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Appendix 1

Search strategies[1]

Randomised controlled trial (Searched on 23rd May 2016)

1.1. Ovid Medline (and all the EBM reviews databases)

1. randomized controlled trial.pt. (n=416317)
2. controlled clinical trial.pt. (n=90707)
3. randomized.ab. (n=346151)
4. placebo.ab. (n=169774)
5. drug therapy.fs. (n=1856488)
6. randomly.ab. (n=248807)
7. trial.ab. (n=358140)
8. groups.ab. (n=1551869)
9. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 (n=3738147)
10. exp animals/ not humans.sh. (n=4241826)
11. 9 not 10 (n=3215742)
12. Ezetimibe, Simvastatin Drug Combination/ or Ezetimibe/ or Ezetimibe.mp. (n=2377)
13. Ezetimibe/ (n=1493)
14. 12 OR 13 n=2377
15. hypercholesterolaemia.af. (n=4470)
16. hypercholesterolemia.af. (n=36109)
17. 15 OR 16 (n=38802)
18. 11 AND 14 AND 17 (n=705)

1.2. Embase

1. 'randomized controlled trial'/exp (n=502428)
2. 'controlled clinical trial'/exp (n=525387)
3. randomized:ti,ab (n=510646)
4. placebo:ti,ab (n=234492)
5. 'drug therapy':lnk (n=3229882)
6. randomly:ti,ab (n=317168)
7. trial:ti,ab (n=582401)
8. groups:ti,ab (n=2076630)
9. 1-8/OR (n=5707959)
10. 'chapter' OR 'editorial' OR 'erratum' OR 'letter' OR 'note' OR 'short survey'/it (n=2520580)
11. 9 NOT 10 (n=5217129)
12. 'Ezetimibe' (n=7778)
13. 'Hypercholesterolemia':ab,ti,de (n=66015)
14. 'Hypercholesterolaemia':ab,ti,de (n=5550)
15. 11 OR 12 (n=66437)

[1] http://guides.library.harvard.edu/c.php?g=309982&p=2079544
McKibbon KA, Wilczynski NL, Haynes RB; Hedges Team. Retrieving randomized controlled trials from medline: a comparison of 38 published search filters. Health Info Libr J. 2009 Sep;26(3):187-202. PubMed PMID: 19712211.
Cochrane Handbook for Systematic Reviews of Interventions (2009) Higgins, J.P.T and Green, S., eds. Available at http://www.cochrane-handbook.org/.

16. 11 AND 12 AND 15 (n=2061)

An 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 2

Lists of the excluded reports of the identified RCTs with reasons

Table A2.1 Excluded studies with reasons

Studies	Excluded with reasons	count
P0217/002246 Gagné C, Bays HE, Weiss SR, Mata P, Quinto K, Melino M, et al. Efficacy and safety of ezetimibe added to ongoing statin therapy for treatment of patients with primary hypercholesterolemia. American Journal of Cardiology. 2002;90(10):1084-91. Simons L, Tonkon M, Masana L, Maccubbin D, Shah A, Lee M, et al. Effects of ezetimibe added to on-going statin therapy on the lipid profile of hypercholesterolemic patients with diabetes mellitus or metabolic syndrome. Current Medical Research & Opinion. 2004;20(9):1437-45. Abstract form of publications from the same study: ○ Bays et al. 2002, Ezetimibe added to ongoing statin therapy for treatment of primary hypercholesterolemia. J. Am Coll Cardiol. 39(Suppl. A) 245A-245A; ○ Mata et al. 2002, Addition of ezetimibe to ongoing statin therapy: incremental reduction in low-density lipoprotein cholesterol is independent of statin type. Eur. Heart J. 23(Abstra. Suppl.) p19-19; ○ Masana et al. 2003, Diabetologia 46(Suppl. 2) A75-A75; ○ Simsons et al. 2003, diabetologia 46(Suppl. 2) A354-A354; ○ Simsons et al. 2002, diabetologia 45 (Suppl. 2) A389-A389;	All excluded due to the background statin treatment including the wrong comparators:.fluvastatin, lovastatin, pravastatin, and cerivastatin. Results were not reported separately by the intervention medication.	1.
P679 Kerzner B, Corbelli J, Sharp S, Lipka LJ, Melani L, LeBeaut A, et al. Efficacy and safety of ezetimibe coadministered with lovastatin in primary hypercholesterolemia. American Journal of Cardiology. 2003;91(4):418-24. Kerzner B, Corbelli J, Sharp S, Lipka LJ, Melani L, LeBeaut A, et al. Combining complementary lipid-lowering agents ezetimibe and lovastatin is superior to either drug alone. Evidence-based Cardiovascular Medicine. 2003; 7(3): 147-9.	Lovastatin was the wrong comparator excluded from EZ combination analysis Retained for EZ monotherapy	2.
P691 Melani L, Mills R, Hassman D, Lipetz R, Lipka L, LeBeaut A, et al. Efficacy and safety of ezetimibe coadministered with pravastatin in patients with primary hypercholesterolemia: A prospective, randomized, double-blind trial. European Heart Journal. 2003;24(8):717-28. Abstract form of the publication of the same study: Melanie et al. 2003, Evidence Based Cardiovascular Medicine 7(4) p179-180	Pravastatin was the wrong comparator excluded from EZ combination analysis Retained for EZ monotherapy	3.
The EASE study Pearson TA, Denke MA, McBride PE, Battisti WP, Brady WE, Palmisano J. A community-based, randomized trial of ezetimibe added to statin therapy to attain NCEP ATP III goals for LDL cholesterol in hypercholesterolemic patients: the ezetimibe add-on to statin for effectiveness (EASE) trial. Mayo Clinic Proceedings. 2005;80(5):587-95. Pearson TA, Denke M, McBride P, Battisti WP, Brady WE, Palmisano	Unknown type of statin used during the trial.	4.

J. Effectiveness of the addition of ezetimibe to ongoing statin therapy in modifying lipid profiles and attaining low-density lipoprotein cholesterol goals in older and elderly patients: Subanalyses of data from a randomized, double-blind, placebo-controlled trial. American Journal Geriatric Pharmacotherapy. 2005;3(4):218-28.
 	
Abstract form of publications from the same study:
o Pearson et al. 2005, Atherosclerosis 6(1, Suppl.) p74-74;
o Denke et al. 2004, American Diabetes Association 64th Annual Scientific Sessions, Abstract 517-P;
o McBride et al. 2004, Diabetologia 47 (Suppl. 1) A204-205;
o Pearson et al. 2004, S. Med. J. 97 (10, Suppl.) S7-S8;
o [Author unknown] 2004, Formulary 39(5) p242-242;
o Murphy et al. 2004, Acc. Curr. J. Rev. 13(7) p14-15).		

Wierzbicki AS, Doherty E, Lumb PJ, Chik G, Crook MA. Efficacy of ezetimibe in patients with statin-resistant and statin-intolerant familial hyperlipidaemias. Current Medical Research & Opinion. 2005;21(3):333-8.	Not a RCT (observational study)	5.
Geiss HC, Otto C, Hund-Wissner E, Parhofer KG. Effects of ezetimibe on plasma lipoproteins in severely hypercholesterolemic patients treated with regular LDL-apheresis and statins. Atherosclerosis. 2005;180(1):107-12. Abstract form of the publication of the same study: Geiss et al. 2004 Atherosclerosis 5(Supp. 1) p120-120;	Lipid –apheresis was the wrong comparator	6.
P802 Farnier M, Volpe M, Massaad R, Davies MJ, Allen C. Effect of co-administering ezetimibe with on-going simvastatin treatment on LDL-C goal attainment in hypercholesterolemic patients with coronary heart disease. International Journal of Cardiology. 2005;102(2):327-32 Abstract form of the publication of the same study: Farnier et al. 2005, Atherosclerosis 6(1, Suppl.) p107-107.	No dispersion parameter(SD/SE/95%CI) of the % reduction in LDL was reported	7.
EXPLORER Ballantyne CM, Weiss R, Moccetti T, Vogt A, Eber B, Sosef F, et al. Efficacy and safety of rosuvastatin 40 mg alone or in combination with ezetimibe in patients at high risk of cardiovascular disease (results from the EXPLORER study). American Journal of Cardiology. 2007;99(5):673-80.	No dispersion parameter(SD/SE/95%CI) of the % reduction in LDL was reported	8.
P044 Baigent C, Landray MJ, Reith C, Emberson J, Wheeler DC, Tomson C, et al. The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomised placebo-controlled trial. The Lancet. 377(9784):2181-92. doi: http://dx.doi.org/10.1016/S0140-6736(11)60739-3.	No dispersion parameter(SD/SE/95%CI) of the % reduction in LDL was reported	9.
Blagden MD, Chipperfield R. Efficacy and safety of ezetimibe co-administered with atorvastatin in untreated patients with primary hypercholesterolaemia and coronary heart disease. Current Medical Research & Opinion. 2007;23(4):767-75.	No dispersion parameter(SD/SE/95%CI) of the % reduction in LDL was reported	10.
P03317 Kosoglou T, Statkevich P, Yang B, Suresh R, Zhu Y, Boutros T, et al. Pharmacodynamic interaction between ezetimibe and rosuvastatin. Current Medical Research & Opinion. 2004;20(8):1185-95.	Excluded due to short period of treatment (14 days only).	11.
P801 Brohet C, Banai S, Alings AM, Massaad R, Davies MJ, Allen C. LDL-C goal attainment with the addition of ezetimibe to ongoing simvastatin treatment in coronary heart disease patients with hypercholesterolemia. Current Medical Research & Opinion. 2005;21(4):571-8.	Results were not reported separately by the intervention medication.	12.
P803/804 Cruz-Fernandez JM, Bedarida GV, Adgey J, Allen C, Johnson-Levonas AO, Massaad R. Efficacy and safety of ezetimibe co-administered with ongoing atorvastatin therapy in achieving low-density lipoprotein goal in patients with hypercholesterolemia and coronary heart disease. International Journal of Clinical Practice. 2005;59(6):619-27.; Cruz-Fernandez et al. 2005, Atherosclerosis 6(1, Suppl.) p104-104	Results were not reported separately by the intervention medication.	13.

