highest tolerate statin dose in this population.

The minimum entry threshold levels of LDL-C in the trials of population with hypercholesterolaemia ranged from from 1.8 to 6.47 mmol/L with or without lipid-lowering medications. The lowest LDL-c level at enrolment of 1.3 mmol/L was required in IMPROVE-IT (Cannon 2015) trial in patients with acute coronary syndrome. This trial enrolled patients who do not necessarily have a diagnosis of hypercholesterolemia and did not require the subjects to have a wash-out period prior the randomisation. This issue was identified in the assessment of the recent Merck and Co submission to

NICE (HTA 2015). However, it was argued by the company that these patient populations are at high risk of CVD and, prescription of ezetimibe or ezetimibe in combination with a statin reflects the current clinical practice. The RCTs by Gaudiani 2005, Goldberg 2006, Constance 2007, Lee 2013 and Cho 2013 enrolled population with diabetes mellitus (DM), but although the evidence of hypercholesterolemia was one of the selection criteria, the second line treatment trials (Constance 2007 and Gaudiani 2005) had one of the lowest mean baseline LDL-C levels (2.4 mmol/L) in patients who were not necessarily inadequately controlled at randomisation. Another second line treatment trial (Leiter 2008) set up a LDL-C entry threshold at 1.8 to 4.1mmol/L, which produced the lowest mean value of 2.3 mmol/L, suggesting that a proportion of patients may not meet the EZ restriction criteria after the run-in on 40 mg of atorvastatin. The mean baseline levels of LDL-C of patients in the remaining second line treatment trials (Stein 2007, Barrios 2005, Dobs 2003, Conard 2008, Pesaro 2013, Zieve 2010, Farnier 2009, McCormac 2010) ranged from 2.7 to 4.8, suggesting that they were not adequately controlled on the run-in treatment.

None of the identified RCTs enrolled the patients who would be fully representative of the populations for whom ezetimibe is currently indicated (e.g. people whose hypercholesterolemia had not been adequately controlled with a maximum tolerated dose of statin or those for who have statin intolerance or contraindications and who meet the other criteria described in the General Statement for Lipid-Lowering Drugs (GSLLD).

Significant variability in background treatment, designs and duration of the identified trials suggests the underlying heterogeneity across the trials.

The population enrolled in the identified RCTs that formed the basis of evidence is not fully representative of the Australian population for whom ezetimibe is currently indicated according to PBS listing.

2.4.2. Treatment details

In all RCTs ezetimibe was administered at the approved dose of 10 mg per day orally either as first-line treatment or second-line treatment. Out of all identified studies, 28 RCTs had a duration that varied from 4 weeks to 24 weeks; two longer term studies were 2 years Kastelein (2008) trial and 7 years IMPROVE-IT trial (Cannon 2015). In the second-line therapy trials ezetimibe was either added to the ongoing treatment with statins or administered following a lead-in phase of statin treatment (Cannon 2015, Stein 2004; Gaudiani 2005; Barrios 2005, Dobs 2003, Conard 2008, Pesaro 2013, Zieve 2010, Farnier 2009, McCormac 2010, Constance 2007, Leiter 2008). The background treatment in RCTs included statins of different potency: simvastatin, atorvastatin and rosuvastatin with different strength of doses. In four RCTs, doses of statin were up-titrated in both the intervention and the comparator arms aiming to reach the maximum potency of the administered statin through the course of trial (Cannon 2015; Ballantyne 2004; McKenney 2007; Stein 2004). In other 18 trials the dose of statin in the comparator arm was up-titrated either in terms of doubling the dose or switching to a more potent statin. Doubling the dose could be administered either forcefully or depending on whether the target in lipid reduction was achieved (dose-response titration) (Gaudiani 2005; Teramoto 2012; Zieve 2010).

In the IMPROVE-IT trial up-titration (doubling the dose of simvastatin to 80 mg/day) was planned in the initial protocol for patients in both arms who did not achieve the target level of LDL-c over the course of trial. However, in response to the FDA guidance (2011) for limiting new 80mg simvastatin prescriptions, amendment was made to the protocol patients were no longer eligible for an increased dose of simvastatin to 80 mg, and any patient who had been receiving the 80-mg dose for less than 1 year had the dose reduced to 40 mg.

In 19 of the identified RCTs intervention was the first-line treatment of ezetimibe in combination with a statin either in only statin-naïve patients or the patients who underwent a wash-out period.

The PBS approved dose regimen of ezetimibe (10 mg/QD) was consistent across all included RCTs however significant variability in background treatment, designs and duration of the identified trials suggests underlying heterogeneity across the trials.

2.4.3. Outcomes

Long-term patient outcomes

The IMPROVE-IT trial (Cannon 2015) was the only RCT that met inclusion criteria and measured final patient outcomes of morbidity and mortality as clinical endpoints. The IMPROVE-IT trial comparted ezetimibe in combination with simvastatin in the intervention arm to simvastatin plus placebo as a comparator in patients with acute coronary syndrome. Table 2.4.3 summarises the definition of composite endpoints in IMPROVE-IT trial.

Table 2.4.3 Definition of clinical outcomes in IMPROVE-IT trial

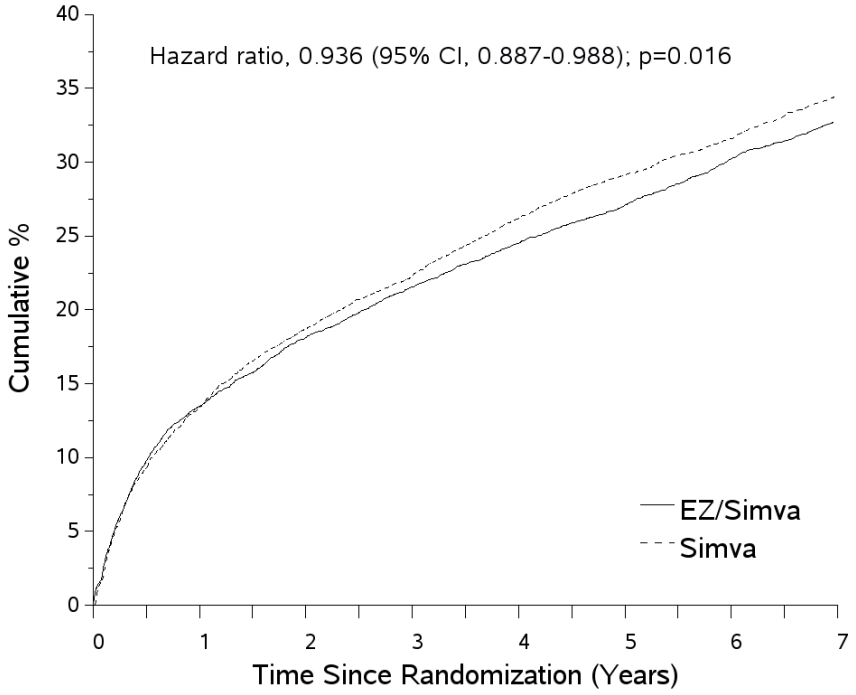
Study	Definition of clinical outcome	Statistical method used to compare difference between groups
IMPROVE-IT (IMProved Reduction of Outcomes: Vytorin Efficacy International Trial) (Cannon 2015)	Primary endpoint: Composite of CV death, major coronary events, and non-fatal stroke Secondary endpoint: Composites of: death from any cause, major coronary events, or non-fatal stroke; CHD death, non-fatal MI, or urgent coronary revascularisation≥30 days after randomization; CV death, non-fatal MI, documented UA requiring hospitalisation, all revascularisation, or non-fatal stroke	Estimates of the hazard ratios and associated 95% confidence intervals for the comparison of simvastatin–ezetimibe with simvastatin monotherapy were obtained with the use of a Cox proportional-hazards model, with study group and stratification factors as covariates. Event rates are Kaplan–Meier failure rates at 7 years.

IMPROVE-IT was a multicentre, randomised, double-blind, active-controlled study in 18,144 patients with stabilised acute coronary syndrome (ACS) and the baseline LDL-c ≥ 1.3 mmol/L if they had not been taking lipid-lowering therapy, or ≤2.6 mmol/L if they had been receiving lipid-lowering therapy. All subjects entering the study were assigned to randomised, double-blind treatment in a 1:1 ratio to either ezetimibe/simvastatin combination 10/40 mg once daily or simvastatin 40 mg and placebo once daily. Subsequently, if LDL-c was found to be >2.05 mmol/L on two consecutive measurements in compliant patients in either treatment group, the dose of simvastatin was increased to 80 mg in a double-blind manner (see the note on protocol alteration in 2.4.2). The trial was specified to end after all subjects had been followed for a minimum of 2.5 years and a primary endpoint event had been documented in at least 5250 subjects. All subjects, including subjects who discontinued treatment, were to be monitored for clinical endpoint events until the termination of the study.

At a median follow-up of 6 years, ezetimibe plus simvastatin produced a 6.4% relative risk (RR) reduction in the primary composite efficacy end point of cardiovascular death, major coronary event, or non-fatal stroke compared with simvastatin alone (hazard ratio [HR] 0.936, 95% confidence interval [CI] 0.89 to 0.99; p=0.016). The primary endpoint occurred in 2,572 of 9,067 subjects (7-year Kaplan-Meier [KM] rate 32.72%) in the ezetimibe/simvastatin group and in 2,742 of 9,077 subjects (7-year KM rate 34.67%) in the simvastatin + placebo group in the protocol-defined ITT population (Figure 2.4.3.1).There

was a reduction in low-density lipoprotein cholesterol at 1 year of 0.43 mmol/L with ezetimibe plus simvastatin compared with simvastatin alone (a relative reduction of 24%).

Figure 2.4.3 1 Kaplan-Meier Curves for the Primary Efficacy End Point IMPROVE-IT



Subjects at risk								
EZ/Simva	9067	7371	6801	6375	5839	4284	3301	1906
Simva	9077	7455	6799	6327	5729	4206	3284	1857

Although IMPROVE-IT successfully demonstrated a statistically significant effect of adding ezetimibe to statin therapy on reducing cardiovascular events, the patient population in the trial was inconsistent with the population for whom ezetimibe is indicated. *Therefore, in its recent submission to the Ezetimibe Review conducted by NICE in UK the sponsor decided not to use the IMPROVE-IT data in its economic model. Instead, the sponsor chose to use the CTTC meta-analysis to model the effect of ezetimibe on cardiovascular outcomes linked to decreased LDL cholesterol. In the 2016 submission to the present Review the sponsor used the results of the trial to validate the model that was used in the previous successful submissions to PBAC. Critique of both models are available in a separate document "Summary of the economic evaluations of ezetimibe*".

Long term patient outcomes reported in the IMPROVE-IT trial may not be fully generalisable to the target population due to incompatibility of the trial selection criteria to the PBS restriction criteria for ezetimibe (i.e. the low LDL-C entry thresholds; no hypercholesterolaemia diagnosis as a selection criterion; use of ezetimibe as the first line of treatment in a large proportion of enrolled patients; the unknown response/tolerance of the background statin treatment in patients who received ezetimibe as the second line treatment).

Surrogate outcomes (LDL-C; HDL-C; TC)

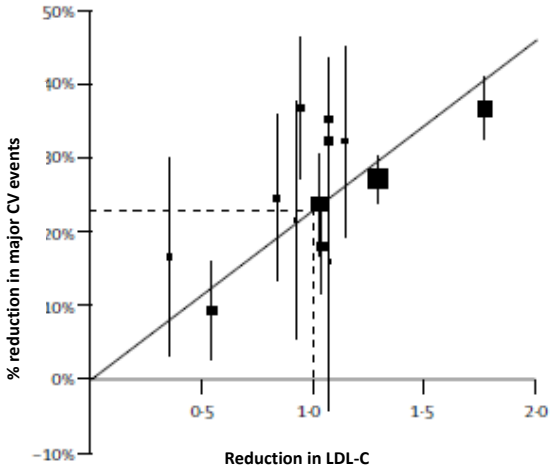
There seems to be a consensus among clinicians that there is a relationship between LDL cholesterol and the risk of cardiovascular disease with no threshold below which the risk ceases to exist in the range of LDL cholesterol levels generally encountered in societies where cardiovascular disease is prevalent. (British Societies' guidelines 2005[83]). The correlation and causal relationship between serum cholesterol

values, particularly LDL cholesterol and the risk of cardiovascular disease, have been established in numerous epidemiological studies (Anderson 1991[84], Neaton 1992[85]), systematic reviews and meta-analyses of clinical outcome trials (Baigent 2005[86], Law 2003[87], Gould 1998[88], Robinson 1995[89]).