P1030 Gagné C, Gaudet D, Bruckert E. Efficacy and safety of ezetimibe coadministered with atorvastatin or simvastatin in patients with homozygous familial hypercholesterolemia. Circulation. 2002;105(21):2469-75.; o Gagne et al. 2002, J Am. Coll. Cardiol. 39(Suppl. A) 227A-227A; o Bruckert et al. 2002, Atherosclerosis 3(2) p81-81	Excluded a special subgroup with HoF hypercholesterolaemia, outside the scope	14.
Patient outcome paper Taylor AJ, Villines TC, Stanek EJ et al. Extended-release niacin or ezetimibe and carotid intima-media thickness. N. Engl. J. Med. 361(22), 2113-2122 (2009).	Ezetimibe+ statin versus niacin+statin	15.
Patient outcome paper Rossebo AB, Pedersen TR, Boman K, Brudi P, Chambers JB, Egstrup K, et al. Intensive lipid lowering with simvastatin and ezetimibe in aortic stenosis. N Engl J Med. 2008;359(13):1343-56.	Ezetimibe+ simvastatin versus placebo	16.
Patient outcome paper Howard BV, Roman MJ, Devereux RB, Fleg JL, Galloway JM, Henderson JA, et al. Effect of lower targets for blood pressure and LDL cholesterol on atherosclerosis in diabetes: the SANDS randomized trial. Jama. 2008;299(14):1678-89	Standard treatment goal (LDL<100 mg/dl and BP<130/85 mmHg) versus aggressive treatment goal (LDL<70 mg/dl and BP<115/75 mmHg), not a comparison of between different interventions.	17.
Roeters van Lennep HWO, Liem AH, Dunselman PHJM, Dallinga-Thie GM, Zwinderman AH, Wouter Jukema J. The efficacy of statin monotherapy uptitration versus switching to ezetimibe/simvastatin: results of the EASEGO study. Current Medical Research and Opinion. 2008;24(3):685-94.	No dispersion parameter(SD/SE/95%CI) of the % reduction in LDL was reported	18.
Robinson JG, Ballantyne CM, Grundy SM, Hsueh WA, Parving HH, Rosen JB, et al. Lipid-altering efficacy and safety of ezetimibe/simvastatin versus atorvastatin in patients with hypercholesterolemia and the metabolic syndrome (from the VYMET study). American Journal of Cardiology. 2009;103(12):1694-702. PubMed PMID: 19539078.	No dispersion parameter (SD/SE/95%CI) of the % reduction in LDL was reported.	19.
Hing Ling PK, Civeira F, Dan AG, Hanson ME, Massaad R, De Tilleghem Cle B, et al. Ezetimibe/simvastatin 10/40 mg versus atorvastatin 40 mg in high cardiovascular risk patients with primary hypercholesterolemia: a randomized, double-blind, active-controlled, multicenter study. Lipids in Health & Disease. 2012;11:18. PubMed PMID: 22293030; PubMed Central PMCID: PMCPMC3306831.	No dispersion parameter (SD/SE/95%CI) of the % reduction in LDL was reported.	20.
Zubaid M, Shakir DK, Bazargani N, Binbrek A, Gopal R, Al-Tamimi O, et al. Effect of ezetimibe coadministration with simvastatin in a Middle Eastern population: a prospective, multicentre, randomized, double-blind, placebo-controlled trial. Journal of Cardiovascular Medicine. 2008;9(7):688-93. PubMed PMID: 18545068.	No dispersion parameter (SD/SE/95%CI) of the % reduction in LDL was reported.	21.
Patel JV, Hughes EA. Efficacy, safety and LDL-C goal attainment of ezetimibe 10 mg-simvastatin 20 mg vs. placebo-simvastatin 20 mg in UK-based adults with coronary heart disease and hypercholesterolaemia. International Journal of Clinical Practice. 2006;60(8):914-21. PubMed PMID: 16893434.	No dispersion parameter (SD/SE/95%CI) of the % reduction in LDL was reported.	22.
Yamazaki D, Ishida M, Watanabe H, Nobori K, Oguma Y, Terata Y, et al. Comparison of anti-inflammatory effects and high-density lipoprotein cholesterol levels between therapy with quadruple-dose rosuvastatin and rosuvastatin combined with ezetimibe. Lipids in Health and Disease. 2013;12. doi: Artn 910.1186/1476-511x-12-9.	Excluded wrong intervention, rosuvastatin 2.5 mg is not listed on PBS	23.
Torimoto K, Okada Y, Mori H, Hajime M, Tanaka K, Kurozumi A, et al. Efficacy of combination of Ezetimibe 10 mg and rosuvastatin 2.5 mg versus rosuvastatin 5 mg monotherapy for hypercholesterolemia in patients with type 2 diabetes. Lipids in Health & Disease. 2013;12:137. PubMed PMID: 24053480; PubMed Central PMCID: PMCPMC3849617.	No dispersion parameter (SD/SE/95%CI) of the % reduction in LDL was reported.	24.
Bays HE, Averna M, Majul C, Muller-Wieland D, De Pellegrin A, Giezek H, et al. Efficacy and safety of ezetimibe added to atorvastatin versus atorvastatin uptitration or switching to rosuvastatin in patients with primary hypercholesterolemia. American Journal of Cardiology. 2013;112(12):1885-95.	No dispersion parameter(SD/SE/95%CI) of the % reduction in LDL was reported	25.
Bays HE, Moore PB, Drehobl MA, Rosenblatt S, Toth PD, Dujovne CA, et al. Effectiveness and tolerability of ezetimibe in patients with primary hypercholesterolemia: Pooled analysis of two phase II studies. Clinical Therapeutics. 2001;23(8):1209-30.	Wrong comparator dose of ezetimibe (5mg); phase II trials; no % reduction in LDL reported;	26.

Kawamura M, Watanabe T, Sakamoto K, Ashidate K, Kohro T, Tanaka A, et al. RESEARCH: Superior effect of ezetimibe was sustained on LDL-C level and the rate of achievement of target value in a 52-week analysis. Diabetologia. 2015;58(1):S82; Shiba T, Kawamura M, Kouro T, Tanaka A, Tagami M, Yamazaki T, et al. Combination regimen of statin/ezetimibe and reduction of SD-LDL-C for Japanese patients with type 2 diabetes (Research, a multicenter RCT). Atherosclerosis. 2014;235(2):e259.	Pitavastatin was the wrong comparator	27.
Krysiak R, Zmuda W, Okopien B. The effect of simvastatin-ezetimibe combination therapy on adipose tissue hormones and systemic inflammation in patients with isolated hypercholesterolemia. Cardiovasc Ther. 2014;32(2):40-6. doi: 10.1111/1755-5922.12057.	Not a randomised trial (patients agreed to received combination therapy were treated by statin+ ezetimibe).	28.
Moutzouri E, Liberopoulos EN, Tellis CC, Milionis HJ, Tselepis AD, Elisaf MS. Comparison of the effect of simvastatin versus simvastatin/ezetimibe versus rosuvastatin on markers of inflammation and oxidative stress in subjects with hypercholesterolemia. Atherosclerosis. 2013;231(1):8-14. Moutzouri E, Tellis CC, Rousouli K, Liberopoulos EN, Milionis HJ, Elisaf MS, et al. Effect of simvastatin or its combination with ezetimibe on Toll-like receptor expression and lipopolysaccharide - induced cytokine production in monocytes of hypercholesterolemic patients. Atherosclerosis. 2012;225(2):381-7.	No % reduction in LDL reported (oxLDL was reported instead).	29.
Sawayama Y. Low-dose pravastatin plus ezetimibe verus standard-dose pravastatin: the effect on the carotid atherosclerosis of patients with hypercholesterolemia. Atherosclerosis Supplements. 2011;12(1):180.	Pravastatin was the wrong comparator	30.
Farnier M, Freeman MW, Macdonell G, Perevozskaya I, Davies MJ, Mitchel YB, et al. Efficacy and safety of the coadministration of ezetimibe with fenofibrate in patients with mixed hyperlipidaemia. European Heart Journal. 2005;26(9):897-905. doi: 10.1093/eurheartj/ehi231.	Ezetimibe was added on to fenofibrate, wrong comparator for a combination therapy, included results of Ez vs Placebo arm (see included studies above).	31.
McKenney JM, Farnier M, Lo KW, Bays HE, Perevozkaya I, Carlson G, et al. Safety and efficacy of long-term co-administration of fenofibrate and ezetimibe in patients with mixed hyperlipidemia. J Am Coll Cardiol. 2006;47(8):1584-7. doi: 10.1016/j.jacc.2005.11.072. PubMed PMID: 16630994.	Ezetimibe was added on to fenofibrate; wrong comparator.	32.
Alvarez-Sala LA, Cachofeiro V, Masana L, Suarez C, Pinilla B, Plana N, et al. Effects of fluvastatin extended-release (80 mg) alone and in combination with ezetimibe (10 mg) on low-density lipoprotein cholesterol and inflammatory parameters in patients with primary hypercholesterolemia: A 12-week, multicenter, randomized, open-label, parallel-group study. Clinical Therapeutics. 2008;30(1):84-97.	Fluvastatin was the wrong comparator	33.
Florentin M, Liberopoulos EN, Moutzouri E, Rizos CV, Tselepis AD, Elisaf MS. The effect of simvastatin alone versus simvastatin plus ezetimibe on the concentration of small dense low-density lipoprotein cholesterol in subjects with primary hypercholesterolemia. Current Medical Research & Opinion. 2011;27(3):685-92	No dispersion parameter(SD/SE/95%CI) of the % reduction in LDL was reported	34.
Foody JM, Brown WV, Zieve F, Adewale AJ, Flaim D, Lowe RS, et al. Safety and efficacy of ezetimibe/simvastatin combination versus atorvastatin alone in adults >65 years of age with hypercholesterolemia and with or at moderately high/high risk for coronary heart disease (the VYTELD study). American Journal of Cardiology. 2010;106(9):1255-63.	No dispersion parameter(SD/SE/95%CI) of the % reduction in LDL was reported	35.
Kouvelos GN, Arnaoutoglou EM, Matsagkas MI, Kostara C, Gartzonika C, Bairaktari ET, et al. Effects of Rosuvastatin With or Without Ezetimibe on Clinical Outcomes in Patients Undergoing Elective Vascular Surgery: Results of a Pilot Study. Journal of Cardiovascular Pharmacology and Therapeutics. 2013;18(1):5-12. doi: 10.1177/1074248412445506. P	No % reduction in LDL reported.	36.
Moutzouri E, Liberopoulos E, Mikhailidis DP, Kostapanos MS, Kei AA, Milionis H, et al. Comparison of the effects of simvastatin vs. rosuvastatin vs. simvastatin/ezetimibe on parameters of insulin resistance. Int J Clin Pract. 2011;65(11):1141-8. doi: 10.1111/j.1742-1241.2011.02779.x.	No % reduction in LDL reported.	37.
Rodney RA, Sugimoto D, Wagman B, Zieve F, Kerzner B, Strony J, et al. Efficacy and safety of coadministration of ezetimibe and	No % reduction in LDL reported (only presented in terms of the between group	38.