For example, a study by Law and colleagues (2003), which investigated the relationship between LDL-C reduction and the risk of CHD events in 58 trials (including 148,321 patients) of cholesterol-lowering drugs, showed that a reduction in LDL-c of 1.0 mmol/l reduced the risk of CHD events by up to 36% over 6 or more years of treatment, regardless of initial risk. A more recent meta-analysis by the Cholesterol Treatment Trialists' Collaborators (CTTC) (Baigent 2005[86]) which included data from 90,056 patients in 14 randomised trials of statins, found that a 1 mmol/l reduction in LDL-c was associated with a 23% reduction in the 5-year incidence of a major coronary event (nonfatal MI or CHD death), and a 21% reduction in major coronary events, coronary revascularisation and strokes. **There is strong evidence in support of LDL-C as a surrogate outcome for reduction in CV outcomes in patients receiving a statin therapy. Although there is uncertainty of whether the outcomes of the IMPROVE-IT trial are fully generalizable to the target population for whom ezetimibe is indicated, the results of the trials are important in testing a hypothesis of whether reduction in LDL-C is a valid surrogate outcome for reduction in risk of CV events in patients receiving ezetimibe.**

A graphic representation of the incidence of major coronary events suggests that the relationship between risk reduction and reduction in LDL-C is linear over the range of reductions in LDL-C observed in the trials included in the CTTC report (Baigent 2005[86]).

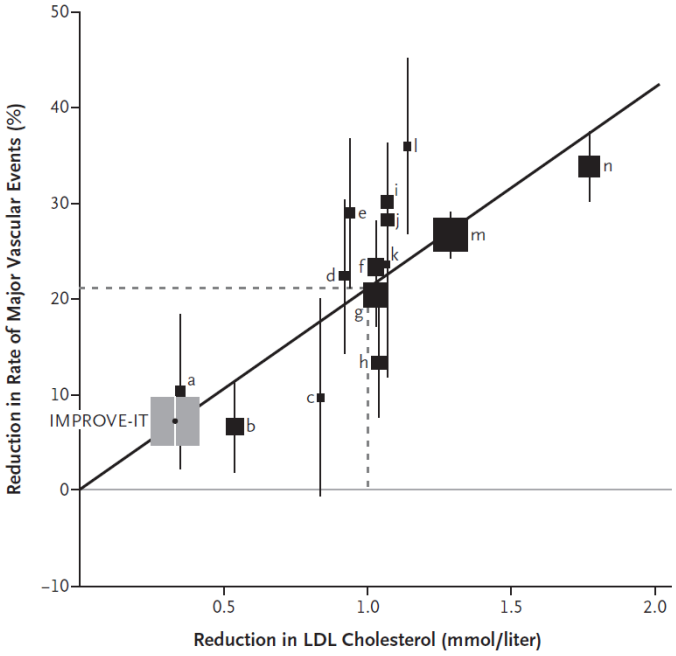
Figure 2.4.3.2 Percent reduction in CV events over reduction in LDL cholesterol (millimole) observed in statin trials



Source: Figure 3, CTTC 2005

Using the same end point that were used by the CTTC, the IMPROVE-IT authors (Cannon, 2015) observed a between-group difference in LDL-C levels (with imputation for missing values) of 12.8 mg/dL and a proportional 7.2% lower rate of major vascular events, a finding consistent with the reduction produced by statins. The hazard ratio for clinical benefit per millimole of LDL cholesterol reduction with ezetimibe in IMPROVE-IT was 0.80 (95% CI 0.68 to 0.94), as compared with 0.78 (95% CI 0.76 to 0.80) observed with statins in the CTTC meta-analysis (Figure 2.4.3.3, reproduced from Figure 2, Cannon, 2015).

Figure 2.4.3.3 Plot of the IMPROVE-IT Trial Data and Statin Trials for Change in Low-Density Lipoprotein (LDL) Cholesterol versus Clinical Benefit.



Source: Figure 2, Cannon 2015.

All identified RCTs reported LDL-C and TC outcomes as either primary or secondary outcomes. Many of the trials also reported HDL-C outcomes. Typically the outcomes were reported in terms of mean percent change in LDL-C from baseline to study endpoint, but frequently the percentage of patients reaching a LDL-C target (e.g. <2.5 mmol/L) was also included. The percent change was analysed using an ANOVA model with terms for treatment and study centre (in the multicentre trials); in some studies the baseline LDL-C pre-randomisation strata were also included. Data were expressed as within-group means and between group differences. The mean percent change in LDL-C has been acknowledged by the PBAC as a clinically relevant outcome and a measure to define responders to treatment.

The analysis of change in LDL-C can be either multiplicative (calculation of LDL-c reduction from the baseline observation based on a stable statin dose) or additive (calculation of LDL-c reduction from the baseline observation based on no treatment). Only the multiplicative effect of ezetimibe in combination with statin is relevant to the PBS- defined eligible population of adults who have inadequately controlled non-familial hypercholesterolemia with an HMG CoA reductase inhibitor (statin) at the maximum tolerated dose meeting the requirements set out by the General Statement For Lipid-Lowering Drugs (GSLLD).

However, since the PBAC agreed (November 2010 meeting) that although the restriction identifies ezetimibe in combination with statin as a second-line treatment, the results of trials in first line use were relevant, given that the outcome of interest is the effect on LDL-C and then modelling survival benefits from this in an appropriate (though different) population. The PBAC agreed that the effect on LDL is not modified by whether use is first- or second- line, although the size of any effect on survival would be.

2.5. Results of the identified trials

2.5.1. Mean per cent change in LDL-C in RCTs of ezetimibe in combination with statin

Apart from IMPROVE-IT trial, no other RCTs that met the inclusion criteria assessed patient outcomes (morbidity and mortality) as clinical end-points. A surrogate end point of percentage LDL-C reduction from the baseline was primary or secondary outcome in all other 29 phase III-IV multi-centre RCTs of varying methodological quality, different duration and design. Of the 30 unique studies listed in Table 2.5.1.1, all but one of the eight "add-on" ezetimibe trials compared EZ+SIM therapy (all doses) with simvastatin monotherapy (all doses or a matching dose). The remaining Ballantyne (2003) factorial study compared EZ+ATOR (all doses) with ATOR (all doses). Of 22 trials that up-titrated the comparator statin either in dose or in more potent statin, only 6 compared EZ+SIM with the higher dose of simvastatin (Dobs 2003, Gaudiani, 2008, Garcia 2016, Pesaro 2013, Ballantyne 2004, Cannon 2015), 7 trials compared EZ+SIM with a matching dose of ATOR, which is a more potent statin (Barrios 2005, Lee 2013, Constance 2007, Cho 2011, McCormack 2010, Ballantyne 2005, Goldberg 2006). The rest of trials in this category either compared EZ+ATOR with a higher dose of ATOR, or EZ+SIM (all doses) with ROSUV (all doses) (Catapano 2006, McKenney 2007, Farnier 2009).

Most of RCTs reported LDL-C values at a study endpoint and calculated mean per cent change in LDL-C with respect to the baseline level. Where there were multiple results at different time-points for the same dose of statin, the results from the last follow-up were extracted; where the standard deviation (SD) of percent decrease in LDL-C was not reported in the original study, it was calculated from the 95% confidence interval or standard error (SE). Table 2.5.1.1 shows the percentage reduction in LDL-c level from the baseline for ezetimibe combination therapy. The studies were grouped into the following categories according to the a) study design; b) type of the population: whether primary or secondary; also, the type of the intervention (whether first- or the second-line treatment) is shown in the superscript at the name of the trial.

Mean per cent reduction in LDL-C from the baseline was greater in every EZ+statin arm in 28 out of 30 identified trials. Mean % LDL-C reduction was greater in the comparator arms of the trials by Cho (2011) and Ostad (2009). The trial by Cho (2011) compared EZ +SIM 20 (N=36) with ATOR 20 (N=38), and the trial by Ostad (2009) compared EZ+ATOR 10 (N=25) with the maximum available dose of atorvastatin (80 mg) (N=24). In both cases the difference did not reach the level of statistical significance as the RCTs were underpowered to detect the difference in mean %LDL-C reduction from the baseline, which was not a primary outcome in either of these trials. In three other trials the difference in mean %LDL-C reduction between the arms, although favouring EZ+statin, was not statistically significant either. These trials by Garcia (2016), Lee (2013) and Pesaro (2013) compared EZ+SIM 20 (Pesaro 2013) or EZ+SIM 10 (Garcia 2016) with either the maximum dose of 80 mg simvastatin or atorvastatin 20 mg (Lee 2013). All three small size RCTs were underpowered to detect the difference in mean %LDL-C reduction from the baseline, which was not a primary outcome in either of these trials.

Table 2.5.1.1: Mean %LDL-C reduction from the baseline

Study Drug dose (mg)	Statin arm			Statin + ezetimibe arm				Percentage reduction		
	N (total randomised) n (arms)	LDL-c baseline (mmol/L)	LDL-c endpoint (mmol/L)	Drug dose (mg)	N (total randomised) n (arms)	LDL-c baseline (mmol/L)	LDL-c endpoint (mmol/L)	Mean %S (SD; SE or 95% CI)	Mean %E+S (SD; SE or 95% CI)	Mean % further reduction (%E+S - %S) (SD; SE or 95% CI)
Up-titrating statin dose+ ezetimibe vs up-titrating statin dose										
Secondary prevention population										
IMPROVE-IT 2015[2] SIM 40-80 (all doses) Up-titrated to 80 mg if target not met at 2 consecutive visits. For some clients 80 mg reduced back to 40 mg	6897	2.43	1.93	EZ+SIM 40-80 (all doses) Up-titrated to 80 mg if target not met at 2 consecutive visits. For some clients 80 mg reduced back to 40 mg	6809	2.43	1.48	NR	NR	-16.75[$] (-17.49, -16.02)***
Mixed (both primary and secondary) prevention population										
P025 Ballantyne 2004[1] ATOR 10 (start dose) Week 7-12 ATOR 20 Week 13-18 ATOR 40 Week 19-24 ATOR 80	262	4.67	NR	EZ +SIM 10 (start dose) Week 7-12 EZ +SIM 20 Week 13-18 EZ +SIM 40 Week 19-24 EZ +SIM 80	263	4.65	NR	Week 6 -37.2 (0.8) Week 12 -44.3 (0.9) Week 18 -49.1 (0.9) Week 24 -52.5 (1.0)	Week 6 -46.1 (0.8) Week 12 -50.2(0.8) Week 18 -55.6(0.6)[#] Week 24 -59.4(0.7)[#]	-8.9 (-11.1,-6.7)* NR NR -6.9 (-9.2, -4.6)*
				EZ +SIM 20 (start dose) Week 7-12 EZ +SIM 40 Week 13-18 EZ +SIM 40 Week 19-24 EZ +SIM 80	263	4.63	NR		Week 6 -50.3(0.8) Week 12 -54.3(0.8) Week 18 -55.6(0.6)[#] Week 24 -59.4(0.7)[#]	-13.1 (-15.2,-10.9)* NR NR -6.9 (-9.2, -4.6)*
P693 Stein 2004[2] ATOR 10 (run-in dose) Week 1-4 ATOR 20 Week 5-8 ATOR 40 Week 9-14 ATOR 80	316 (all) 303 (96%) NR 270 (85%)	4.8	NR	 Week 4 EZ+ ATOR 10 Week 8 EZ + ATOR 20 Week 14 EZ + ATOR 40	305 (all) 293(96%) NR 84 (60%)	4.8	NR	 -8.6(0.7) -20.3(0.9)	 -22.8(0.7) -33.2(0.9)	 -14.2 (–16.24,–12.20)** -12.9 (NR)

McKenney 2007[1] Week 1-4 ROSUV 10 Week 5-8 ROSUV 20 Week 9-12 ROSUV 40	76	5.12	 2.53 2.35	Week 1 EZ +SIM 20 Week 4 EZ +SIM 20 Week 8 EZ +SIM 40	77	5.22	 2.43 2.22	−50 (−53, −47) −53 (−57, −50)	−53 (−56, −50) −57 (−61, −54)	-3 (NR) p=.105 -4 (NR) p=0.09
Fixed dose of statin +ezetimibe vs up-titrating the dose of statin										
Primary prevention population										
Teramoto 2012[1] ATOR 10 (run in) ATOR 20	46	5.54	NR	EZ+ATOR 10	47	5.54	NR	-15.1 (-18.6,-11.7)	-25.8(-29.2,-22.4)	-10.6(-15.4,-5.8)***
P079 Conard 2008[2] ATOR 20 (run in) ATOR 40	98^	3.05	NR	EZ+ATOR 20	98^	3.1	NR	-11 (-15, -7)	-31 (-35, -27)	• -20 (-25, -15)***
Lee 2013[1] ATOR 20	63	3.46	1.81	EZ+SIM 20	62	3.60	1.88	-47.2(15.6)	-47.9(20.7)	NR (not significant)
Garcia 2016[1] SIM 80	16	3.44	NR	EZ+SIM 10	16	3.85	NR	-27 (31)	-30(29)	NR p=0.57
P090 Leiter 2008[2] ATOR 40 (run in) ATOR 80	291^	2.33	NR	EZ+ATOR 40	288^	2.30	NR	-11 (-13,-9)	-27 (-30,-25)	-16 (-19, -13) ***
P058 Catapano 2006[1] ROSU 10 ROSU 20 ROSU 40	 492 495 494	 4.5 4.5 4.5	 NR NR NR	 EZ +SIM 20 EZ +SIM 40 EZ +SIM 80	 492 493 493	 4.5 4.5 4.5	 NR NR NR	 -45.8 (0.5) -52.3 (0.5) -56.7 (0.5)	 -51.5 (0.5) -54.8 (0.5) -61.0 (0.5)	 -5.7 (0.8)*** -2.5 (0.8)*** -3.9 (0.8)***
Secondary prevention population										
Pesaro 2013[2] SIM 20 (run in) SIM 80	31	2.72	NR	EZ+SIM 20	37	2.74	NR	-21 (33)	-29(13)	NR p=0.46