simvastatin in African-American patients with primary hypercholesterolemia. Journal of the National Medical Association. 2006;98(5):772-8	difference).	
Stein EA, Ballantyne CM, Windler E, Sirnes PA, Sussekov A, Yigit Z, et al. Efficacy and Tolerability of Fluvastatin XL 80 mg Alone, Ezetimibe Alone, and the Combination of Fluvastatin XL 80 mg With Ezetimibe in Patients With a History of Muscle-Related Side Effects With Other Statins. American Journal of Cardiology. 2008;101(4):490-6.	Fluvastatin was the wrong comparator	39.
Stojakovic T, de Campo A, Scharnagl H, Sourij H, Schmolzer I, Wascher TC, et al. Differential effects of fluvastatin alone or in combination with ezetimibe on lipoprotein subfractions in patients at high risk of coronary events. European Journal of Clinical Investigation. 2010;40(3):187-94.	Fluvastatin was the wrong comparator	40.
Baigent C, Landray MJ, Reith C, Emberson J, Wheeler DC, Tomson C, et al. The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomised placebo-controlled trial. The Lancet. 377(9784):2181-92.	No dispersion parameter(SD/SE/95%CI) of the % reduction in LDL was reported	41.
Zinellu A, Sotgia S, Loriga G, Deiana L, Satta AE, Carru C. Oxidative stress improvement is associated with increased levels of taurine in CKD patients undergoing lipid-lowering therapy. Amino Acids. 2012;43(4):1499-507. PubMed PMID: 22278741; Zinellu A, Sotgia S, Pisanu E, Loriga G, Deiana L, Satta AE, et al. LDL S-homocysteinylation decrease in chronic kidney disease patients undergone lipid lowering therapy. Eur J Pharm Sci. 2012;47(1):117-23. doi: 10.1016/j.ejps.2012.05.006. PubMed PMID: 22659373.	No dispersion parameter(SD/SE/95%CI) of the % reduction in LDL was reported	42.
Haynes R, Lewis D, Emberson J, Reith C, Agodoa L, Cass A, et al. Effects of lowering LDL cholesterol on progression of kidney disease. J Am Soc Nephrol. 2014;25(8):1825-33. doi: 10.1681/ASN.2013090965. PubMed PMID: 24790178; PubMed Central PMCID: PMCPMC4116066.	No dispersion parameter(SD/SE/95%CI) of the % reduction in LDL was reported	43.
Reckless JP, Henry P, Pomykaj T, Lim ST, Massaad R, Vandormael K, et al. Lipid-altering efficacy of ezetimibe/simvastatin 10/40 mg compared with doubling the statin dose in patients admitted to the hospital for a recent coronary event: the INFORCE study. International Journal of Clinical Practice. 2008;62(4):539-54.	% reduction in LDL was not reported.	44.
Sasaki J, Otonari T, Sawayama Y, Hata S, Oshima Y, Saikawa T, et al. Double-dose pravastatin versus add-on ezetimibe with low-dose pravastatin - effects on LDL cholesterol, cholesterol absorption, and cholesterol synthesis in japanese patients with hypercholesterolemia (PEAS study). Journal of Atherosclerosis and Thrombosis. 2012;19(5):485-93.	Pravastatin was the wrong comparator	45.
Arimura T, Miura S, Ike A, Sugihara M, Iwata A, Nishikawa H, et al. Comparison of the efficacy and safety of statin and statin/ezetimibe therapy after coronary stent implantation in patients with stable angina. J Cardiol. 2012;60(2):111-8. doi: 10.1016/j.jjcc.2012.03.002. PubMed PMID: 22542530.	% reduction in LDL was not reported.	46.
Habara M, Nasu K, Terashima M, Ko E, Yokota D, Ito T, et al. Impact on optical coherence tomographic coronary findings of fluvastatin alone versus fluvastatin + ezetimibe. Am J Cardiol. 2014;113(4):580-7. doi: 10.1016/j.amjcard.2013.10.038. PubMed PMID: 24388622.	Fluvastatin was the wrong comparator	47.
Kinouchi K, Ichihara A, Bokuda K, Morimoto S, Itoh H. Effects of adding ezetimibe to fluvastatin on kidney function in patients with hypercholesterolemia: a randomized control trial. Journal of Atherosclerosis & Thrombosis. 2013;20(3):245-56. PubMed PMID: 23197250.	Fluvastatin was the wrong comparator	48.
Clement AW, M v. Comparing the effect of Monotherapies of Hyperlipidemia over Placebo Treatment International Journal of Drug Development & Research. 2014;6(3):68-76.	No dispersion parameter (SD/SE/95%CI) of the % reduction in LDL was reported.	49.
Kerzner B, Corbelli J, Sharp S, Lipka LJ, Melani L, LeBeaut A, et al. Efficacy and safety of ezetimibe coadministered with lovastatin in primary hypercholesterolemia. American Journal of Cardiology. 2003;91(4):418-24.	Lovastatin was the wrong comparator excluded from EZ combination analysis Retained for EZ monotherapy	50.
Krysiak R, Okopien B. The effect of ezetimibe and simvastatin on	% reduction in LDL was not reported.	51.

monocyte cytokine release in patients with isolated hypercholesterolemia. Journal of Cardiovascular Pharmacology. 2011;57(4):505-12. PubMed PMID: 21297492; Krysiak R, Zmuda W, Okopien B. The effect of ezetimibe and simvastatin on hemostasis in patients with isolated hypercholesterolemia. Fundamental & Clinical Pharmacology. 2012;26(3):424-31. PubMed PMID: 21392096. Krysiak R, Zmuda W, Okopien B. The effect of ezetimibe, administered alone or in combination with simvastatin, on lymphocyte cytokine release in patients with elevated cholesterol levels. Journal of Internal Medicine. 2012;271(1):32-42. PubMed PMID: 21623963.		
Melani L, Mills R, Hassman D, Lipetz R, Lipka L, LeBeaut A, et al. Efficacy and safety of ezetimibe coadministered with pravastatin in patients with primary hypercholesterolemia: A prospective, randomized, double-blind trial. European Heart Journal. 2003;24(8):717-28.	Pravastatin was the wrong comparator	52.
Dujovne CA, Suresh R, McCrary Sisk C, Maccubbin D, Strony J, Veltri E. Safety and efficacy of ezetimibe monotherapy in 1624 primary hypercholesterolaemic patients for up to 2 years. International Journal of Clinical Practice. 2008;62(9):1332-6. PubMed PMID: 18564342.	Only the % reduction in LDL for ezetimibe was reported; but this study is included in the assessment of long-term safety of ezetimibe.	53.
Bang CN, Greve AM, Boman K, Egstrup K, Gohlke-Baerwolf C, Kober L, et al. Effect of lipid lowering on new-onset atrial fibrillation in patients with asymptomatic aortic stenosis: the Simvastatin and Ezetimibe in Aortic Stenosis (SEAS) study. Am Heart J. 2012;163(4):690-6. doi: 10.1016/j.ahj.2012.01.026. PubMed PMID: 22520536.	No % reduction in LDL was reported.	54.
Brudi P, Reckless JP, Henry DP, Pomykaj T, Lim ST, Massaad R, et al. Efficacy of ezetimibe/simvastatin 10/40 mg compared to doubling the dose of low-, medium- and high-potency statin monotherapy in patients with a recent coronary event. Cardiology. 2009;113(2):89-97. PubMed PMID: 19018143.	Pravastatin and lovastatin were wrong comparators.	55.
Inazawa T, Sakamoto K, Kohro T, Iijima R, Kitazawa T, Hirano T, et al. RESEARCH (Recognized effect of Statin and ezetimibe therapy for achieving LDL-C Goal), a randomized, doctor-oriented, multicenter trial to compare the effects of higher-dose statin versus ezetimibe-plus-statin on the serum LDL-C concentration of Japanese type-2 diabetes patients design and rationale. Lipids in Health and Disease. 2013;12(1).	Protocol paper; no % reduction in LDL was reported; pitavastatin was the wrong comparator	56.
Rossebo AB, Pedersen TR, Boman K, Brudi P, Chambers JB, Egstrup K, et al. Intensive lipid lowering with simvastatin and ezetimibe in aortic stenosis. N Engl J Med. 2008;359(13):1343-56. doi: 10.1056/NEJMoa0804602. PubMed PMID: 18765433.	Simvastatin+ ezetimibe was compared with placebo. wrong comparator	57.
Saito I, Azuma K, Kakikawa T, Oshima N, Hanson ME, Tershakovec AM. A randomized, double-blind, placebo-controlled study of the effect of ezetimibe on glucose metabolism in subjects with type 2 diabetes mellitus and hypercholesterolemia. Lipids in Health & Disease. 2015;14:40. PubMed PMID: 25929253; PubMed Central PMCID: PMCPMC4450465.	% reduction in LDL was not reported.	58.
Torimoto K, Okada Y, Mori H, Hajime M, Tanaka K, Kurozumi A, et al. Efficacy of combination of Ezetimibe 10 mg and rosuvastatin 2.5 mg versus rosuvastatin 5 mg monotherapy for hypercholesterolemia in patients with type 2 diabetes. Lipids in Health & Disease. 2013;12:137. PubMed PMID: 24053480; PubMed Central PMCID: PMCPMC3849617.	No dispersion parameter (SD/SE/95%CI) of the % reduction in LDL was reported.	59.
Ahmed S, Ullah E, Ahmed M, Abbas R, Khan MA, Iqbal J. Efficacy of combination of ezetimibe and simvastatin versus atorvastatin in reducing low density lipoprotein-cholesterol in male patients of hypercholesterolemia, at Bahawalpur. Medical Forum Monthly. 2008;19(5):3-9.	Unable to retrieve the full text.	60.
Averna M, Zaninelli A, Le Grazie C, Gensini GF. Ezetimibe/simvastatin 10/20 mg versus simvastatin 40 mg in coronary heart disease patients. Journal of Clinical Lipidology. 2010;4(4):272-8	No dispersion parameter (SD/SE/95%CI) of the % reduction in LDL was reported.	61.
Ballantyne CM, Hoogeveen RC, Raya JL, Cain VA, Palmer MK, Karlson BW, et al. Efficacy, safety and effect on biomarkers related to	Rosuvastatin+ ezetimibe was compared with simvastatin+ ezetimibe.	62.