Cho 2011[1] ATOR 20	43	3.42	1.89	EZ +SIM 20	42	3.47	2.00	-44.2 (14.0)	-41.1(17.3)	NR (not significant)
Barrios 2005[2] ATOR 10 (run in) ATOR 20	214	3.24	NR	EZ+ SIM 20	221	3.19	NR	-20.3 (1.2)	-32.8 (1.2)	-12.6 (1.6)***
Ostad 2009[2] ATOR 80	24	3.83	1.53	EZ+ATOR 10	25	3.90	1.73	-60 (11)	-54(18)	NR p=0.73
Mixed (both primary and secondary) prevention population										
P021 Gaudiani 2005[2] SIM 20 (run in) SIM 40	107	2.37	2.33	EZ + SIM 20	103	2.43	1.91	-0.3 (22.8)	-20.8(22.3)	-20.5 (NR)***
P112 Zieve 2010[2] ATOR 10 (run-in dose) Week 1-6 ATOR 20 Week 7-12 ATOR 40	 526 515 509	 2.64	 NR	 Week 6 EZ + ATOR 10 Week 12 EZ + ATOR 10	 527 516 516	 2.66	 NR	 -13 (-15,-11) -18 (-21,-15)	 -27 (-29,-25) -23 (-25,-20)	 -14 (-16,-12)*** -5 (-7,-2)***
P700 Dobs 2003[1] SIM 20 (run-in dose) Week 4 SIM 40 mg Week 14 SIM 80 mg	34	4.32	NR	Week 4 EZ + SIM 20 Week 14 EZ + SIM 20	66	4.42	NR	-10.73 (2.43) -13.78 (2.54)	-24.71 (2.16) -21.47 (2.19)	-13.98 (NR)** -7.69 (NR)[‡]
McCormack 2010[2] SIM 40 (run in) ATOR 40 ROSU 5/10[##]	259 262	2.6 2.5	NR NR	EZ+SIM 40	255	2.6	NR	-11.1 (-14.0, -8.2) -3.0 (-5.9, -0.1)	 -26.2 (-29.1, -23.2)	NR NR

P051 Ballantyne 2005[1]	927				923					
ATOR 10 mg	235	4.53	NR	EZ +SIM 10	230	4.57	NR	-36.1 (0.9)	-47.1 (1.0)	-11.0 (1.3)***
ATOR 20 mg	230	4.61	NR	EZ +SIM 20	233	4.62	NR	-43.7 (1.0)	-50.6 (0.9)	-6.9 (1.3)***
ATOR 40 mg	232	4.65	NR	EZ +SIM 40	236	4.60	NR	-48.3 (0.9)	-57.4 (0.9)	-9.1 (1.3)***
ATOR 80 mg	230	4.72	NR	EZ +SIM 80	224	4.60	NR	-52.9 (1.0)	-58.6 (1.0)	-5.7 (1.4)***
P077Goldberg 2006[1] VYTAL										
ATOR 10 mg	237	3.75	NR	EZ +SIM 10	247	3.75	NR	-38.3 (-40.1,-36.5)	-53.6 (-55.4,-51.8)	-15.3 (-17.7;-12.8)***
ATOR 20 mg	240	3.79	NR	EZ +SIM 20	NR	NR	NR	-44.6 (-46.4,-42.8)	NR	-9.0 (-11.5;-6.5)***
ATOR 40 mg	241	3.77	NR	EZ +SIM 40	247	3.72	NR	-50.9 (-52.7,-49.1)	-57.6 (-59.4,-55.8)	-6.6 (-9.1;-4.2)***
Constance 2007[2] ATOR 10 (run in)										
ATOR 20	219	2.43	NR	EZ + SIM 20	220	2.34	NR	-8.49 (26.83)	-26.15 (26.89)	NR
				EZ + SIM 40	222	2.48	NR		-30.13 (26.99)	
Farnier 2009 ROSU 10 mg	292	3.24	NR	EZ+SIM 20	301	3.21	NR	-16.9 (23.07)	-27.7(23.42)	-10.7(-14.1, -7.3)***
Fixed dose statin +ezetimibe vs matching fixed dose of statin										
Primary prevention population										
P692 Ballantyne 2003[1]	248				255					
ATOR 10	60	4.75	3.06	EZ + ATOR 10	65	4.52	2.22	-35.45 (1.94)	-50.37 (1.85)	-14.92 (-20.18, -9.66)**
ATOR 20	60	4.52	2.72	EZ + ATOR 20	62	4.72	2.17	-39.77 (1.92)	-53.70 (1.89)	-13.93 (-19.23, -8.63)**
ATOR 40	66	4.64	2.65	EZ + ATOR 40	65	4.69	2.13	-43.05 (1.86)	-54.33 (1.88)	-11.28 (-16.47, -6.09)**
ATOR 80	62	4.71	2.29	EZ + ATOR 80	63	4.68	1.88	-51.35 (1.89)	-59.70 (1.89)	-8.34 (-13.0, -3.09)**

P038 Bays 2004[1]	612^				604^					
SIM 10	155	4.60	3.1	EZ +SIM 10	151	4.60	2.5	-32.7(-35.0, -30.4)	-44.8(-47.1, -42.4)	-12.1(-15.3, -8.8)***
SIM 20	147	4.60	3.0	EZ +SIM 20	153	4.50	2.2	-34.2(-36.6, -31.9)	-51.9(-54.2, -49.6)	-17.7(-21.0, -14.4)***
SIM 40	154	4.50	2.7	EZ +SIM 40	146	4.50	2.0	-40.6(-42.9, -38.3)	-55.2(-57.6, -52.9)	-14.7(-18.0, -11.4)***
SIM 80	156	4.60	2.4	EZ +SIM 80	154	4.60	1.8	-48.5(-50.8, -46.2)	-60.2(-62.5, -57.9)	-11.7(-14.9, -8.5)***
P068 Davidson 2002[1]	263				274					
SIM 10	70	4.54	3.29	EZ +SIM 10	67	4.53	2.51	-27.42(1.72)	-44.44(1.75)	-17.01 (-21.83, -12.2)**
SIM 20	61	4.70	2.97	EZ +SIM 20	69	4.60	2.54	-36.30(1.84)	-44.78(1.74)	-8.49 (-13.46, -3.52)**
SIM 40	65	4.57	2.89	EZ +SIM 40	73	4.50	2.09	-36.32(1.79)	-53.48(1.69)	-17.16 (-22.01,-12.30)**
SIM 80	67	4.67	2.61	EZ +SIM 80	65	4.61	1.97	-44.25 (1.77)	-56.81(1.84)	-12.55 (-17.56, -7.55)**
P005 Goldberg 2004[1]	349^				353^					
SIM 10	81	4.50	3.10	EZ +SIM 10	87	4.50	2.40	-31.3 (-34.5, -28.1)	-46.2(-49.2, -43.2)	-14.9 (-19.3, -10.5)***
SIM 20	90	4.50	2.90	EZ +SIM 20	86	4.60	2.30	-34.9 (-34.5, -28.1)	-50.5(-53.6, -47.5)	-15.6 (-19.9, -11.3)***
SIM 40	91	4.50	2.70	EZ +SIM 40	89	4.40	2.00	-41.5 (-44.5, -38.6)	-54.9(-57.9, -52.0)	-13.4 (-17.6, -9.2)***
SIM 80	87	4.50	2.40	EZ +SIM 80	91	4.50	1.70	-45.6 (-48.6, -42.5)	-60.8(-63.7, -57.8)	-15.2(-19.4, -11.0)***
Kastelein 2008[1] SIM 80	363	8.22	4.98	EZ+SIM 80	357	8.25	3.65	-39.1(0.9)	-55.6(0.9)	NR
Chirinos 2010[1] SIM 20	30	3.83	NR	EZ+SIM 20	28	3.83	NR	-20.9(-27.4, -14.5)	-37.4(-45.6,-29.3)	NR
Shankar 2007[1] SIM 10	116	3.25	2.40	EZ+SIM 10	114	3.37	2.24	-26.3(19.9)	-33.7(44.8)	NR
Mixed prevention population										
P023 Feldman 2004[1] SIM 20[‖]	246	4.5	N/R	EZ +SIM 10	242	4.3	NR		-47 (0.8)	NR
				EZ +SIM 20	108	4.3	NR	-38 (0.8)	-53 (1.2)	-14.8(-17.6,-12.0)***
				EZ +SIM 40	96	4.4	NR		-59 (1.3)	NR

Superscripts: 1 first-line treatment RCT; 2 second-line treatment RCT; #Data pooled for common doses of ezetimibe simvastatin at weeks 18 and 24; ##Data pooled across the rosuvastatin doses ^ number of randomised patients ≠ the number included in the analysis (e.g. modified ITT population); [§]Least Squares Estimate Difference in Means at 1 year (mg/dL); [‖] The comparison between EZ+SIM 10 and SIM 20 was used in the meta-analysis of maintaining a dose of both statin and ezetimibe in the intervention arm versus up-titrating statin dose or using a more potent statin in the comparator arm.

* statistically significant p≤0.05; **statistically significant p≤0.01; *** statistically significant p≤0.001; [‡]p-value not reported;

2.5.2. Mean per cent change in HDL-C in RCTs of ezetimibe in combination with statin

Table 2.5.2.1 shows the percentage change in HDL-C level from the baseline for ezetimibe combination therapy. As in the presentation of LDL-C results, the studies were grouped by the a) study design; b) type of the population: whether primary or secondary; and by the type of the intervention: whether first- or the second-line treatment (shown in the superscript at the name of the trial).

Mean per cent change in HDL-C from the baseline was reported in 25 RCTs. Authors of IMPROVE-IT trial reported the HDL-C results in the estimated least squares difference in means at 1 year (mg/dL) and found HDL cholesterol statistically significantly higher in ezetimibe+statin arm. %HDL-C change in patients receiving ezetimibe+statin was higher in 50 arms of 18 trials, but the difference reached the level of statistical significance only in eight arms of four up-titration trials (Barrios 2005, Zieve 2010, Ballantyne 2005, Goldberg 2006) and in three out of 21 arms in "add-on" trials where ezetimibe+statin was compared with the matching dose of statin. Eight RCTs (Lee 2013, Gaudiani 2005, Cho 2011, Ostad 2009, Leiter 2008, McCormac 2010 (in EZ+SIM 40 vs ATOR 40) and Catapano 2006 (in EZ+SIM80 vs ROSUV 40), Farnier 2009 (in EZ+SIM vs ROSU 10) reported HDL-C achieving a higher level in patients in the comparator arms, although the difference was not statistically significant (Table 2.5.2.1).

There is insufficient evidence to confirm the conclusion of the authors of the AHQR 2014 report that low- and mid- potency statins raises HDL-C as compared to mid- and high potency statin monotherapy.

Results of comparisons of mean per cent reduction in TC from the baseline in ezetimibe+statin and the comparator arms are generally consistent with the results in mean per cent reduction in LDL-C. These are presented in Appendix 5.

Table 2.5.2.1: Mean %HDL-C reduction from the baseline

Study	Statin arm			Statin + ezetimibe arm				Percentage reduction		
Drug dose (mg)	N (total randomised) n (arms)	HDL-c baseline (mmol/L)	HDL-c endpoint (mmol/L)	Drug dose (mg)	N (total randomised) n (arms)	HDL-c baseline (mmol/L)	HDL-c endpoint (mmol/L)	Mean %S (SD; SE or 95% CI)	Mean %E+S (SD; SE or 95% CI)	Mean % further reduction (%E+S - %S) (SD; SE or 95% CI)
Up-titrating statin dose+ ezetimibe vs up-titrating statin dose										
Secondary prevention population										
IMPROVE-IT 2015[2] SIM 40-80 (all doses) Up-titrated to 80 mg if target not met at 2 consecutive visits. For some clients 80 mg reduced back to 40 mg	6897	1.09	1.24	EZ+SIM 40-80 (all doses) Up-titrated to 80 mg if target not met at 2 consecutive visits. For some clients 80 mg reduced back to 40 mg	6809	1.09	1.26	NR	NR	0.67[$] (0.36, 0.99)***
Mixed (both primary and secondary) prevention population										
P025 Ballantyne 2004[1] ATOR 10 (start dose) Week 7-12 ATOR 20 Week 13-18 ATOR 40 Week 19-24 ATOR 80	262	1.2	NR	EZ +SIM 10 (start dose) Week 7-12 EZ +SIM 20 Week 13-18 EZ +SIM 40 Week 19-24 EZ +SIM 80	263	1.2	NR	Week 6 -5.1 (0.8) Week 12 6.9 (0.9) Week 18 -7.8 (1.0) Week 24 -6.5 (1.0)	Week 6 8.0 (0.8) Week 12 9.0(0.9) Week 18 11.4(0.7)[#] Week 24 12.3(0.7)[#]	NR NR NR NR
				EZ +SIM 20 (start dose) Week 7-12 EZ +SIM 40 Week 13-18 EZ +SIM 40 Week 19-24 EZ +SIM 80	263	1.2	NR		Week 6 9.5(0.8) Week 12 12.4 (0.9) Week 18 11.4(0.7)[#] Week 24 12.3(0.7)[#]	NR NR NR NR
P693 Stein 2004[2] ATOR 10 (run-in dose) Week 1-4 ATOR 20 Week 5-8 ATOR 40 Week 9-14 ATOR 80	316 (all) 303 (96%) NR 270 (85%)	1.29	NR	 Week 4 EZ+ ATOR 10 Week 8 EZ + ATOR 20 Week 14 EZ + ATOR 40	305 (all) 293(96%) NR 84 (60%)	1.29	NR	 1.3 (0.6) 1.0 (0.7)	 2.1 (0.6) 3.7 (0.7)	 0.9 (NS) N/R

McKenney 2007[1] Week 1-4 ROSUV 10 Week 5-8 ROSUV 20 Week 9-12 ROSUV 40	76	1.24	NR	Week 1 EZ +SIM 20 Week 4 EZ +SIM 20 Week 8 EZ +SIM 40	77	1.27	NR	7(4, 10) 7 (4, 11)	8 (5, 11) 10 (6, 13)	NR NR
Fixed dose of statin +ezetimibe vs up-titrating the dose of statin										
Primary prevention population										
Teramoto 2012[1] ATOR 10 (run in) ATOR 20	46	1.34	NR	EZ+ATOR 10	47	1.36	NR	0.6 (-2.5, 3.6)	4.5 (1.5, 7.6)	4.0 (-0.3, 8.3) NS
P079 Conard 2008[2] ATOR 20 (run in) ATOR 40	98^	1.34	NR	EZ+ATOR 20	98^	1.32	NR	1 (-2, 4)	3 (0, 6)	2 (-2, 7) NS
Lee 2013[1] ATOR 20	63	1.24	1.22	EZ+SIM 20	62	1.27	1.32	4.2 (12.7)	-0.2 (14.8)	NR (NS)
Garcia 2016[1] SIM 80	16	1.27	1.32	EZ+SIM 10	16	1.40	1.34	NR	NR	NR
P090 Leiter 2008[2] ATOR 40 (run in) ATOR 80	291^	1.22	NR	EZ+ATOR 40	288^	1.24	NR	-1 (-2, 0)	0 (-2, 1)	1 (-1, 2) (NS)
Secondary prevention population										
Pesaro 2013[2] SIM 20 (run in) SIM 80	31	1.14	NR	EZ+SIM 20	37	1.16	NR	1.6 (14)	2.0 (12)	NR
Cho 2011[1] ATOR 20	43	1.19	1.21	EZ +SIM 20	42	1.17	1.20	4.4 (17.8)	2.3 (26,6)	NR (NS)

Barrios 2005[2] ATOR 10 (run in) ATOR 20	214	1.44	NR	EZ+ SIM 20	221	1.38	NR	-0.4 (0.8)	1.8 (0.8)	2.5 (1.2)*
Ostad 2009[2] ATOR 80	24	1.34	1.37	EZ+ATOR 10	25	1.50	1.50	4 (15)	2 (15)	NR (NS)
Mixed (both primary and secondary) prevention population										
P021 Gaudiani 2005[2] SIM 20 (run in) SIM 40	107	1.27	NR	EZ + SIM 20	103	1.23	NR	0.3 (12.4)	0.2 (12.1)	-0.1 (-3.4, 3.2)
P112 Zieve 2010[2] ATOR 10 (run-in dose) Week 1-6 ATOR 20 Week 7-12 ATOR 40	 526 515 509	 1.42	 NR	 Week 6 EZ + ATOR 10 Week 12 EZ + ATOR 10	 527 516 516	 1.42	 NR	 1 (-1, 2) -1 (-2, 1)	 3 (1, 4) 2 (1, 4)	 2 (0.3, 4)* 3 (2, 5)***
McCormack 2010[2] SIM 40 (run in) ATOR 40 ROSU 5/10[##]	259 262	1.4 1.4	NR NR	EZ+SIM 40	255	1.4	NR	-2.3 (-3.7, -0.9) -0.1 (-1.5, 1.3)	 -1.4 (-2.9, 0.0)	NR (NS) NR (NS)
P051 Ballantyne 2005[1] ATOR 10 mg ATOR 20 mg ATOR 40 mg ATOR 80 mg	927 235 230 232 230	 1.25 1.26 1.30 1.24	 NR NR NR NR	 EZ +SIM 10 EZ +SIM 20 EZ +SIM 40 EZ +SIM 80	923 230 233 236 224	 1.27 1.27 1.27 1.27	 NR NR NR NR	 6.9 (0.9) 5.1 (0.9) 3.8 (0.9) 1.4 (0.9)	 7.7 (0.9) 7.2 (0.9) 9.0 (0.9) 7.6 (0.9)	 0.8 (1.2) 2.1 (1.2) 5.2 (1.3)*** 6.2 (1.2)***

P077Goldberg 2006[1] VYTAL ATOR 10 mg ATOR 20 mg ATOR 40 mg	 237 240 241	 1.16 1.20 1.19	 NR NR NR	 EZ +SIM 20 EZ +SIM 40	 247 247	 1.15 3.72	 NR NR	 4.3 (NR) 4.5 (NR) 2.3 (NR)	 8.0 (NR) 6.3 (NR)	 NR*** NR** NR***
P058 Catapano 2006[1] ROSU 10 ROSU 20 ROSU 40	 492 495 494	 1.32 1.29 1.29	 NR NR NR	 EZ +SIM 20 EZ +SIM 40 EZ +SIM 80	 492 493 493	 1.32 1.29 1.29	 NR NR NR	 6.7 (0.5) 8.1 (0.5) 8.1 (0.5)	 7.0 (0.5) 8.3 (0.5) 7.6 (0.5)	 0.3 (0.7)(NS) 0.2 (0.7)(NS) -0.6 (0.7)(NS)
Constance 2007[2] ATOR 10 (run in) ATOR 20	 219	 1.25	 NR	 EZ + SIM 20 EZ + SIM 40	 220 222	 1.27 1.31	 NR NR	 1.63(13.85)	 2.37(13.85) 1.29(13.89)	 NR
Farnier 2009 ROSU 10 mg	292	1.43	NR	EZ+SIM 20	301	1.43	NR	3(16.06)	2.1(15.96)	-0.9(-3.2, 1.4)
Fixed dose statin +ezetimibe vs matching fixed dose of statin										
Primary prevention population										
P692 Ballantyne 2003[1] ATOR 10 ATOR 20 ATOR 40 ATOR 80	248 60 60 66 62	 1.39 1.43 1.37 1.36	 1.47 1.48 1.41 1.39	 EZ + ATOR 10 EZ + ATOR 20 EZ + ATOR 40 EZ + ATOR 80	255 65 62 65 63	 1.34 1.28 1.32 1.32	 1.45 1.39 1.37 1.40	 6.46 (1.49) 3.96 (1.49) 3.76 (1.45) 2.81 (1.47)	 9.01 (1.43) 9.21 (1.41) 4.58 (1.45) 6.55 (1.47)	 2.55 (-1.52, 6.61) (NS) 5.26 (1.14, 9.37)** 0.82 (-3.19, 4.83) (NS) 3.74 (-0.34, 7.82) (NS)
P038 Bays 2004[1] SIM 10 SIM 20 SIM 40 SIM 80	612^ 155 147 154 156	 1.3 1.4 1.3 1.3	 1.4 1.5 1.4 1.4	 EZ +SIM 10 EZ +SIM 20 EZ +SIM 40 EZ +SIM 80	604^ 151 153 146 154	 1.3 1.3 1.4 1.4	 1.4 1.4 1.4 1.4	 5.4 (3.3, 7.4) 7.4 (5.3, 9.6) 7.5 (5.4, 9.6) 7.1 (5.0, 9.1)	 8.0 (5.9, 10.2) 9.8 (7.7, 11.8) 5.5 (3.4, 7.7) 5.6 (3.6, 7.7)	 2.6 (-0.4, 5.5) (NS) 2.3 (-0.6, 5.3) (NS) -1.9 (-4.9, 1.0) (NS) -1.4 (-4.3, 1.5) (NS)

P068 Davidson 2002[1]	263				274					
SIM 10	70	1.30	1.40	EZ +SIM 10	67	1.26	1.36	7.61 (1.49)	8.55 (1.52)	0.95 (-3.24, 5.13) (NS)
SIM 20	61	1.33	1.40	EZ +SIM 20	69	1.33	1.44	5.55 (1.60)	9.17 (1.51)	3.62 (-0.69, 7.94) (NS)
SIM 40	65	1.31	1.38	EZ +SIM 40	73	1.30	1.42	6.08 (1.56)	10.97 (1.47)	4.89 (0.68, 9.09)*
SIM 80	67	1.34	1.45	EZ +SIM 80	65	1.32	1.41	8.20 (1.53)	8.38 (1.58)	0.18 (-4.15, 4.51) (NS)
P005 Goldberg 2004[1]	349^				353^					
SIM 10	81	1.3	1.40	EZ +SIM 10	87	1.26	1.36	7.61 (1.49)	8.55 (1.52)	0.95 (-3.24, 5.13) (NS)
SIM 20	90	1.2	1.40	EZ +SIM 20	86	1.33	1.44	5.55 (1.60)	9.17 (1.51)	3.62 (-0.69, 7.94) (NS)
SIM 40	91	1.3	1.38	EZ +SIM 40	89	1.30	1.42	6.08 (1.56)	10.97 (1.47)	4.89 (0.68, 9.09)*
SIM 80	87	1.3	1.45	EZ +SIM 80	91	1.32	1.41	8.20 (1.53)	8.38 (1.58)	0.18 (-4.15, 4.51) (NS)
Kastelein 2008[1] SIM 80	363	1.23	1.31	EZ+SIM 80	357	1.21	1.32	7.8 (0.9)	10.2 (1.0)	NR
Chirinos 2010[1] SIM 20	30	1.06	NR	EZ+SIM 20	28	1.14	NR	NR	NR	NR
Shankar 2007[1] SIM 10	116	1.08	1.10	EZ+SIM 10	114	1.08	1.13	3.3 (20.1)	6.0 (20.6)	NR
Secondary prevention population										
P023 Feldman 2004[1] SIM 20	246	1.2	N/R	EZ +SIM 10	242	1.15	NR		6.2 (0.7)	NR
				EZ +SIM 20	108	1.17	NR	5.1 (0.7)	8.0 (1.0)	NR
				EZ +SIM 40	96	1.20	NR		7.4 (1.1)	NR

Superscripts: 1 first-line treatment RCT; 2 second-line treatment RCT; #Data pooled for common doses of ezetimibe simvastatin at weeks 18 and 24; ##Data pooled across the rosuvastatin doses ^ number of randomised patients ≠ the number included in the analysis (e.g. modified ITT population); $Least Squares Estimate Difference in Means at 1 year (mg/dL)

* statistically significant p≤0.05; **statistically significant p≤0.01; *** statistically significant p≤0.001; ‡p-value not reported;

2.5.3 Narrative summary of results of RCTs of ezetimibe in combination with a statin

For each category of patients (i.e. primary, secondary or mixed prevention category) and for the first or the second line therapy the following analyses were carried out:

- Comparison 1: up-titrating statin dose while maintaining ezetimibe dose in the intervention arm versus up-titrating statin (either in dose or potency) in the comparator arm
- Comparison 2: maintaining a dose of both statin and ezetimibe in the intervention arm versus up-titrating statin dose or using a more potent statin in the comparator arm
- Comparison 3: maintaining a dose of both statin and ezetimibe in the intervention arm versus the matching statin dose in the comparator arm

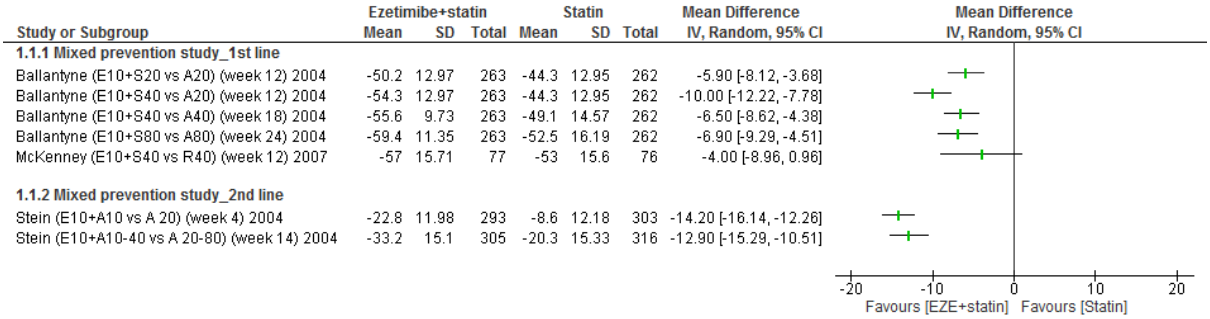
For most of the comparisons only a descriptive synthesis of data was conducted (i.e. individual mean differences with 95% CIs for individual studies grouped by prevention category population and the line of therapy). The pooled estimates of the mean difference (MD) in per cent reduction from the baseline in the surrogate outcomes was not calculated given the small number of heterogeneous trials in some of the subgroups (as little as two RCTs).