cholesterol and lipoprotein metabolism of rosuvastatin 10 or 20 mg plus ezetimibe 10 mg vs. simvastatin 40 or 80 mg plus ezetimibe 10 mg in high-risk patients: Results of the GRAVITY randomized study. Atherosclerosis. 2014;232(1):86-93. PubMed PMID: 24401221.	Wrong research question	
Bardini G, Giorda CB, Pontiroli AE, Le Grazie C, Rotella CM. Ezetimibe + simvastatin versus doubling the dose of simvastatin in high cardiovascular risk diabetics: a multicenter, randomized trial (the LEAD study). Cardiovascular Diabetology. 2010;9:20. PubMed PMID: 20492655; PubMed Central PMCID: PMCPMC2887787.	No dispersion parameter (SD/SE/95%CI) of the % reduction in LDL was reported.	63.
Baruch L, Gupta B, Haynos A, Agarwal S, Johnson S, Kelly-Johnson K, et al. Efficacy of ezetimibe 2.5 mg with a novel tablet-splitting strategy. American Journal of Pharmacy Benefits. 2010;2(4):261-6.	Wrong dose of ezetimibe (2.5mg)	64.
Bays H, Rhyne J, Abby S, Lai YL, Jones M. Lipid-lowering effects of colesevelam HCl in combination with ezetimibe. Current Medical Research & Opinion. 2006;22(11):2191-200. PubMed PMID: 17076980.	Ezetimibe+ colesevelam was compared to ezetimibe monotherapy. Wrong intervention	65.
Bays HE, Chen E, Tomassini JE, McPeters G, Polis AB, Triscari J. Fixed-dose combination ezetimibe+atorvastatin lowers LDL-C equivalent to co-administered components in randomized trials: use of a dose-response model. Fundamental & Clinical Pharmacology. 2015;29(2):209-18. PubMed PMID: 25431239.	Fixed-dose combination ezetimibe+ atorvastatin was compared to co-administered components	66.
Bays HE, Davidson MH, Massaad R, Flaim D, Lowe RS, Tershakovec AM, et al. Safety and efficacy of ezetimibe added on to rosuvastatin 5 or 10 mg versus up-titration of rosuvastatin in patients with hypercholesterolemia (the ACTE Study). American Journal of Cardiology. 2011;108(4):523-30. PubMed PMID: 21596364. Companion study [abstract only] to 'Bays HE, Davidson M, Massaad R, Flaim D, Lowe R, Tershakovec A, et al. Efficacy and safety of ezetimibe plus rosuvastatin versus rosuvastatin up-titration in hypercholesterolemic patients at risk for atherosclerotic coronary heart disease. Journal of Clinical Lipidology. 2011;5(3):217-8.'	No dispersion parameter (SD/SE/95%CI) of the % reduction in LDL was reported.	67.
Bissonnette S, Habib R, Sampalis F, Boukas S, Sampalis JS. Efficacy and tolerability of ezetimibe 10 mg/day coadministered with statins in patients with primary hypercholesterolemia who do not achieve target LDL-C while on statin monotherapy: A Canadian, multicentre, prospective study - The Ezetrol® Add-On Study. Canadian Journal of Cardiology. 2006;22(12):1035-44.	Single arm study; background statin includes other statins (pravastatin, lovastatin, fluvastatin)	68.
Bozzetto L, Annuzzi G, Della Corte G, Patti L, Cipriano P, Strazzullo A, et al. Less atherogenic profile of triglycerides-rich lipoproteins after ezetimibe in type 2 diabetic patients. Atherosclerosis Supplements. 2010;11(2):87.	Companion study to Bozzetto L, Annuzzi G, Corte GD, Patti L, Cipriano P, Mangione A, et al. Ezetimibe beneficially influences fasting and postprandial triglyceride-rich lipoproteins in type 2 diabetes. Atherosclerosis. 2011;217(1):142-8. PubMed PMID: 21481394.	69.
Chenot F, Montant PF, Marcovitch O, Blaimont M, de Meester A, Descamps OS. Co-administration of ezetimibe and simvastatin in acute myocardial infarction. European Journal of Clinical Investigation. 2007;37(5):357-63. PubMed PMID: 17461981.	Only 7 days of treatment	70.
Geiss HC, Otto C, Parhofer KG. Effect of ezetimibe on low-density lipoprotein subtype distribution: results of a placebo-controlled, double-blind trial in patients treated by regular low-density lipoprotein apheresis and statins. Metabolism: Clinical & Experimental. 2006;55(5):599-604. PubMed PMID: 16631435.	Companion study to Geiss 2005.	71.
Goldberg RB, Guyton JR, Mazzone T, Weinstock RS, Polis AB, Tipping D, et al. Relationships between metabolic syndrome and other baseline factors and the efficacy of ezetimibe/simvastatin and atorvastatin in patients with type 2 diabetes and hypercholesterolemia. Diabetes Care. 2010;33(5):1021-4. PubMed PMID: 20150290; PubMed Central PMCID: PMCPMC2858166.	*Post-hoc analysis of the study* by 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. PubMed PMID: 17165637.	72.
Grigore L, Raselli S, Garlaschelli K, Redaelli L, Norata GD, Pirillo A, et al. Effect of treatment with pravastatin or ezetimibe on endothelial	Pravastatin was the wrong comparator	73.

function in patients with moderate hypercholesterolemia. European Journal of Clinical Pharmacology. 2013;69(3):341-6. PubMed PMID: 22777149.		
Her AY, Kim JY, Kang SM, Choi D, Jang Y, Chung N, et al. Effects of atorvastatin 20 mg, rosuvastatin 10 mg, and atorvastatin/ ezetimibe 5 mg/5 mg on lipoproteins and glucose metabolism. Journal of Cardiovascular Pharmacology and Therapeutics. 2010;15(2):167-74.	Wrong dose of ezetimibe (5 mg was used)	74.
Hernandez-Mijares A, Banuls C, Rovira-Llopis S, Diaz-Morales N, Escribano-Lopez I, de Pablo C, et al. Effects of simvastatin, ezetimibe and simvastatin/ezetimibe on mitochondrial function and leukocyte/endothelial cell interactions in patients with hypercholesterolemia. Atherosclerosis. 2016;247:40-7. PubMed PMID: 26868507.	Two groups were compared: 1. Simvastatin (40 mg/day) for 4 weeks, after which ezetimibe (10 mg/day) was added for the following 4 weeks; 2. Ezetimibe (10mg/day) for the first 4 weeks, after which simvastatin (40mg/day) was added for the following 4 weeks. No baseline data to compare the outcomes separately by the dose was reported	75.
Jakulj L, Trip MD, Sudhop T, von Bergmann K, Kastelein JJ, Vissers MN. Inhibition of cholesterol absorption by the combination of dietary plant sterols and ezetimibe: effects on plasma lipid levels. Journal of Lipid Research. 2005;46(12):2692-8. PubMed PMID: 16162943.	Ezetimibe+ plant sterol/control spread versus plant sterol/PBO with control spread Wrong comparator	76.
Koh K. Significant differential metabolic effects of simvastatin combined with ezetimibe and simvastatin alone in patients with hypercholesterolemia. European Journal of Cardiovascular Nursing. 2015;14:25. Koh K, Han S, Oh P. Significant differential vascular and metabolic effects of simvastatin combined with ezetimibe and simvastatin alone in patients with hypercholesterolemia. Atherosclerosis. 2015;241(1):e196. Koh KK, Oh PC, Han SH, Kang WC. Vascular and metabolic effects of ezetimibe depend on dosages of simvastatin in patients with hypercholesterolemia. Journal of Hypertension. 2015;33:e24. Koh KK, Oh PC, Sakuma I, Kim EY, Lee Y, Hayashi T, et al. Vascular and metabolic effects of ezetimibe combined with simvastatin in patients with hypercholesterolemia. International Journal of Cardiology. 2015;199:126-31. PubMed PMID: 26188833.	No reporting of the level of LDL-c as an outcome	77.
Lee SH, Kang SM, Park S, Jang Y, Chung N, Choi D. The effects of statin monotherapy and low-dose statin/ezetimibe on lipoprotein-associated phospholipase A2. Clinical Cardiology. 2011;34(2):108-12. PubMed PMID: 21298654.	Wrong dose of ezetimibe (5 mg)	78.
Lewandowski J, Sinski M, Puchalska L, Symonides B, Gaciong Z. Simvastatin but not ezetimibe reduces sympathetic activity despite similar reductions in cholesterol levels. Journal of the American Society of Hypertension. 2014;8(10):715-23. PubMed PMID: 25418493	Wrong dose of ezetimibe (20 mg); simvastatin was compared to ezetimibe	79.
Lin X, Racette SB, Lefevre M, Lina M, Spearie CA, Steger-May K, et al. Combined effects of ezetimibe and phytosterols on cholesterol metabolism a randomized, controlled feeding study in humans. Circulation. 2011;124(5):596-601.	Ezetimibe placebo+ phytosterol placebo versus ezetimibe+ phytosterol placebo versus ezetimibe + phytosterol for three weeks Wrong comparator	80.
Olijhoek JK, Hajer GR, van der Graaf Y, Dallinga-Thie GM, Visseren FL. The effects of low-dose simvastatin and ezetimibe compared to high-dose simvastatin alone on post-fat load endothelial function in patients with metabolic syndrome: a randomized double-blind crossover trial. Journal of Cardiovascular Pharmacology. 2008;52(2):145-50. PubMed PMID: 18670365.	Crossover study design; No reporting of results before crossover.	81.
Pearson TA, Denke MA, McBride PE, Battisti WP, Gazzara RA, Brady WE, et al. Effectiveness of ezetimibe added to ongoing statin therapy in modifying lipid profiles and low-density lipoprotein cholesterol goal attainment in patients of different races and ethnicities: a substudy of the Ezetimibe add-on to statin for effectiveness trial. Mayo Clinic Proceedings. 2006;81(9):1177-85. PubMed PMID: 16970214.	Companion study to Pearson TA, Denke M, McBride P, Battisti WP, Brady WE, Palmisano J. Effectiveness of the addition of ezetimibe to ongoing statin therapy in modifying lipid profiles and attaining low-density lipoprotein cholesterol goals in older and elderly patients: Subanalyses of data from a randomized, double-blind, placebo-controlled trial. American Journal Geriatric	82.

	Pharmacotherapy. 2005;3(4):218-28. The ezetimibe or placebo was added on to patients' background statin treatment. The background statin includes other statins like pravastatin, lovastatin	
Piorkowski M, Fischer S, Stellbaum C, Jaster M, Martus P, Morguet AJ, et al. Treatment with ezetimibe plus low-dose atorvastatin compared with higher-dose atorvastatin alone: is sufficient cholesterol-lowering enough to inhibit platelets? Journal of the American College of Cardiology. 2007;49(10):1035-42. PubMed PMID: 17349882.	No % reduction in LDL was reported (only reported the actual level LDL post treatment)	83.
Robinson JG, Ballantyne CM, Grundy SM, Hsueh W, Parving HH, Rosen JB, et al. Ezetimibe/simvastatin versus atorvastatin in metabolic syndrome patients with hypercholesterolemia. Diabetes. 2009;58.	Abstract form of publication; no data extractable	84.
Robinson JG, Ballantyne CM, Hsueh W, T J, Lin J, Shah A, et al. Achievement of specified low-density lipoprotein cholesterol, non-high-density lipoprotein cholesterol apolipoprotein B, and high-sensitivity C-reactive protein levels with ezetimibe/simvastatin or atorvastatin in metabolic syndrome patients with and without atherosclerotic vascular disease (from the VYMET study). Journal of Clinical Lipidology. 2011;5(6):474-82. PubMed PMID: 22108151.	No dispersion parameter (SD/SE/95%CI) of the % reduction in LDL was reported.	85.
Rosen JB, Jimenez JG, Pirags V, Vides H, Hanson ME, Massaad R, et al. A comparison of efficacy and safety of an ezetimibe/simvastatin combination compared with other intensified lipid-lowering treatment strategies in diabetic patients with symptomatic cardiovascular disease. Diabetes & Vascular Disease Research. 2013;10(3):277-86. PubMed PMID: 23288881.	No dispersion parameter (SD/SE/95%CI) of the % reduction in LDL was reported.	86.
Rudofsky G, Reismann P, Groener JB, Djuric Z, Fleming T, Metzner C, et al. Identical LDL-cholesterol lowering but non-identical effects on NF-kappaB activity: High dose simvastatin vs combination therapy with ezetimibe. Atherosclerosis. 2012;223(1):190-6. PubMed PMID: 22633472.	No dispersion parameter (SD/SE/95%CI) of the % reduction in LDL was reported.	87.
Ruggenenti P, Cattaneo D, Rota S, Iliev I, Parvanova A, Diadei O, et al. Effects of combined ezetimibe and simvastatin therapy as compared with simvastatin alone in patients with type 2 diabetes: A prospective randomized double-blind clinical trial. Diabetes Care. 2010;33(9):1954-6.	% reduction in LDL could be calculated, however, cannot obtain the SD/SE/95%CI of it.	88.
Sharma AD, Balasubramanian S, Periyandavar I, Bolmall C, Baliga VP. Comparative evaluation of the efficacy, tolerability, and safety of rosuvastatin + Ezetimibe and Atorvastatin + Ezetimibe in Indian patients with dyslipidemia. Arteriosclerosis, Thrombosis, and Vascular Biology. 2008;28(6):e97.	Comparison was between rosuvastatin+ ezetimibe and atorvastatin+ ezetimibe Wrong research question	89.
Shekhar Pandey A, Bissonnette S, Boukas S, Rampakakis E, Sampalis JS. Effectiveness and tolerability of ezetimibe co-administered with statins versus statin dose-doubling in high-risk patients with persistent hyperlipidemia: The EZE(STAT)2 trial. Archives of Medical Science. 2011;7(5):767-75. PubMed PMID: 22291820; PubMed Central PMCID: PMCPMC3258811.	Ezetimibe was added on to background statin treatment, which including lovastatin, pravastatin and lovastatin and pravastatin that were the wrong comparators	90.
Sudhop T, Lutjohann D, Kodal A, Igel M, Tribble DL, Shah S, et al. Inhibition of intestinal cholesterol absorption by ezetimibe in humans. Circulation. 2002;106(15):1943-8. PubMed PMID: 12370217.	2 weeks of ezetimibe treatment	91.
Sudhop T, Reber M, Tribble D, Sapre A, Taggart W, Gibbons P, et al. Changes in cholesterol absorption and cholesterol synthesis caused by ezetimibe and/or simvastatin in men. Journal of Lipid Research. 2009;50(10):2117-23. PubMed PMID: 19380898; PubMed Central PMCID: PMCPMC2739752.	Ezetimibe monotherapy was compared to ezetimibe+ simvastatin combination therapy.	92.
Triscari J, Civeira F, Dan AG, Ling PKH, Hanson M, Massaad R, et al. Ezetimibe/simvastatin 10/40 mg versus atorvastatin 40 mg in high cardiovascular risk patients with primary hypercholesterolemia. Journal of Clinical Lipidology. 2011;5(3):203.	No dispersion parameter (SD/SE/95%CI) of the % reduction in LDL was reported.	93.
Snowden SG, Grapov D, Settergren M, D'Alexandri FL, Haeggstrom JZ, Fiehn O, et al. High-dose simvastatin exhibits enhanced lipid-lowering effects relative to simvastatin/ezetimibe combination therapy. Circulation Cardiovascular Genetics. 2014;7(6):955-64.	No % reduction in LDL was reported	94.