Data analyses included lipid measurements at baseline and at least one post-baseline lipid measurement. Pooled-effect estimates for continuous efficacy data were obtained by comparing the least squares mean (SD) and were expressed as the weighted mean difference (WMD) between the treatment groups. When SD was unavailable, it was computed from the 95% confidence intervals [SD=(Upper Confidence Limit-Lower Confidence Limit)/3.92x(SQRT(N))]. If the CI was not presented, then the SD was calculated from the standard error estimates if available [SD=SE x SQRT(N)]. The primary efficacy analyses were based on the Intention-to-Treat (ITT) population in each study (where applicable), including all patients received at least one dose of randomised treatment. Meta-analyses were performed using the Mantel-Haenszel fixed effects model unless there was evidence of substantial heterogeneity in the treatment effect among studies. Statistical heterogeneity between trial results was assessed using the chi-squared test and I^2-measure. The chi-squared test measures the amount of variation in a set of trials. As this test has low power to detect heterogeneity when the number of included studies have small sample sizes or few in number, a P-value <0.1 was considered significant. The I^2-measure is the proportion of variation that is due to heterogeneity rather than sampling error (chance); Where I^2 >50%, an inverse variance random effect model was applied in the meta-analysis. Pooled-effect estimates and their 95%CI are presented for all meta-analyses. The Z-statistic was used to assess overall effect and a P-value of <0.05 was considered significant. All the analysis was performed using Review Manager (Revman) 5.3 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014).

Figures 2.5.3.1 – 2.5.3.4 show the forest plots with weighted mean difference (WMD) for each study. The WMD was calculated with respect to each surrogate outcome within the scope of the review (LDL-C; HDL-C and TC). However, only selected forest plots, mainly for the LDL-C reduction, are reproduced here. For the results of the analysis of the mean % change in HDL-C and TC refer to Figures A5.2-A5.6 in the Appendix.

Comparison 1: Up-titration of statin dose+ ezetimibe vs up-titration of statin (either in dose or potency (LDL-C outcomes)

Figure 2.5.3.1 Comparison 1: Mean percentage change in LDL-C concentrations from baseline



CI=confidence interval; df=degrees of freedom; N=total number of patients; SD=standard deviation; WMD=weighted mean difference

Comparison 1 (Figure 2.5.3.1) includes three RCTs by Ballantyne (2004), Stein (2004) and McKenney (2007) that enrolled mixed population of primary and secondary prevention patients. The duration of the RCTs varied from 4 to 24 weeks. The baseline lipid results in the eligible patients were above the NCEP ATP III lipid goals. At the subsequent follow-up appointments every 6 or 4 weeks, the patients were assigned a double dose of simvastatin. Up-titration was forceful in the studies by Ballantyne (2004) and (McKenny 2007) and depended on the dose response in Stein (2004) study. However, only one study (Stein 2004) enrolled the population that was not adequately controlled with atorvastatin 10 mg after a run-in period. In Ballantyne (2004) and (McKenney 2007) trials ezetimibe in combination with simvastatin was administered as the first line therapy. At each follow up appointment patients receiving EZ+SIM (Ballantyne 2004, McKenney 2007) or EZ+ATOR (Stein 2004) combination therapy achieved a greater %LDL-C reduction compared to patients receiving ATOR monotherapy. However the difference was not statistically significant in the trial by McKenney (2007) that compared ezetimibe co-administered with simvastatin vs rosuvastatin.

Results for the TC and HDL-C endpoints are presented in Appendix (Figures A5.2 – A5.5). Results for the total cholesterol endpoints are consistent with LDL-C results. The HDL-C results also generally favour ezetimibe in combination with statin. However, although at the end of the 12 week trial by McKenny (2007) the patients receiving EZ 10+SIM40 as the first line therapy achieved the higher %HDL-C raise (by 3% on average) than the patients receiving ROSUV 40, the difference was not statistically significant. The same was also true with respect to the HDL-C outcomes observed in week 4 in the trial by Stein (2004).

Three studies that "parallel-titrated" (either forced or depending on patients' response) the simvastatin and atorvastatin doses to LDL-C targets demonstrated that ezetimibe in combination with simvastatin or atorvastatin was more effective in reducing LDL-C concentrations than simvastatin or atorvastatin monotherapies (statistically significant for all studies). However, this effect was not observed when ezetimibe in combination with simvastatin was compared with the more potent rosuvastatin.

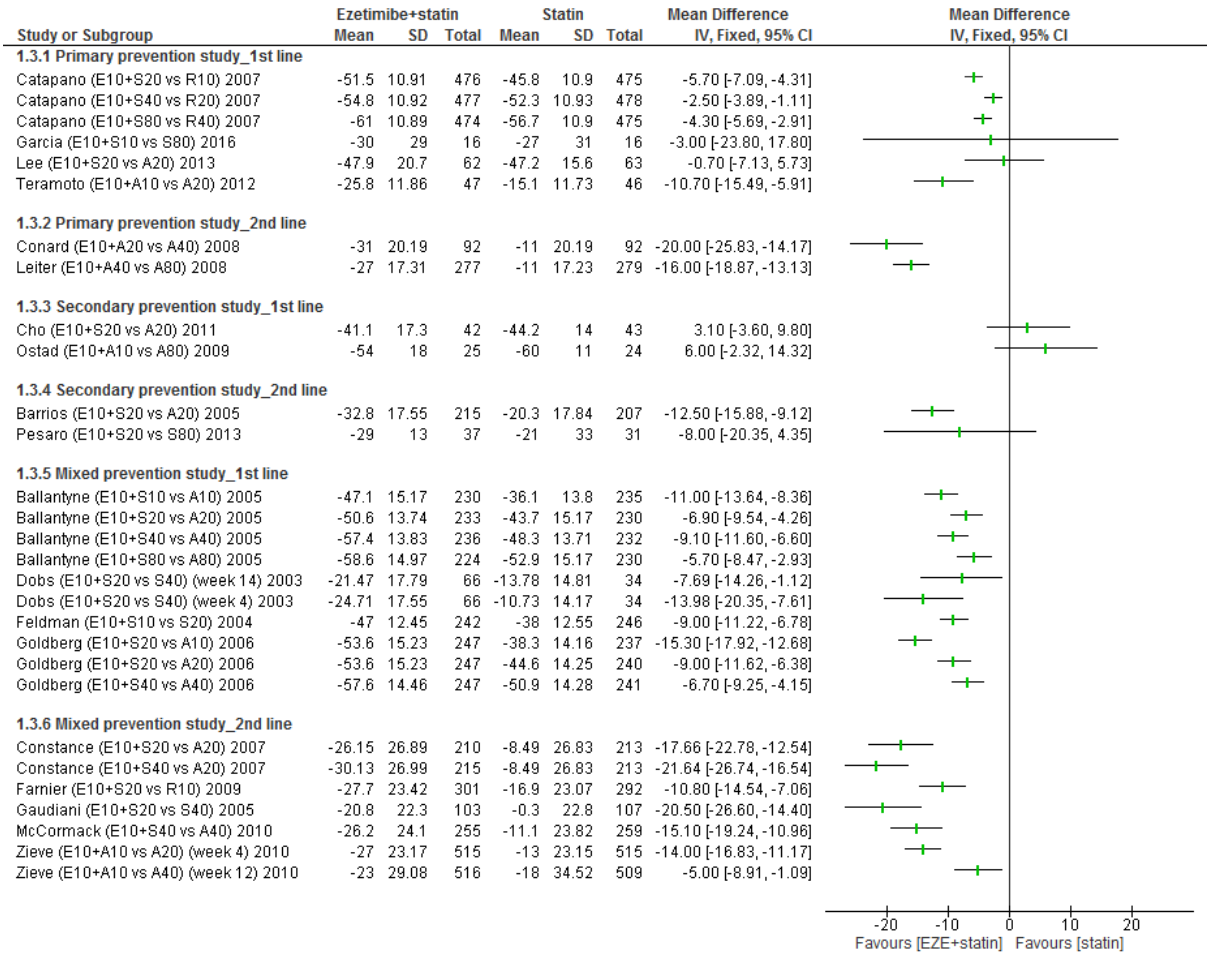
The PBAC previously accepted the submission's claim that EZ+SIM 20 is superior in terms of effect on LDL compared with simvastatin 40 mg, atorvastatin 20 mg and atorvastatin 40 mg and equi-effective compared with rosuvastatin 20 mg daily (PBAC March 2009 minutes). However at that time no data was presented to support the conclusion that the same comparative effectiveness would be demonstrated in the second-line setting.

Comparison 2: maintaining a dose of both statin and ezetimibe in the intervention arm versus up-titrating statin dose or using a more potent statin in the comparator arm

This comparison involved the largest number of identified RCTs that enrolled primary, secondary and mixed prevention population, however in some of the subgroups there were only two studies.

Figure 2.5.3.2 shows mean %LDL-C reduction in ezetimibe in combination with statin vs statin monotherapy

Figure 2.5.3.2 Comparison 2: Mean percentage change in LDL-C concentrations from baseline



Study or Subgroup	Ezetimibe+statin Mean	SD	Total	Statin Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
1.3.1 Primary prevention study_1st line							
Catapano (E10+S20 vs R10) 2007	-51.5	10.91	476	-45.8	10.9	475	-5.70 [-7.09, -4.31]
Catapano (E10+S40 vs R20) 2007	-54.8	10.92	477	-52.3	10.93	478	-2.50 [-3.89, -1.11]
Catapano (E10+S80 vs R40) 2007	-61	10.89	474	-56.7	10.9	475	-4.30 [-5.69, -2.91]
Garcia (E10+S10 vs S80) 2016	-30	29	16	-27	31	16	-3.00 [-23.80, 17.80]
Lee (E10+S20 vs A20) 2013	-47.9	20.7	62	-47.2	15.6	63	-0.70 [-7.13, 5.73]
Teramoto (E10+A10 vs A20) 2012	-25.8	11.86	47	-15.1	11.73	46	-10.70 [-15.49, -5.91]
1.3.2 Primary prevention study_2nd line							
Conard (E10+A20 vs A40) 2008	-31	20.19	92	-11	20.19	92	-20.00 [-25.83, -14.17]
Leiter (E10+A40 vs A80) 2008	-27	17.31	277	-11	17.23	279	-16.00 [-18.87, -13.13]
1.3.3 Secondary prevention study_1st line							
Cho (E10+S20 vs A20) 2011	-41.1	17.3	42	-44.2	14	43	3.10 [-3.60, 9.80]
Ostad (E10+A10 vs A80) 2009	-54	18	25	-60	11	24	6.00 [-2.32, 14.32]
1.3.4 Secondary prevention study_2nd line							
Barrios (E10+S20 vs A20) 2005	-32.8	17.55	215	-20.3	17.84	207	-12.50 [-15.88, -9.12]
Pesaro (E10+S20 vs S80) 2013	-29	13	37	-21	33	31	-8.00 [-20.35, 4.35]
1.3.5 Mixed prevention study_1st line							
Ballantyne (E10+S10 vs A10) 2005	-47.1	15.17	230	-36.1	13.8	235	-11.00 [-13.64, -8.36]
Ballantyne (E10+S20 vs A20) 2005	-50.6	13.74	233	-43.7	15.17	230	-6.90 [-9.54, -4.26]
Ballantyne (E10+S40 vs A40) 2005	-57.4	13.83	236	-48.3	13.71	232	-9.10 [-11.60, -6.60]
Ballantyne (E10+S80 vs A80) 2005	-58.6	14.97	224	-52.9	15.17	230	-5.70 [-8.47, -2.93]
Dobs (E10+S20 vs S40) (week 14) 2003	-21.47	17.79	66	-13.78	14.81	34	-7.69 [-14.26, -1.12]
Dobs (E10+S20 vs S40) (week 4) 2003	-24.71	17.55	66	-10.73	14.17	34	-13.98 [-20.35, -7.61]
Feldman (E10+S10 vs S20) 2004	-47	12.45	242	-38	12.55	246	-9.00 [-11.22, -6.78]
Goldberg (E10+S20 vs A10) 2006	-53.6	15.23	247	-38.3	14.16	237	-15.30 [-17.92, -12.68]
Goldberg (E10+S20 vs A20) 2006	-53.6	15.23	247	-44.6	14.25	240	-9.00 [-11.62, -6.38]
Goldberg (E10+S40 vs A40) 2006	-57.6	14.46	247	-50.9	14.28	241	-6.70 [-9.25, -4.15]
1.3.6 Mixed prevention study_2nd line							
Constance (E10+S20 vs A20) 2007	-26.15	26.89	210	-8.49	26.83	213	-17.66 [-22.78, -12.54]
Constance (E10+S40 vs A20) 2007	-30.13	26.99	215	-8.49	26.83	213	-21.64 [-26.74, -16.54]
Farnier (E10+S20 vs R10) 2009	-27.7	23.42	301	-16.9	23.07	292	-10.80 [-14.54, -7.06]
Gaudiani (E10+S20 vs S40) 2005	-20.8	22.3	103	-0.3	22.8	107	-20.50 [-26.60, -14.40]
McCormack (E10+S40 vs A40) 2010	-26.2	24.1	255	-11.1	23.82	259	-15.10 [-19.24, -10.96]
Zieve (E10+A10 vs A20) (week 4) 2010	-27	23.17	515	-13	23.15	515	-14.00 [-16.83, -11.17]
Zieve (E10+A10 vs A40) (week 12) 2010	-23	29.08	516	-18	34.52	509	-5.00 [-8.91, -1.09]