PubMed PMID: 25516625; PubMed Central PMCID: PMCNIHMS623866 [Available on 12/01/15] PMC4270085 [Available on 12/01/15].		
Viigimaa M, Vaverkova H, Farnier M, Averna M, Missault L, Hanson ME, et al. Ezetimibe/simvastatin 10/20 mg versus rosuvastatin 10 mg in high-risk hypercholesterolemic patients stratified by prior statin treatment potency. Lipids in Health & Disease. 2010;9:127. PubMed PMID: 21050476; PubMed Central PMCID: PMCPMC2992529.	No % reduction in LDL was reported (only figure showed the approximate % reduction, on actual value could be derived).	95.
Yoon HS, Kim SH, Kim JK, Ko SH, Ko JE, Park SJ, et al. Comparison of effects of morning versus evening administration of ezetimibe/simvastatin on serum cholesterol in patients with primary hypercholesterolemia.[Erratum appears in Ann Pharmacother. 2011 Sep;45(9):1172]. Annals of Pharmacotherapy. 2011;45(7-8):841-9. PubMed PMID: 21693699.	Wrong intervention: Comparison between ezetimibe+ simvastatin morning versus evening administration	96.
Yu CC, Lai WT, Shih KC, Lin TH, Lu CH, Lai HJ, et al. Efficacy, safety and tolerability of ongoing statin plus ezetimibe versus doubling the ongoing statin dose in hypercholesterolemic Taiwanese patients: an open-label, randomized clinical trial. BMC Research Notes. 2012;5:251. PubMed PMID: 22621316; PubMed Central PMCID: PMCPMC3403927.	No dispersion parameter (SD/SE/95%CI) of the % reduction in LDL was reported.	97.
Bozzetto L, Annuzzi G, Corte GD, Patti L, Cipriano P, Mangione A, et al. Ezetimibe beneficially influences fasting and postprandial triglyceride-rich lipoproteins in type 2 diabetes. Atherosclerosis. 2011;217(1):142-8. PubMed PMID: 21481394.	Number of randomised subjects in each groups was not reported.	98.
Efrati S, Averbukh M, Dishy V, Faygenzo M, Friedensohn L, Golik A. The effect of simvastatin, ezetimibe and their combination on the lipid profile, arterial stiffness and inflammatory markers. European Journal of Clinical Pharmacology. 2007;63(2):113-21. PubMed PMID: 17200833.	Not a RCT.	99.
Lakoski SG, Xu F, Vega GL, Grundy SM, Chandalia M, Lam C, et al. Indices of cholesterol metabolism and relative responsiveness to ezetimibe and simvastatin. J Clin Endocrinol Metab. 2010;95(2):800-9. doi: 10.1210/jc.2009-1952. PubMed PMID: 19965915; PubMed Central PMCID: PMCPMC3079219.	Cross over study design, the results before cross-over were not reported	100.
Theodore Feldman, Neil Fraser, Arvind Shah, Darbie Maccubbin, Diane Tribble. Efficacy and Safety of Ezetimibe/Simvastatin in Elderly Patients with Primary Hypercholesterolemia. Journal of the American College of Cardiology. 2005;45(Suppl 3):392A.	Subgroup study comparing treatment effect between age group <65 years and age group > 65 years old	101.
Civeira F, Dan AG, Hing PLK, Hanson ME, Massaad R, Milardo C, et al. Ezetimibe/simvastatin 10/40MG versus atorvastatin 40MG in high cardiovascular risk patients with primary hypercholesterolemia: A randomized, double-blind, active-controlled, multicenter study. Atherosclerosis Supplements. 2011;12(1):21.	Number of subjects randomised was not reported; no SD/SE/95%CI for the % reduction in lipid profiles.	102.
Geiss HC, Otto C, Hund-Wissner E, Parhofer KG. Effects of ezetimibe on plasma lipoproteins in severely hypercholesterolemic patients treated with regular LDL-apheresis and statins. Atherosclerosis. 2005;180(1):107-12. PubMed PMID: 15823282.	Ezetimibe and statin were added on to apheresis; cross-over design	103.
Rey R, Sanchez E, Lorenzatti A, Redruello M, Pineiro D, Altamirano J, et al. Efficacy, safety and tolerability of ezetimibe added to ongoing treat-ment with atorvastatin in subjects with primary hypercholesterolemia and coronary heart disease. European Journal of Cardiovascular Prevention and Rehabilitation. 2010;17:S33.	Number of subjects randomised to each group was not reported.	104.
Madan M, Vira T, Rampakakis E, Gupta A, Khithani A, Balleza L, et al. A Randomized Trial Assessing the Effectiveness of Ezetimibe in South Asian Canadians with Coronary Artery Disease or Diabetes: The INFINITY Study. Advances in Preventive Medicine. 2012;2012:103728. PubMed PMID: 23304534; PubMed Central PMCID: PMCPMC3529456.	Atorvastatin doses were pooled together (% reduction in LDL-c did not differentiate between different doses)	105.
Okada K, Kimura K, Iwahashi N, Endo T, Himeno H, Fukui K, et al. Clinical usefulness of additional treatment with ezetimibe in patients with coronary artery disease on statin therapy. - From the viewpoint of cholesterol metabolism. Circ J. 2011;75(10):2496-504. PubMed PMID: 21817821	% change from the baseline are not reported separately by the intervention medication	106.
Strony J, Hoffman R, Hanson M, Veltri E. Tolerability and effects on lipids of ezetimibe coadministered with pravastatin or simvastatin for twelve months: results from two open-label extension studies in	Wrong comparator: ezetimibe+ pravastatin versus ezetimibe+ simvastatin	107.

hypercholesterolemic patients. Clinical Therapeutics. 2008;30(12):2280-97		
Chow D, Chen H, Glesby MJ, Busti A, Souza S, Andersen J, et al. Short-term ezetimibe is well tolerated and effective in combination with statin therapy to treat elevated LDL cholesterol in HIV-infected patients. AIDS. 2009;23(16):2133-41.	Cross-over study, the results of % reduction of LDL-c were not reported before cross-over.	108.
Muñoz RP, Fernández SP, Conde AH, Morales JR, Serrano MG, Solero MM, et al. Efficacy and safety of adding ezetimibe to low-dose atorvastatin for highly active antiretroviral therapy-related hypercholesterolaemia. Clinica e Investigacion en Arteriosclerosis. 2009;21(4):185-9.	Non-English and uncertain duration of treatment	109.
Robinson J, Ballantyne C, Grundy S, Hsueh W, Parving H, Rosen J, et al. Ezetimibe/Simvastatin (E/S) vs Atorvastatin (A) in patients with hypercholesterolemia (HC) and metabolic syndrome (METS) grouped by presence of atherosclerotic vascular disease (AVD). Atherosclerosis Supplements. 2009;10(2).	Duplicate publication of: Robinson JG, Ballantyne CM, Grundy SM, Hsueh WA, Parving HH, Rosen JB, et al. Lipid-altering efficacy and safety of ezetimibe/simvastatin versus atorvastatin in patients with hypercholesterolemia and the metabolic syndrome (from the VYMET study). American Journal of Cardiology. 2009;103(12):1694-702.	110.
Trip M, Huijgen R, Bruckert E, Abbink E, Stalenhoef A, Imholz B, et al. Colesevelam added to stable combination of statin and ezetimibe in patients with familial hypercholesterolemia; the triple trial. Atherosclerosis Supplements. 2009;10(2).	Colesvelam added on to ezetimibe and statin compared to ezetimibe and statin dual treatment.	111.
Bertino G, Ardiri AM, Calvagno GS, Boemi PM, Santonocito MM, Campagna D, et al. Combination therapy ezetimibe/simvastatin decreases the supersaturation in gallbladder bile and prevents cholesterol gallstones formation. Digestive and Liver Disease. 2010;42:S314.	Ezetimibe+ simvastatin versus placebo	112.
Kostapanos MS, Spyrou AT, Tellis CC, Gazi IF, Tselepis AD, Elisaf M, et al. Ezetimibe treatment lowers indicators of oxidative stress in hypercholesterolemic subjects with high oxidative stress. Lipids. 2011;46(4):341-8. Kostapanos MS, Spyrou AT, Tellis CC, Gazi IF, Tselepis AD, Liberopoulos EN, et al. Effect of ezetimibe on markers of oxidative stress in patients with hypercholesterolemia. Atherosclerosis Supplements. 2011;12(1):56.	Lifestyle change was the wrong comparator	113.
Yamagishi T, Kato M, Omata K, Hasegawa H, Kanai H. Comparison of effects of ezetimibe on carotid arterial elastic modulus and C-reactive protein with fluvastatin in patients with hypercholesterolemia. Atherosclerosis Supplements. 2011;12(1):178.	Ezetimibe monotherapy versus fluvastatin	114.
Takase H, Dohi Y, Okado T, Hashimoto T, Goto Y, Kimura G. Effects of ezetimibe on visceral fat in the metabolic syndrome: a randomised controlled study. European Journal of Clinical Investigation. 2012;42(12):1287-94.	Unable to extract the % reduction in LDL-c from the figure.	115.
Liberopoulos EN, Makariou SE, Moutzouri E, Kostapanos MS, Challa A, Elisaf M. Effect of simvastatin/ezetimibe 10/10 mg versus simvastatin 40 mg on serum vitamin D levels. Journal of Cardiovascular Pharmacology & Therapeutics. 2013;18(3):229-33.	No SD/SE/95%CI for % reduction in LDL-c	116.
Moutzouri E, Liberopoulos EN, Florentin M, Liamis G, Elisaf MS. Effects of statin monotherapy versus statin plus ezetimibe combination on serum uric acid levels. Journal of Cardiovascular Pharmacology & Therapeutics. 2013;18(1):13-8.	No reporting of % reduction in LDL-c	117.
Thompson P, Ballantyne C, McKenney J, Orloff D, MacDougall D, Margulies J, et al. ETC-1002 lowers LDL-C more than ezetimibe in patients with hypercholesterolemia with or without statin intolerance and has a similar safety and tolerability profile. Journal of the American College of Cardiology. 2015;65(10):A1349.	ETC-1002 was the wrong comparator	118.
Identified from ClinicalTrials.gov: A Multicenter, Randomized, Open Label Study to Evaluate the Lipid Lowering Efficacy and Safety of Vytorin® 10/20 vs. Atorvastatin 10mg in Hypercholesterolemia Patients With Metabolic Syndrome in Korea (0653A-129)(COMPLETED) Identifier:NCT 00496730	Unable to retrieve the full-text (Korean study)	119.
Identified from ClinicalTrials.gov: Vytorin (10/20 Or 10/40) Compared to Atorvastatin (10 mg or 20 mg) in Patients With Coronary Artery	Unable to retrieve the full-text (Korean study)	120.

Disease (0653A-126)(COMPLETED) Identifier:NCT00442897		
Identified from ClinicalTrials.gov: Ezetimibe Plus (+) Simvastatin Versus Atorvastatin Comparative Study (0653A-092)(COMPLETED) Identifier: NCT00166504	Unable to retrieve the full-text (Korean study)	121.
Identified from systematic reviews		
Araujo DB, Bertolami MC, Ferreira WP, Abdalla DS, Faludi AA, Nakamura Y, et al. Pleiotropic effects with equivalent low-density lipoprotein cholesterol reduction: comparative study between simvastatin and simvastatin/ezetimibe coadministration. J Cardiovasc Pharmacol. 2010;55(1):1-5. doi: 10.1097/FJC.0b013e3181bfb1a2. PubMed PMID: 19770669.	Cross-over study design, the results before cross-over was not reported	1.
Assmann G, Kannenberg F, Ramey DR, Musliner TA, Gutkin SW, Veltri EP. Effects of ezetimibe, simvastatin, atorvastatin, and ezetimibe-statin therapies on non-cholesterol sterols in patients with primary hypercholesterolemia. Current Medical Research and Opinion. 2008;24(1):249-59. doi: 10.1185/030079908x253663. PubMed PMID: WOS:000252694300025.	Post-hoc analysis	2.
Ben-Yehuda O, Wenger NK, Constance C, Zieve F, Hanson ME, Lin JX, et al. The comparative efficacy of ezetimibe added to atorvastatin 10 mg versus uptitration to atorvastatin 40 mg in subgroups of patients aged 65 to 74 years or greater than or equal to 75 years. J Geriatr Cardiol. 2011;8(1):1-11. doi: 10.3724/Sp.J.1263.2011.00001. PubMed PMID: WOS:000296322400001.	Subgroup report from Zieve F, Wenger NK, Ben-Yehuda O, et al. Safety and Efficacy of Ezetimibe Added to Atorvastatin Versus Up Titration of Atorvastatin to 40 mg in Patients >= 65 Years of Age (from the ZETia in the ELDerly [ZETELD] Study). American Journal of Cardiology. 2010;105(5):656-63	3.
Berthold HK, Naini A, Di Mauro S, Hallikainen M, Gylling H, Krone W, et al. Effect of ezetimibe and/or simvastatin on coenzyme Q10 levels in plasma: a randomised trial. Drug safety. 2006;29(8):703-12. Epub 2006/07/29. PubMed PMID: 16872244.	Subjects were healthy male without hypercholesterolemia Wrong population	4.
Derosa G, D'Angelo A, Franzetti IG, Ragonesi PD, Gadaleta G, Scalise F, et al. Efficacy and safety of ezetimibe/simvastatin association on non-diabetic and diabetic patients with polygenic hypercholesterolemia or combined hyperlipidemia and previously intolerant to standard statin treatment. J Clin Pharm Ther. 2009;34(3):267-76. PubMed PMID: 19650249.	Single arm study (ezetimibe+ simvastatin)	5.
Fazio S, Guyton JR, Polis AB, Adewale AJ, Tomassini JE, Ryan NW, et al. Long-term safety and efficacy of triple combination ezetimibe/simvastatin plus extended-release niacin in patients with hyperlipidemia. Am J Cardiol. 2010;105(4):487-94. doi: 10.1016/j.amjcard.2009.10.001. PubMed PMID: 20152243.	Triple combination ezetimibe/simvastatin plus extended-release niacin. Wrong intervention	6.
Fleg JL, Mete M, Howard BV, Umans JG, Roman MJ, Ratner RE, et al. Effect of statins alone versus statins plus ezetimibe on carotid atherosclerosis in type 2 diabetes: the SANDS (Stop Atherosclerosis in Native Diabetics Study) trial. J Am Coll Cardiol. 2008;52(25):2198-205. doi: 10.1016/j.jacc.2008.10.031. PubMed PMID: 19095139; PubMed Central PMCID: PMCPMC2854549.	Comparison was between the aggressive LDL lowering treatment and standard LDL lowering treatment.	7.
Gouni-Berthold I, Berthold HK, Chamberland JP, Krone W, Mantzoros CS. Short-term treatment with ezetimibe, simvastatin or their combination does not alter circulating adiponectin, resistin or leptin levels in healthy men. Clinical endocrinology. 2008;68(4):536-41. Epub 2007/11/02. doi: 10.1111/j.1365-2265.2007.03080.x. PubMed PMID: 17973945; Gouni-Berthold I, Berthold HK, Gylling H, Hallikainen M, Giannakidou E, Stier S, et al. Effects of ezetimibe and/or simvastatin on LDL receptor protein expression and on LDL receptor and HMG-CoA reductase gene expression: a randomized trial in healthy men. Atherosclerosis. 2008;198(1):198-207. Epub 2007/11/06. doi: 10.1016/j.atherosclerosis.2007.09.034. PubMed PMID: 17980884.	Subjects were healthy people and treatment duration was 14 days. Wrong population	8.
Hamdan R, Hajj F, Kadry Z, Kassab R, Salame E, Aboujaoude S, et al. Benefit and tolerability of the coadministration of ezetimibe and atorvastatin in acute coronary syndrome patients. J Med Liban. 2011;59(2):65-9. PubMed PMID: 21834489.	Unable to retrieve the full-text of the article	9.
Hildemann SK, Barho C, Karmann B, Darius H, Bestehorn K. Dual cholesterol inhibition with ezetimibe/simvastatin in pre-treated hypercholesterolaemic patients with coronary heart disease or diabetes mellitus: prospective observational cohort studies in clinical practice. Curr Med Res Opin. 2007;23(4):713-9. doi:	Non-RCT (prospective observational study)	10.

10.1185/030079907X178702. PubMed PMID: 17407627.		
Jakulj L, Vissers MN, Groen AK, Hutten BA, Lutjohann D, Veltri EP, et al. Baseline cholesterol absorption and the response to ezetimibe/simvastatin therapy: a post-hoc analysis of the ENHANCE trial. J Lipid Res. 2010;51(4):755-62. doi: 10.1194/jlr.M001487. PubMed PMID: 19828909; PubMed Central PMCID: PMCPMC2842149.	Post-hoc analysis of ENHANCE trial	11.
Jimenez JG, Rosen JB, Pirags V, Massaad R, Hanson ME, Brudi P, et al. The efficacy and safety of ezetimibe/simvastatin combination compared with intensified lipid-lowering treatment strategies in diabetic subjects with and without metabolic syndrome. Diabetes Obes Metab. 2013;15(6):513-22. doi: 10.1111/dom.12059. PubMed PMID: WOS:000318441500003.	Post-hoc analysis	12.
Kawagoe Y, Hattori Y, Nakano A, Aoki C, Tanaka S, Ohta S, et al. Comparative study between high-dose fluvastatin and low-dose fluvastatin and ezetimibe with regard to the effect on endothelial function in diabetic patients. Endocrine journal. 2011;58(3):171-5. Epub 2011/02/10. PubMed PMID: 21304215.	Fluvastatin was the wrong comparator	13.
Liska B, Khattab AA, Herrmann L, Abdel-Wahab M, Westphal R, Tolg R, et al. Simvastatin and ezetimibe in addition to nonpharmacological risk factor modification for achieving new low-density lipoprotein cholesterol targets. Herz. 2008;33(5):362-7. doi: 10.1007/s00059-008-3084-6. PubMed PMID: 18773156.	Comparison was between simvastatin+ ezetimibe+ cardiac rehabilitation program and fluvastatin+ cardiac rehab program Wrong intervention and comparator	14.
Migdalis I, Efthimiadis A, Pappas S, Alexopoulos D, Vlasserou F, Mikhailidis DP. Clinical experience with ezetimibe/simvastatin in a Mediterranean population. Curr Med Res Opin. 2009;25(10):2571-6. doi: 10.1185/03007990903169031. PubMed PMID: 19739939.	Single arm observational study	15.
Moro J, Almenar L, Martinez-Dolz L, Izquierdo M, Aguero J, Sanchez-Lazaro I, et al. Ezetimibe in heart transplantation: initial experience. Transplant Proc. 2007;39(7):2389-92. doi: 10.1016/j.transproceed.2007.06.043. PubMed PMID: 17889199.	Single arm observational study	16.
Quarta CC, Potena L, Grigioni F, Scalone A, Magnani G, Coccolo F, et al. Safety and efficacy of ezetimibe with low doses of simvastatin in heart transplant recipients. J Heart Lung Transplant. 2008;27(6):685-8. doi: 10.1016/j.healun.2008.02.014. PubMed PMID: 18503971.	Single arm observational study	17.
Rosen JB, Jimenez JG, Pirags V, Vides H, Massaad R, Hanson ME, et al. Consistency of effect of ezetimibe/simvastatin compared with intensified lipid-lowering treatment strategies in obese and non-obese diabetic subjects. Lipids Health Dis. 2013;12:103. doi: 10.1186/1476-511X-12-103. PubMed PMID: 23866306; PubMed Central PMCID: PMCPMC3722050.	Post-hoc analysis	18.
Tomassini JE, Mazzone T, Goldberg RB, Guyton JR, Weinstock RS, Polis A, et al. Effect of ezetimibe/simvastatin compared with atorvastatin on lipoprotein subclasses in patients with type 2 diabetes and hypercholesterolaemia. Diabetes Obes Metab. 2009;11(9):855-64. doi: 10.1111/j.1463-1326.2009.01061.x. PubMed PMID: 19508464.	Post-hoc analysis of Goldberg RB, Guyton JR, Mazzone T et al. Ezetimibe/ simvastatin vs atorvastatin in patients with type 2 diabetes mellitus and hypercholesterolemia: the VYTAL study. Mayo Clin Proc 2006; 81: 1579–1588.	19.
van der Graaf A, Cuffie-Jackson C, Vissers MN, Trip MD, Gagne C, Shi G, et al. Efficacy and safety of coadministration of ezetimibe and simvastatin in adolescents with heterozygous familial hypercholesterolemia. J Am Coll Cardiol. 2008;52(17):1421-9. doi: 10.1016/j.jacc.2008.09.002. PubMed PMID: 18940534.	Study enrolled adolescents only.	20.
Hildemann SK, Barho C, Karmann B, Darius H, Bestehorn K. Dual cholesterol inhibition with ezetimibe/simvastatin in pre-treated hypercholesterolaemic patients with coronary heart disease or diabetes mellitus: prospective observational cohort studies in clinical practice. Curr Med Res Opin. 2007;23(4):713-9. doi: 10.1185/030079907X178702. PubMed PMID: 17407627.	Observational study	21.
Hildemann SK, Barho C, Karmann B, Darius H, Bode C. Sustained effects in hypercholesterolaemic patients on combined simvastatin/ezetimibe treatment: observational cohort study in clinical practice. Current Medical Research and Opinion. 2008;24(10):2777-84. doi: 10.1185/03007990802381406. PubMed PMID: WOS:000260261100007.	Observational study	22.