CI=confidence interval; df=degrees of freedom; N=total number of patients; SD=standard deviation; WMD=weighted mean difference

The earlier studies in mixed population compared different doses of EZ+SIM with the matching (mg per mg) doses of ATOR (Feldman 2004; Ballantyne 2005; Goldberg 2006) or with the higher doses of simvastatin Dobs (2003). These studies required a sufficient wash-out period to ensure that the treatment is received as the first line. Each of these trials showed a statistically significant additional percentage mean reduction in LDL-C associated with ezetimibe combination therapy. The difference ranged from -5.7% in EZ+SIM 80 vs ATOR 80 in Ballantyne (2005) trial to -15.3% in EZ+SIM20 vs ATOR 10 in Goldberg (2006). The only large first line therapy trial conducted in the primary prevention population (Catapano 2007) assessed the effectiveness of ezetimibe in combination with every dose of simvastatin (SIM 20 40 80) vs the corresponding doses of rosuvastatin (ROSUV 10 20 40)

monotherapy. For each individual comparison ezetimibe + statin was significantly more effective in reducing LDL-c than statin monotherapy however the effect size was considerably smaller across all arms of this trial (ranging from -2.5% to -5.7%).

Results of four large RCTs are consistent with the conclusion of the AHRQ 2014 systematic review (section 2.2.3) that ezetimibe administered as the first line therapy in combination with simvastatin of any potency more effectively lowers LDL-C than the statin monotherapy of the equivalent or a higher potency. The size of the clinical gain decreases with the increase in the dose or potency of the comparator statin suggesting the existence of equi-effective doses between ezetimibe co-administered with statin and statin monotherapy. *However the large degree of heterogeneity observed in the meta-analysis conducted for the present Review and the AHRQ 2014 systematic review suggest that there is a considerable uncertainty associated with the reported results*.

The results of ezetimibe + simvastatin combination administered as the second line treatment in mixed population (Constance 2007, Farnier 2009, Gaudiani 2005, McCormack 2010) or the secondary prevention population (Barrios 2005) also showed a statistically significant additional percentage mean reduction in LDL-C compared to statin monotherapy. The only exception is the underpowered RCTs by Pesaro (2013) that failed to demonstrate the statistical significance of the difference in %LDL-C reduction (see section 2.5.1. for description of the deficiencies of this and other small size trials included in the review). There were no trial that compared the second line EZ+SIM combination with a higher dose of simvastatin or a more potent statin in the primary prevention population. However in the mixed and primary prevention population the combination of EZ+ATOR as the second line therapy more effectively lowers LDL-C than the higher dose of ATOR monotherapy (Conard 2008, Leiter 2008, Zieve 2010).

Results of five large RCTs also seem to confirm the conclusion that ezetimibe administered as the second line therapy in combination with simvastatin of any potency more effectively lowers LDL-C than the statin monotherapy of the equivalent or a higher potency. The size of the clinical gain in terms of percentage mean reduction in LDL-C appears to be larger than the clinical gain achieved if ezetimibe+ simvastatin is administered as the first line therapy. *However the large degree of heterogeneity prevented the quantitative assessment and highlights the uncertainty of the results.*

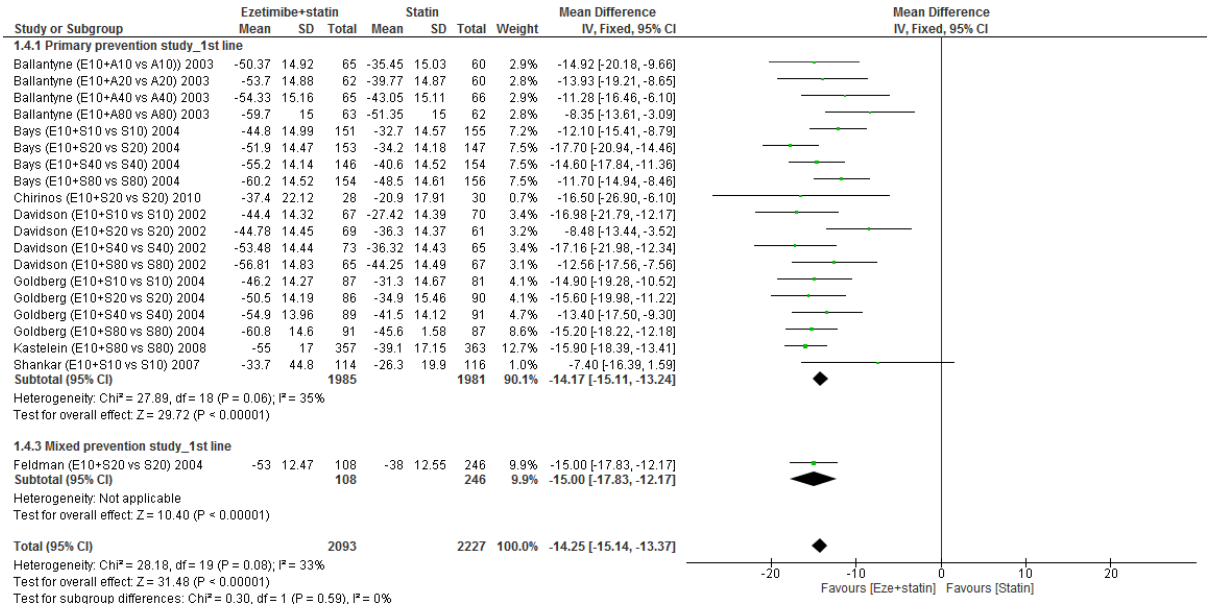
Results for TC and HDL-C endpoints are presented in Appendix (Figures A5.4 – A5.5). Results for the total cholesterol endpoints are consistent with the LDL-C results. There is no apparent evidence to suggest a statistically significant difference in the percentage mean change in HDL-C observed in ezetimibe + statin arms vs statin monotherapy arms. *The direction of the mean difference is inconsistent across the studies included in this dataset and the high degree of heterogeneity in the selected RCTs prevents the pooling of the individual mean differences*.

Comparison 3: maintaining a dose of both statin and ezetimibe in the intervention arm versus the matching statin dose in the comparator arm

This comparison involved seven RCTs (including four multiple arm trials) assessing clinical effectiveness of EZ+SIM combination therapy with the matching dose of SIM monotherapy. Only one multiple arm trial by Ballantyne (2003) compared EZ+ATOR with ATOR monotherapy. With exception of the trial by Feldman (2004) that enrolled the secondary prevention population, all trials recruited primary prevention patients without a diagnosed CHD. There was no significant heterogeneity in this set of trials, allowing for the pooled analysis of mean differences to be carried out.

Figure 2.5.3.3 shows mean %LDL-C reduction in ezetimibe in combination with statin vs statin monotherapy.

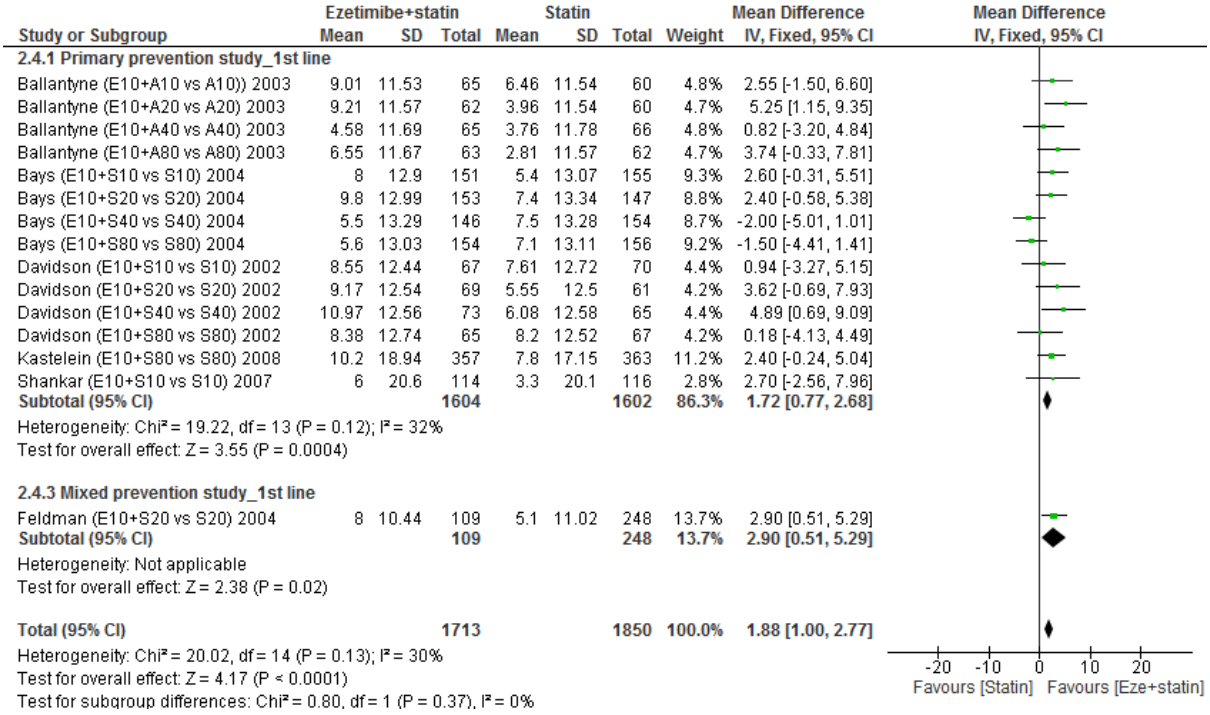
Figure 2.5.3.3 Comparison 3: Mean percentage change in LDL-C concentrations from baseline



CI=confidence interval; df=degrees of freedom; N=total number of patients; SD=standard deviation; WMD=weighted mean difference

Figure 2.5.3.4 shows mean %HDL-C change in ezetimibe in combination with statin vs statin monotherapy.

Figure 2.5.3.3 Comparison 3: Mean percentage change in HDL-C concentrations from baseline



CI=confidence interval; df=degrees of freedom; N=total number of patients; SD=standard deviation; WMD=weighted mean difference

A meta-analyses of eight studies included in Comparison 3 shows that combination of ezetimibe with statin significantly reduced LDL-C by -14.58% (95% CI: -17.83 to -12.17) (P < 0.00001) and significantly increases HDL-C by 1.88% (95% CI: 1.00 to 2.77) (P < 0.00001). The test for heterogeneity did not reach statistical significance (Chi^2 =28.18 df=19; P= 0.08; I^2=33% in LDL-C analysis and Chi^2 =20.02 df=14; P= 0.13; I^2=30%). *The results were observed in the population predominately without the history of CHD who were administered ezetimibe + statin as the first line therapy. Exclusion of the study in mixed prevention population (Feldman 2004) did not alter the estimated WMD. The results may not be generalizable to the secondary prevention population or the population who did not achieve the recommended lipid targets on the maximum tolerated dose of statin monotherapy*.

Results for mean %TC reduction are presented in Appendix (Figure A5.6). Results for the total cholesterol endpoints are consistent with the LDL-C results.