Appendix 3:Assessment of quality of systematic reviews identified in the literature search

Systematic Review	Objective	Search strategy	Inclusion/exclusion criteria	Method	Review quality	Conclusion
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.	To compare the benefits and harms of high-dose statin monotherapy with those of combination therapy in adults **at high risk for coronary disease.** 1. For patients who require intensive lipid-modifying therapy, what are the comparative long-term benefits and rates of serious adverse events of co-administration of different lipid-modifying agents (that is, a statin plus another lipid-modifying agent) compared with those of higher-dose statin monotherapy? 2. Do these regimens differ in achievement of LDL cholesterol targets (or other surrogate markers), short-term side effects, tolerability, or adherence?	MEDLINE, EMBASE, and the Cochrane Library were searched (with dates from 1966 to May 2009). Additional searching was conducted via Scopus for references that cited eight expert-nominated articles, the Internet, and the US Food and Drug Administration statistical and medical reviews of drug applications. Further published and unpublished material was requested from Abbott,AstraZeneca, and Merck/ Schering-Plough Pharmaceuticals, and from study authors. English-language studies were eligible for inclusion.	Design: RCTs; Randomised comparative studies longer than 24 weeks duration, and reporting on clinical outcomes, serious adverse events, and cancer incidence. Population: The review attempted to focus on high-risk patients requiring intensive lipid-lowering therapy (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 millimoles/litre (≥190 milligrams/ decilitre, or both). Intervention: combinations of statins and bile-acid sequestrants, fibrates, ezetimibe, niacin, or ω-3 fatty acids Comparator: statin plus another lipid-modifying therapy versus statin monotherapy (with or without a placebo) Outcomes all-cause mortality and vascular death; myocardial infarction, acute coronary syndrome, stroke, transient ischaemic attack, and revascularisation procedures. Surrogate outcomes: attainment of adenosine triphosphate and ATP III low-density lipoprotein cholesterol goals, LDL-C and HDL-C levels, and measures of carotid or coronary atherosclerosis. SAEs; cancer; withdrawals due to AEs and incidence of at least one AE; elevated serum aminotransferase levels; hepatitis; myalgia; creatine kinase levels > 10 times the ULN; rhabdomyolysis; and treatment adherence.	A reviewer screened records, and a second reviewer verified selection of RCTs. The authors assessed trial quality using predefined criteria to score the included trials as good, fair, or poor. The Grading of Recommendations Assessment, Development and Evaluation approach was used to further assess the strength of evidence. Data were extracted using standardized forms in order to calculate mean differences or odds ratios and 95% confidence intervals. In the absence of heterogeneity, meta-analyses were conducted using the DerSimonian and Laird method. The Peto odds ratio was used for rare events. The main analysis (in high-risk patients) compared a statin combined with another lipid-lowering agent with a high dose of the same statin in monotherapy. Double counting was avoided in trials with multiple unequal numbers of treatment groups.	Good quality review. Most studies were of fair quality, used strict eligibility criteria, excluded very sick patients, and compared similar doses of statins in combination and monotherapy, focusing on surrogate outcomes over a short-term period. The review question and inclusion criteria were clear. **The inclusion of diverse-risk patients, in addition to those at high-risk, was a departure from the objective.** The search strategy included several sources of published and unpublished material, which minimised the threat of publication bias. The restriction to English language studies may mean that relevant material was missed. The absence of reporting of any detailed study quality assessment limits the interpretation of the review's reliability, as it was not possible to verify the authors' conclusions about overall methodological quality. Although the inclusion of study details was prohibitive due to the large number included, there was very little information by way of summary characteristics. The method of synthesis appeared to be appropriate in the presence of heterogeneity, however the method of assessing heterogeneity was not reported. Similarly, the method to assess variation was not reported.	102 studies met eligibility criteria. Very-low-strength evidence showed that statin– ezetimibe (2 trials; n =439) did not reduce mortality more than high dose statin monotherapy. No trials compared the effect of combination therapy versus high-dose statin monotherapy on the incidence of myocardial infarction, stroke, or revascularization procedures. Two statin– ezetimibe trials (n=295) demonstrated higher low-density lipoprotein cholesterol goal attainment with combination therapy (odds ratio, 7.21 [95% CI, 4.30 to 12.08]). All statin-ezetimibe trials found additional low-density lipoprotein cholesterol reductions (4 to 27%).Trials in lower-risk patients did not show a difference in mortality. There was insufficient evidence to support the benefit for mortality, myocardial infarction, stroke and revascularisation procedures of combination therapy over high-dose statin monotherapy in high-risk patients needing intensive lipid-lowering therapy. Very-low-quality evidence favours statin– ezetimibe treatment for attainment of low-density lipoprotein cholesterol goals. Studies were generally short, focused on surrogate outcomes, and were heterogeneous in the sample's risk for coronary disease.

Systematic Review	Objective	Search strategy	Inclusion/exclusion criteria	Method	Review quality	Conclusion
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 Full text in Anne K. Monroe, Combination Therapy Versus Intensification of Statin Monotherapy: An Update AHRQ Publication No. 14-EHC013-EF February 2014 Update of the 2009 review Sharma M, et al. Systematic review: comparative effectiveness and harms of combination therapy and monotherapy for dyslipidemia. Ann Intern Med. 2009; 151:622-30: using different selection criteria	To compare effectiveness, safety, and tolerability of moderated combination therapy (bile acid sequestrant, ezetimibe, fibrate, niacin, or -3 fatty acid) with higher-intensity statin monotherapy among high-risk patients with LDL cholesterol levels of 4.91 mmol/L or greater (190 mg/dL), pre-existing atherosclerotic cardiovascular disease (ASCVD), or diabetes mellitus (DM). Also to evaluate clinical/surrogate benefits and harms among the following subgroups: females, patients older than 75, diabetics, patients with established vascular disease, and participants of African and Asian descent as well as Hispanics	MEDLINE,EMBASE, and Cochrane Central Register of Controlled Trials were searched from inception to July 2013 (the MEDLINE to November 2013) for articles published in English. Articles from a prior review and the reference lists of other relevant articles and reviews were screened. ClinicalTrials.gov was searched. Scientific information from pharmaceutical manufacturers was reviewed. Also considered nonrandomized extensions of clinical trials of more than 24 weeks' duration and U.S. Food and Drug Administration reports for evaluation of long-term benefits, serious adverse events, and harms. Included were 36 studies reported in 43 articles.	Population. **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). 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, Included participants were men aged from 50 to 65 years old. None of the included trials contained patients with statin intolerance. Baseline mean LDL-C levels varied; some were measured while participants were receiving lipid-modifying therapy. Intervention. A "moderated" combination therapy with a lower-intensity statin and another lipid-modifying medication Comparator Placebo + a **higher intensity statin** Outcome mortality, acute coronary events, cerebrovascular events, revascularization procedures; LDL-C; Adherence (investigator defined) and Harm (AEs, AEs withdrawals) Exclusion Studies where comparator was of the same or lower intensity statin than combination arm or placebo only	Two team members extracted data on study design, setting, population characteristics, and intervention characteristics. We rated the strength of evidence (SOE) by evaluating the risk of bias, consistency of results, directness, and precision. We assessed risk of bias using the Cochrane Collaboration's tool for studies identified in the new search and the Jadad score for studies identified during the prior review. Two reviewers independently assessed the risk of bias for each included study. Data were extracted by two reviewers to calculate mean differences and 95% confidence intervals. Statin doses were classified as being of low, mid, or high intensity (exact details were presented in a separate supplementary online table). We assessed precision on the basis of the studies' variance estimates and sufficiency of the sample size by comparing them to the optimal information size. For all comparisons, we report the qualitative synthesis of data by calculating and displaying the individual mean differences with 95% CIs (if calculable) for individual studies grouped by combination therapy agent, statin intensity, and high-risk population. We performed no meta-analyses given the small number of heterogeneous trials.	Good quality review: research question and inclusion criteria were adequately specified. Appropriate data sources were searched although language and publication restrictions may result in relevant studies overlooked. Steps to help minimise error and bias were undertaken. The population was limited to high risk patients according to ACC/AHA classification, which may limit generalisability of the conclusions. Up-titration studies were also included, but limited to higher initial dose of statins. Relevant quality assessment tools were used to assess the included studies, but full results of this assessment were not reported. Variation amongst the included studies meant that a narrative synthesis was appropriate.	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. Most studies that reported events lasted less than 20 weeks; event rates were very low or no events occurred. Mid-intensity statin plus ezetimibe reduced LDL-C by 5% to 15% in ASCVD patients (12 RCTs; moderate strength of evidence) and by 3% to 21% in patients with DM (11 RCTs; moderate strength of evidence) compared with high-intensity statin monotherapy. The combination of ezetimibe and lower-intensity statin would offer LDL-C – lowering benefits similar to or better than those of higher intensity statin monotherapy among patients at high ASCVD risk while producing similar rates of short-term adverse events. Previous reviews link ezetimibe use with diarrhea, and the incidence of elevated liver aminotransferase levels may increase with coadministration of ezetimibe and statin. No trials in this review had statistically significant between-group differences in liver aminotransferase elevations, although event rates were low. Combination of lower intensity statin and ezetimibe to decrease LDL cholesterol level among high-risk patients who are intolerant or unresponsive to statins, may be considered but may not result in reduced ASCVD risk.