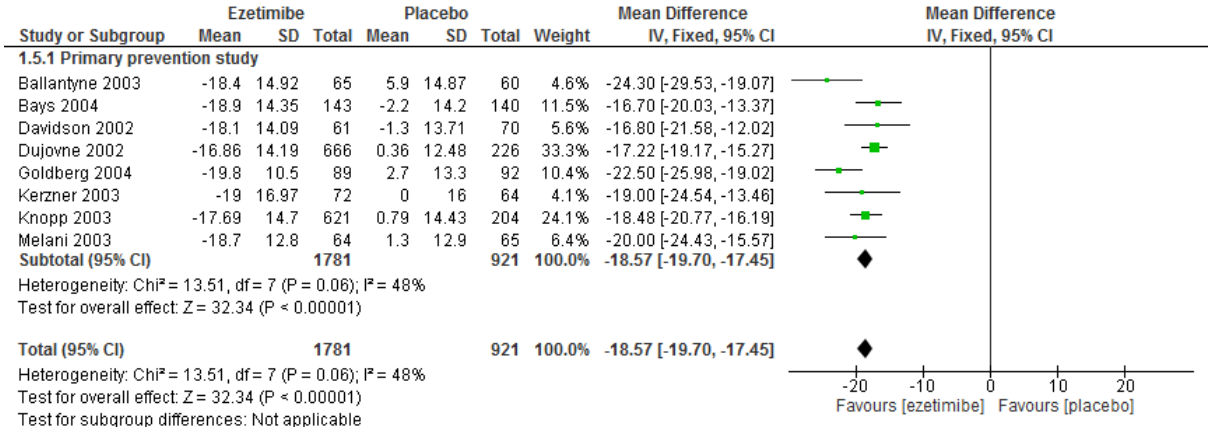
The PBAC previously commented that there is uncertainty about whether the results of the trials are representative of the true likely effect of ezetimibe 10 mg added to either atorvastatin or rosuvastatin compared with up-titration in patients' whose cholesterol is inadequately controlled as defined by the current restriction (PBAC November 2010). *For example, although the results of percentage reductions in LDL-C indicate superiority of ezetimibe over up-titrated statin, the patients were not necessarily receiving the maximum tolerated dose of statin during the stabilisation period prior to randomisation. In all but one trial by McCormack (2010) where the patients were assessed over 12 weeks prior to randomisation, the stabilisation period was less than the duration required by the current restriction to determine adequate response to lipid lowering therapy*.

2.5.4 Pooled results of ezetimibe as monotherapy

No RCT in the population of patients with intolerance or contraindication to statins was identified. In this review the body of clinical evidence for the first line therapy with ezetimibe as monotherapy consists of the trials listed in Table 2.2.4.3. The list of ezetimibe monotherapy studies includes nine trials, eight of which (Ballantyne 2003[5]; Bays 2004[19]; Davidson 2002[4]; Dujovne 2002[2]; Goldberg 2004; Melani 2003[73]; Kerzner 2003[65]; Knopp 2003[3]) were included in the comprehensive high quality systematic review and meta-analysis by Pandor (2009)[35] described in section 2.2.3. The results of meta-analysis of the mean % LDL-C reduction from the baseline reported by Pandor (2009) are reproduced in Table 2.2.3.3. We have identified one additional study by Farnier (2005)[82] that met the selection criteria, and updated the published meta-analysis results. Characteristics of the trials are presented in Table 2.4.2.

Table A5.2 in Appendix shows the percentage reduction in LDL-c level from the baseline in nine ezetimibe monotherapy trials. Addition of the study by Farnier (2005) did not alter the conclusions reported by Pandor (2009). Figures 2.5.4.1 – 2.5.4.3 show the forest plots with weighted mean difference for each study and for the pooled data. Figures 2.5.4.1 and 2.5.4.3 replicated the meta-analyses reported in the systematic review by Pandor (2009). Results reported in Farnier (2005) were not included in these analyses as no measure of variation around LDL-C or TC endpoints was reported in this study. Figure 2.5.4.1 shows that ezetimibe monotherapy significantly reduced LDL-C concentrations by -18.57% (95% CI: -19.70 to -17.45) compared with placebo (P < 0.00001). Note: the degree of heterogeneity (assessed in Chi-square and I^2 are borderline significant).

Figure 2.5.4.1 Mean percentage change in LDL cholesterol concentrations from baseline

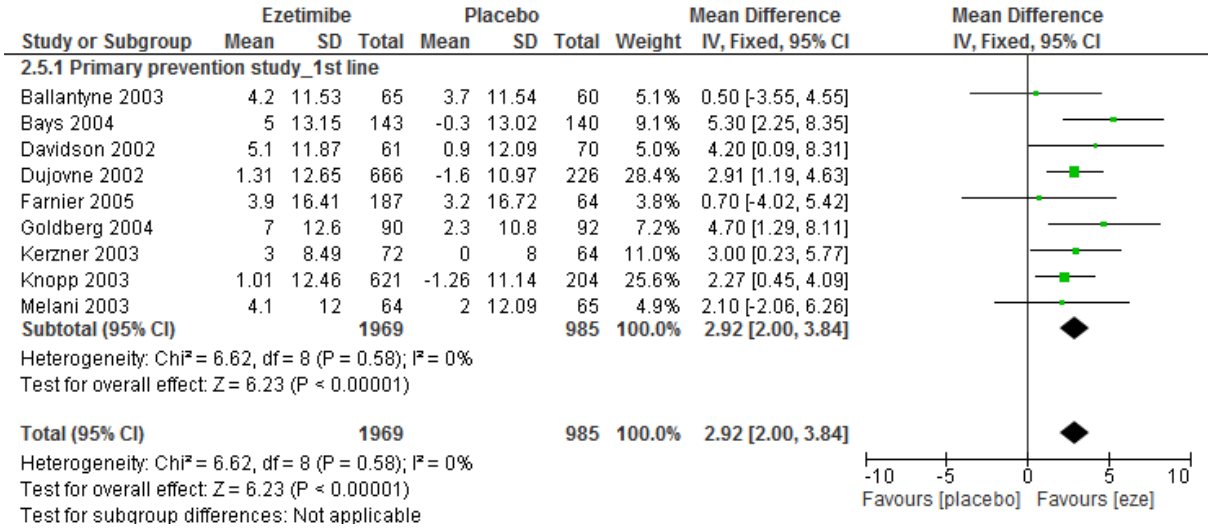


CI=confidence interval; df=degrees of freedom; N=total number of patients; SD=standard deviation; WMD=weighted mean difference

Farnier (2005) reported a measure of variation only around HDL-C endpoints, which allowed us to add these results to the results reported by Pandor (2009), although the pooled weighted mean difference changed very little.

Figures 2.5.4.2 shows that ezetimibe monotherapy significantly raised HDL-C concentrations by 2.9% (95% CI: 2.00 to 3.84) compared with placebo (P < 0.00001). The test for heterogeneity produced a non-significant value (I^2=0%).

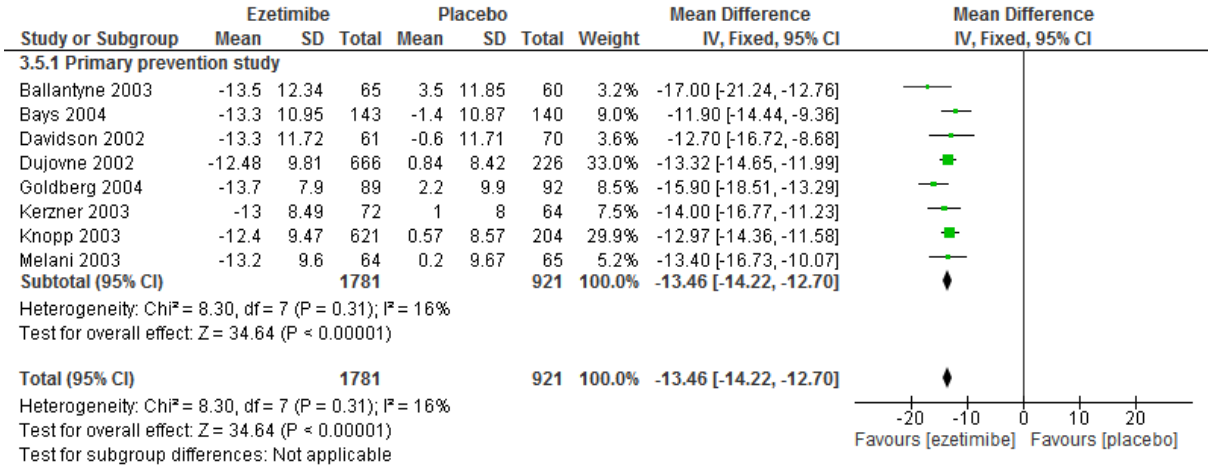
Figure 2.5.4.2 Mean percentage change in HDL cholesterol concentrations from baseline



CI=confidence interval; df=degrees of freedom; N=total number of patients; SD=standard deviation; WMD=weighted mean difference

Systematic review by Pandor (2009) found that ezetimibe monotherapy also significantly improved total cholesterol (-13.46%, 95% CI: -14.22 to -12.70), (P < 0.00001) (Figure 2.5.4.3).

Figure 2.5.4.3 Mean percentage change in total cholesterol concentrations from baseline



CI=confidence interval; df=degrees of freedom; N=total number of patients; SD=standard deviation; WMD=weighted mean difference

Results of the meta-analyses of eight RCTs (nine for HDL-C results) reported in the systematic review by Pandor (2009), and confirmed by the independent assessment conducted for this review, indicated that ezetimibe monotherapy significantly reduced LDL cholesterol concentrations compared with placebo. Significant potentially favourable changes were also observed in total cholesterol and HDL cholesterol. However none of the trials included in the meta-analyses enrolled the patients with confirmed statin intolerance of contraindication to statin therapy. Therefore results of the meta-analyses my not be fully generalizable to the target population.

2.6 Safety

2.6.1 Ezetimibe administered in combination with statin

In November 2006 the PBAC considered that it was reasonable to conclude that ezetimibe had a slightly different adverse effects profile to that of the statins and so could be co-administered with a statin without any increase in toxicity compared to up-titration of the statin dose (PBAC minute 5.2.7).

In its submission to NICE in 2015, the sponsor identified 15 studies of ezetimibe compared to placebo and 14 studies of ezetimibe+ simvastatin compared to a statin. Therapy with ezetimibe co-administered with a statin was found to have a similar adverse event profile to that of statin therapy alone. The most commonly reported adverse events were gastrointestinal (2–18%) and musculoskeletal disorders (2–17%). It was found that treatment-related adverse events ranged from 7% to 23% in the ezetimibe plus statin arm and from 13% to 19% in the statin-only arm. The number of people that discontinued treatment because of treatment-related adverse events was similar across both treatment groups (2% to 4% in the ezetimibe plus statin arm and 1% to 4% in the statin-only arm).

A summary of adverse events (including any adverse event, any serious adverse event, withdrawals from treatment due to adverse events, hospitalisations and deaths) reported in the trial identified in this review is provided in Table A6.1 in Attachment 6. *A formal meta-analysis of the adverse events*

reported in the identified trials would be inappropriate due to the inconsistency in reporting adverse events across trials, differences in the methods of assessment of clinical and laboratory adverse events and different duration of the trials that affect their capacity to detect the rare events. Incidences of any adverse event, any serious adverse event and withdrawals from treatment due the adverse events are comparable between ezetimibe+statin arms and the respective comparators in each of the trials. The investigators of the trials where hospitalisations and deaths were reported did not attribute any of such events to study drug therapy.

It is acknowledged that, with exception of IMPROVE-IT trails (see below), the trials identified for the review are unlikely to be adequately powered to detect significant differences between therapies in terms of safety outcomes.

A systematic review (section 2.2.3) conducted for NICE (UK) in 2008 (Ara, 2008) assessed the safety profile of ezetimibe in combination with a statin versus statin monotherapy. On the basis of adverse events reported in the RCTs that met the selection criteria (Bays 2004, Davidson 2002, Goldberg 2004, Rodney 2006, Ballantyne 2003, Melani 2003,Stein 2004, Ballantyne 2004a,b, Masana 2005) ezetimibe plus statin appeared to be well tolerated, having a similar overall safety profile to that of statin alone. Some 63% and 65% of participants reported having adverse effects in combination and statin alone arms, respectively. Of these, 17.5% of patients in the pooled statin arm and 18.5% in the ezetimibe plus statin arm were considered treatment-related adverse events. Serious treatment-related adverse events were not statistically significant between the statin group and the combination group. The numbers of patients discontinuing because of these adverse events were similar across the treatment groups (4.9 and 5.9%, respectively). A total of four deaths were reported. The causes of death were CV incidences (n = 2), respiratory failure (n = 1) and an accident (n = 1). All deaths were considered by investigators not to be related to the treatments. The total incidence of musculoskeletal adverse events was similar in both combination and monotherapy groups (9 and 10%, respectively). No cases of rhabdomyolysis were reported. Consecutive and presumed consecutive elevations in alanine aminotransferase levels (ALT) and/or AST level more than three times the upper limit of normal (ULN) were uncommon apart from the study by Ballantyne (2004b) which reported 2.3 versus 2.4% for ALT and 1.2 versus 0.8% for AST in the ezetimibe plus statin versus statin monotherapy arms, respectively. Creatine kinase (CK) values more than 10 times the ULN were reported by <1% of patients across all trials and had a similar incidence in the combination and monotherapy arms. Overall, the majority of the adverse events were considered to be of mild or moderate intensity. Specific clinical syndromes such as myopathy defined by the presence of myalgia in conjunction with CK elevations more than 10 times the ULN and liver function tests showed no pattern of relationship with respect to ezetimibe, administered either alone or with statins. No particular trend was found for any adverse event category in either treatment group. There were no clinically meaningful differences in the ezetimibe combination and monotherapy groups for the incidence of adverse events or in the number of discontinuations because of the adverse events. However the authors acknowledged that the low frequency of adverse events observed in the current review may be explained by the relatively short duration of the RCTs.

In the discussion section Pandor and colleagues (2009) commented on the fact that results from the (SEAS) trial (Rossebo 2008[90]) of ezetimibe (10 mg per day) + simvastatin (40 mg per day) led to controversy about the safety of ezetimibe. This randomized, double-blind trial involving 1873 patients with mild to moderate, asymptomatic aortic stenosis found that after a mean follow-up of approximately 4 years, new onset of cancer was higher in simvastatin+ ezetimibe arm compared with placebo (105 cases vs. 70 respectively, P = 0.006). To address the concerns a preliminary

hypothesis-testing analysis of interim cancer data from two large ongoing trials – the study of heart and renal protection (SHARP trial) in which simvastatin plus ezetimibe is compared with placebo (9264 patients with mean follow-up of 2.7 years), and the IMPROVE-IT trial in which simvastatin plus ezetimibe is compared with simvastatin plus placebo (11353 patients with mean follow-up of 1.0 years *at the time of the analysis*) – was undertaken by Peto (2008[91]). In this combined analysis there was no significant excess of cancer, either overall (313 active-treatment vs. 326 control, P = 0.61) or at any particular site and there was no suggestion of an emerging trend with longer treatment and follow-up periods. This analysis suggest that the findings of the SEAS trial were a chance effect as was once seen with statins (Wierzbicki 2006[92]).

The comments from NICE to the TA385 ezetimibe guidance (see Comparison of Guidelines report) (https://www.nice.org.uk/guidance/TA385/documents/committee-papers) stated that there is no known association between ezetimibe and new onset diabetes, and historically RCTs have not evaluated this outcome. However, because of an apparent association between statins and new onset diabetes, such an analysis was performed using the IMPROVE-IT trial database. For the purpose of this assessment, new onset of diabetes was defined at the individual level as any individual with no recorded prior history of diabetes who had a diabetes-related adverse event reported during IMPROVE-IT and/or received antidiabetic medication post-randomisation when such medication was not reported at baseline. Overall, approximately 7.2% of individuals were either reported or deduced to have developed diabetes over the course of the trial. No clinically meaningful differences between treatment groups were noted; there were 650 (7.2%) individuals with New Onset Diabetes in the ezetimibe/simvastatin group and 659 (7.3%) in the simvastatin group.

Pre-specified safety variables in the IMPROVE-IT trial (Cannon, 2015) included liver enzyme levels and creatine kinase levels, episodes of myopathy or rhabdomyolysis, gallbladder related adverse events and cancer. No significant between-group differences were seen in the percentage of patients who had elevations in alanine aminotransferase levels that exceeded three times the upper limit of the normal range or in the rates of gallbladder-related adverse events, cholecystectomy, muscle-related adverse events, or new, relapsing, or worsening cancer. Discontinuation of study medication owing to an adverse event occurred in 10.1% of the patients in the simvastatin-monotherapy group and in 10.6% of those in the simvastatin–ezetimibe group (Figure 2.6.1)

Figure 2.6.1 Safety end point reported in the IMPROVE-IT trial

Table 3. Prespecified Safety End Points.*

End Point	Simvastatin Monotherapy (N=9077)	Simvastatin–Ezetimibe (N=9067)	P Value
	no. of patients (%)		
ALT, AST, or both ≥3×ULN	208 (2.3)	224 (2.5)	0.43
Cholecystectomy	134 (1.5)	133 (1.5)	0.96
Gallbladder-related adverse events	321 (3.5)	281 (3.1)	0.10
Rhabdomyolysis	18 (0.2)	13 (0.1)	0.37
Myopathy	10 (0.1)	15 (0.2)	0.32
Rhabdomyolysis or myopathy	28 (0.3)	27 (0.3)	0.90
Rhabdomyolysis, myopathy, myalgia with creatine kinase elevation ≥5×ULN	58 (0.6)	53 (0.6)	0.64
Cancer†	732 (10.2)	748 (10.2)	0.57
Death from cancer†	272 (3.6)	280 (3.8)	0.71

* Adverse events were assessed in the intention-to-treat population. The database for the analysis presented here was locked on October 21, 2014. All muscle and cancer events were adjudicated by a clinical events committee, whose members were unaware of the study-group assignments. Detailed definitions of the adverse events are provided in the Supplementary Appendix. ALT denotes alanine aminotransferase, AST aspartate aminotransferase, and ULN upper limit of the normal range.

† Percentages for cancer are 7-year Kaplan–Meier estimates. Cancer includes any new, relapsing, or progressing cancer, excluding nonmelanoma skin cancer. Death from cancer includes death from nonmelanoma skin cancer.

Source: Table 3, Cannon 2015

From the results of the published systematic reviews in side-effects of ezetimibe treatment, analysis of adverse events presented in the 2015 company submission to NICE and the rates of serious adverse events reported in the randomised trials identified for this review, it appears that ezetimibe in combination with a statin has a similar safety profile to a statin monotherapy.

2.6.2 Ezetimibe administered as monotherapy

A systematic review (section 2.2.3) conducted for NICE (UK) in 2008 (Ara, 2008) assessed the safety profile of ezetimibe monotherapy and concluded that ezetimibe alone (compared with placebo) was well tolerated. Overall adverse event profiles across 7 trials seven trials (2,577 patients) (Ballantyne 2003[5]; Bays 2004[19]; Davidson 2002[4]; Dujovne 2002[2]; Goldberg 2004[38]; Melani 2003[73]; Knopp 2003[3]) were similar between the ezetimibe and placebo groups. Approximately 61% of subjects in the placebo group and 63% in the ezetimibe group reported adverse events. The most commonly reported adverse events, regardless of relationship to study drug, were musculoskeletal disorders (2–5%) and upper respiratory infections (7–11%). Other common adverse events included headache, back pain and gastrointestinal adverse events. There were no significant between-group differences in laboratory or clinical parameters. Creatine phosphokinase (CPK) and liver enzymes [alanine aminotransferase (ALT) and aspartate aminotransferase (AST)] were not influenced by treatments. Treatment-related adverse events ranged from 9 to 20% of all adverse events. Serious adverse events occurred rarely (up to 1.4%) and all trials reported no serious treatment related adverse events. A death which occurred in the ezetimibe arm was considered by investigators not to be related to study treatment.

Table A6.2 in Appendix % (reproduced from Pandor, 2009 and complimented with results of the study by Farnier, 2005) shows adverse events reported in each of the included RCTs assessing ezetimibe monotherapy vs placebo.

In the nine short-term studies, identified for this review ezetimibe monotherapy was found to have a similar adverse event profile to placebo. Adverse events (any) ranged from 45–74% in the ezetimibe monotherapy groups and 47–72% in the placebo groups. Of these, 6–18% were considered due to treatment in the ezetimibe monotherapy group and 8–24% in the placebo group (mainly gastrointestinal adverse events or musculoskeletal disorders). Clinically important elevations in creatine phosphokinase (≥10 times upper limit of normal) and liver enzymes (alanine aminotransferase and aspartate aminotransferase ≥3 times upper limit of normal) were not influenced by treatment (<1% in both groups). Discontinuation rates were comparable between both arms and serious adverse events were rare and occurred with similar frequency in the ezetimibe monotherapy and placebo groups. No cases of hepatitis, jaundice, or other clinical signs of liver dysfunction were observed in eight of the nine trials (Ballantyne 2003[5]; Bays 2004[19]; Davidson 2002[4]; Goldberg 2004; Melani 2003[73]; Kerzner 2003[65]; Knopp 2003[3], Farnier 2005[82]) (data not reported by Dujovne (2002[2]). No deaths were attributable to ezetimibe monotherapy in any of the included studies.

Ezetimibe monotherapy appeared to be well tolerated with a safety profile similar to placebo. However, the evidence base consisting of the limited number of the short-term (12 weeks) trials included in the review is too limited to address the long-term safety of ezetimibe monotherapy.

Conclusion

ToR 1 – Collate and evaluate any recent clinical studies of ezetimibe that report on long term patient relevant outcomes, and use this data to review the cost-effectiveness of ezetimibe

The research questions that related to the clinical effectiveness task in ToR 1 include:

Q1: Is addition of ezetimibe (EZ) to the maximum tolerated dose of statin is associated with superior long-term outcomes of survival, quality- adjusted survival, fatal and non-fatal CVD events in comparison to placebo + maximum tolerated dose of statin?
There is insufficient evidence to address this question.

Q2: Is addition of EZ to the maximum tolerated dose of statin associated with superior surrogate outcomes i.e., lipid endpoints (e.g. Total-C, LDL-C and HDL-C)?
There is insufficient evidence to address this question.

Q3: Is addition of EZ to various fixed doses of statin associated with superior long-term patient outcomes or surrogate outcomes in comparison to placebo + matching dose of statin?

a) **There is insufficient evidence to assess long-term patient outcomes;**
b) **A meta-analyses of eight studies that compare ezetimibe in combination with fixed dose of statin vs matching fixed dose of statin shows that ezetimibe combination with statin significantly reduced LDL-C by -14.58% (95% CI: -17.83 to -12.17) (P < 0.00001) and significantly increases HDL-C by 1.88% (95% CI: 1.00 to 2.77) (P < 0.00001).** The results were observed in the population without the history of CHD who were administered ezetimibe + statin as the first line therapy. Results may not be

generalizable to the secondary prevention population or the population who did not achieve the recommended lipid targets on the maximum tolerated dose of statin.

Q4: Is addition of EZ to statins associated with superior long-term patient outcomes or surrogate outcomes compared with up-titration of statins (either in terms of dose or potency)?

- **a)** Only one RCT with long-term patient outcomes met the selection criteria for the review (IMPROVE-IT, Cannon 2015). **Long term patient outcomes reported in the IMPROVE-IT trial may not be fully generalizable to the target population for who ezetimibe is indicated due to incompatibility of the trial inclusion criteria to the PBS restrictions** (i.e. the low LDL-C entry thresholds; no hypercholesterolaemia diagnosis as a selection criterion; use of ezetimibe as the first line of treatment in a large proportion of enrolled patients; the unknown response/tolerance to the background statin treatment in patients who received ezetimibe as the second line treatment).
- **c) Results of the studies that up-titrated the statin doses to achieve LDL-C targets generally showed that the co-administration of ezetimibe and statin was more effective in reducing LDL-C than statin monotherapy.** However, the observed high degree of heterogeneity in the identified trials prevented a pooled analysis of the individual mean differences**.** Although the results of percentage reductions in LDL-C indicate superiority of ezetimibe over up-titrated statin, the patients were not necessarily receiving the maximum tolerated dose of statin during the stabilisation period prior to randomisation. *The population enrolled in the identified RCTs that formed the basis of evidence is not fully representative of the Australian population for whom ezetimibe is currently indicated according to PBS restrictions.*
- **b) Results of the meta-analyses of eight RCTs (nine for HDL-C results) reported in the systematic review by Pandor (2009), and confirmed by the independent assessment conducted for this review, indicated that ezetimibe monotherapy significantly reduced LDL cholesterol concentrations compared with placebo. Significant potentially favourable changes were also observed in total cholesterol and HDL cholesterol.** However none of the trials included in the meta-analyses enrolled the patients with confirmed statin intolerance of contraindication to statin therapy. Therefore results of the meta-analyses my not be fully generalizable to the population for whom ezetimibe is indicated
- **c) Ezetimibe monotherapy appeared to be well tolerated with a safety profile similar to placebo.** However, the evidence base consisting of the limited number of the short-term (12 weeks) trials included in the review is too limited to address the long-term safety of ezetimibe monotherapy**.**

Q5: If it is established, that addition of EZ to statins is associated with superior final or surrogate outcomes, whether the listed price for EZ is justified considering the additional benefits?
There is a considerable uncertainty about the cost-effectiveness of ezetimibe in combination with statin versus statin monotherapy arising from the variability in estimates of clinical efficacy in terms of TC:HDL ratio *(not presented here).* **Results of the economic evaluations previously considered by PBAC and the one presented for the post-market Review seem to be overestimating the incremental long-term benefits associated with a combination of ezetimibe and statin** (See Section on critique of Modelled Economic evaluations).

Q6: Is reduction in LDL-C a valid surrogate for reduction in risk of cardiovascular (CV) events?
There is strong evidence in support of LDL-C as a surrogate outcome for reduction in CV outcomes in patients receiving a statin therapy. Results of the IMPROVE-IT trial are important in testing a hypothesis of whether reduction in LDL-C is a valid surrogate outcome

for reduction in risk of CV events in patients receiving ezetimibe (see Section 2.4.3 for details).

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