Systematic Review	Objective	Search strategy	Inclusion/exclusion criteria	Method	Review quality	Conclusion
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 CRD review http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0031837/ Also, Tunceli,et al 2010 abstract of the 13th European conference, Value in Health, 13 (7) A342 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	To assess the efficacy of statin titration versus the addition of ezetimibe, for the treatment of primary hypercholesterolaemia. To systematically review and analyse evidence for cholesterol-lowering efficacy of at least 4 weeks of add-on ezetimibe **vs doubling statin dose**, in adults with primary hypercholesterolaemia.	The following databases were searched for articles from January 1993 to March 2010: MEDLINE, EMBASE and Cochrane Database of Systematic Reviews. Search terms were reported. Reference lists of relevant reviews were screened.	Design: Randomised controlled trials (RCTs), of parallel-group, double-blind, single-blind or open-label design of at least four week duration, for each treatment, and have a cholesterol-lowering diet or placebo run-in period of four weeks. Population: Patients had to be adults (>18 years), with primary hypercholesterolaemia or hyperlipidaemia (defined using recognised criteria). Patients who had not received statin therapy before, or whose cholesterol levels were not controlled by their existing statin monotherapy, were included. Intervention: ezetimibe plus a statin Comparator: up titration of statin monotherapy, with or without placebo Outcomes of primary interest were the proportion of patients achieving their low-density lipoprotein (LDL)-cholesterol goal, and the changes from baseline in LDL-cholesterol, high-density lipoprotein (HDL)-cholesterol, and total cholesterol.	Two reviewers independently assessed studies for inclusion, with any disagreements resolved by discussion. The quality of the trials was assessed using the Cochrane Collaboration's risk of bias assessment tool. This covered selection bias, performance bias, detection bias, attrition bias, and selective reporting. A quality rating of low, high or unclear was given for each trial. Quality was assessed by one reviewer and checked by a second. For continuous variables, the means and standard deviations were extracted to calculate mean differences, with 95% confidence intervals. For dichotomous variables, event rates were extracted to calculate odds ratios, with 95% confidence intervals. The intention-to-treat data were extracted for the outcomes of primary interest. The data were extracted by one reviewer and checked by a second reviewer. Where appropriate, data from the included trials were combined in a meta-analysis. The pooled weighted mean differences or odd ratios, with 95% confidence intervals, were calculated. Statistical heterogeneity was assessed using I^2. A random-effects model was used for the meta-analysis if there was substantial heterogeneity, otherwise a fixed-effect model was used. Subgroup analyses were performed for different types of statin, and different treatment periods. Sensitivity analysis was performed by excluding one trial that evaluated rosuvastatin and had a high risk of bias.	This review's inclusion criteria were clear. But not limited to RCTs. Only surrogate outcomes were extracted. **Only first line therapy trials were included.** Relevant databases were searched. Sufficient attempts were made to minimise errors and bias in the review process. Appropriate criteria were used to assess trial quality, but the number of included trials with a low risk of bias was unclear. Statistical heterogeneity was assessed, and the sources of heterogeneity were explored. Appropriate methods were used to pool the results. The authors' conclusions should be interpreted with caution, due to the inclusion of trials with unclear risks of bias, and substantial variation observed for the pooled outcomes.	Thirteen RCTs were included in the meta-analysis (5,080 patients); 15 trials were eligible, but two open-label trials, with a high risk of bias, were excluded. Nine trials had a low or unclear risk of bias, and one other open-label trial (the only trial of rosuvastatin) had a high risk of bias. Most of the included trials compared ezetimibe plus simvastatin or atorvastatin versus simvastatin or atorvastatin monotherapy. Three compared ezetimibe plus simvastatin versus atorvastatin monotherapy, and one compared ezetimibe plus simvastatin versus rosuvastatin monotherapy. The methods of statin titration varied between trials; in some, the dose was increased at regular intervals, while in others, the dose was increased only at baseline. Where reported, the run-in period before randomisation ranged from one to 14 weeks, and the duration of the intervention ranged from six weeks to 12 months. This review concluded that the addition of ezetimibe to a statin was more effective in reducing low-density lipoprotein cholesterol and enabling more patients to achieve their goal, than doubling the dose of statin monotherapy, for the treatment of primary hypercholesterolaemia. These conclusions should be interpreted with caution due to the substantial variation observed for the pooled outcomes.

Systematic Review	Objective	Search strategy	Inclusion/exclusion criteria	Method	Review quality	Conclusion
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) http://www.journalslibrary.nihr.ac.uk/__data/assets/pdf_file/0019/65206/FullReport-hta12210.pdf	To review the clinical and cost-effectiveness of ezetimibe for treatment of primary hyper-cholesterolaemia.	Twelve electronic databases were searched from inception to June 2006. Search terms were detailed in the report. Publications lists and current research registers of seven health services research-related organisations were consulted alongside keyword searching using Google search engine. Submissions of evidence to NICE (National Institute for Health and Clinical Excellence) by sponsors and references of retrieved papers were hand-searched. There were no language restrictions.	Design: RCTs of at least 12 weeks' duration, except for adverse events when non-randomised studies were permitted. Included studies needed to be in English and have sufficient methodological details to allow critical appraisal. Population: Adults (over 18 years) with primary (heterozygous familial or non-familial) hyper-cholesterolaemia. homozygous familial hyper-cholesterolaemia or homozygous sitosterolaemia were excluded. Intervention: For patients whose condition was not adequately controlled by a statin alone, ezetimibe could be administered with a statin or a fixed-dose combination tablet that contained ezetimibe and simvastatin. For patients who could not tolerate a statin or for whom it was contraindicated, ezetimibe could be given as monotherapy. Comparator optimal statin monotherapy or treatment with a statin in combination with other lipid-regulating drugs. The appropriate comparator for patients who could not tolerate a statin was an alternative lipid-regulating agent or no treatment. Outcomes: 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.	Two reviewers were involved in the selection of studies for the review. Disagreements were resolved by discussion. Study quality was assessed against criteria proposed by the Centre for Reviews and Dissemination (CRD). Quality data were assessed by one reviewer and checked by a second. Any disagreements were resolved by consensus. Data were extracted by one reviewer into a standardised form and independently checked by a second reviewer. Any discrepancies were resolved by consensus. A narrative review was conducted. Meta-analyses were performed, where appropriate, using analyses based on intention-to-treat (ITT) or modified ITT. Fixed-effect and random-effects models were used. Heterogeneity was explored through consideration of study populations, methods and intervention by visualisation of the results and statistically through use of the X^2 test and I^2 measure. Efficacy results were reported as least squares mean per cent change from baseline to study endpoint for each comparison group and were expressed as the weighted mean difference between treatments	Well-conducted review using comprehensive search strategy. This review was based on clear inclusion criteria for participants, interventions, outcomes and study designs. The search for studies was extensive and thorough and included attempts to find unpublished studies. Studies in languages other than English were excluded, which risked language bias. Quality was assessed and its overall impact on the results was discussed. Study selection, data extraction and quality assessment were carried out by more than one reviewer, which helped to minimise bias. Meta-analysis techniques were used appropriately with consideration of heterogeneity.	Thirteen multicentre RCTs with surrogate end-point data were included in the review. No published clinical outcome trials that examined the cardiovascular benefit of ezetimibe were identified. None of the trials reported allocation concealment. Five trials did not clarify whether outcome assessors were blinded. All patients were blinded, although none of the trials assessed the success of blinding. All trials except one used ITT or modified ITT analysis. Most trials reported a power calculation. Overall trials were considered by the authors to be relatively well designed and conducted and included relatively balanced populations. Sample sizes ranged from 246 to 1,528 patients. RCTs were of 12 to 48 weeks' duration. Mean age across the trials was 58. Between 19% and 36% of the trial population were aged 65 years and over. Mean baseline low density lipoprotein cholesterol (LDL-C) levels ranged from 3.36 to 6.50mmol/L. Patients with both primary and secondary cardiovascular disease were included in all trials. Both combination therapy (for those inadequately controlled with a statin alone) and monotherapy (for whom a statin was inappropriate or not tolerated) were evaluated. **Most studies required washout or discontinuation of all ongoing lipid-altering treatments before randomisation and no information was available on pre-trial treatment history and previous treatment success**. Therefore, it was unclear whether the study population was inadequately controlled with or intolerant of statins. Ezetimibe alone or in combination with a statin was effective in reducing low density lipoprotein cholesterol in short-term studies. **When used alone, ezetimibe is less effective than statins**. The authors' conclusions reflect the evidence and their recommendations for research appear appropriate given the lack of long-term data in the included studies.

Systematic Review	Objective	Search strategy	Inclusion/exclusion criteria	Method	Review quality	Conclusion
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. *Compare with Pearson, 2009* pooled analyses of randomized, placebo-controlled trials of ezetimibe 10 mg/day in patients with hypercholesterolemia: 6 12-week trials as monotherapy (n = 1,372). With monotherapy and add-on to statin therapy, LDL cholesterol reduction with ezetimibe was significantly greater than with placebo (treatment differences -19% and -23%, respectively, p <0.001).	To study the evidence on the efficacy and safety of ezetimibe monotherapy for the treatment of primary (heterozygous familial and non-familial) hypercholesterolaemia.	Eleven electronic bibliographic databases covering the biomedical, scientific and grey literature were searched from inception to September 2008 (including the Cochrane Library, MEDLINE, EMBASE and CINAHL). The search strategy used free text and thesaurus terms and combined synonyms relating to the intervention (e.g. ezetimibe, ezetrol, zetia, vytorin, inegy and Chemical Abstracts Service Registry number or Enzyme Commission number: 163222-33-1) with synonyms relating to the condition (e.g. hypercholesterolemia, hypercholesterolaemia) Language restrictions were not used on any database. Searches were supplemented by hand searching relevant journals, conference proceedings, and consulting experts in the field.	<u>Design</u> Randomized controlled trials (RCTs) of minimum duration of 12 weeks <u>Population</u>: individuals (over 18 years of age) with heterozygous familial and non-familial hypercholesterolaemia. Excluded: adults with homozygous familial hypercholesterolaemia, homozygous sitosterolaemia, or mixed hyperlipidaemia <u>Intervention</u> ezetimibe monotherapy (10 mg per day) <u>Comparator</u> placebo <u>Outcomes</u> The primary outcomes of interest were survival, fatal and non-fatal cardiovascular events, adverse effects of treatment, and health-related quality of life. In the absence of the primary outcomes, surrogate endpoints such as changes in total serum cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides were used as indicators of clinical outcomes	Two reviewers independently screened the searches for potentially relevant studies. The full manuscripts were retrieved and each study was assessed independently by two reviewers for inclusion using predetermined eligibility criteria. Any differences were resolved through discussion to achieve consensus. Study quality was assessed independently by two reviewers. RCTs were evaluated according to criteria based on those proposed by the NHS Centre for Reviews and Dissemination (i.e. method of randomisation, details of allocation concealment, baseline comparability, blinding of participant, investigator, outcome assessors and data analysts, details of losses to follow-up and intention-to-treat analysis). Data were extracted by one reviewer into a standardized data extraction form and independently checked for accuracy by a second. Meta-analyses were carried out using fixed and random effect models, with the Cochrane Collaboration Review Manager 4.2.10 software. The Z-statistic was used to assess overall effect and a P <0.05 was considered significant. Statistical heterogeneity between trial results was assessed using the chi-squared test and I2 -measure. The chi-squared 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.	High quality review. A comprehensive research strategy. Efficacy results were reported as least squares mean per cent change from baseline to study endpoint for each comparison group and were expressed as the weighted mean difference between treatments	A meta-analysis of eight randomized, double-blind, placebo-controlled trials (all 12 weeks) showed 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. 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). **Ezetimibe monotherapy appeared to be well tolerated with a safety profile similar to placebo.** Adverse events (any) ranged from 53–74% in the ezetimibe monotherapy groups and 54–72% in the placebo groups. Of these, 9–18% were considered due to treatment in the ezetimibe monotherapy group and 9–24% 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 seven of the eight trials (data not reported by Dujovne et al.) No deaths were attributable to ezetimibe monotherapy in any of the included studies. **However, this systematic review cannot address the long-term safety of ezetimibe monotherapy**

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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.	to quantify the risk of adverse events, as well as the efficacy of combination ezetimibe and statin therapy, through a systematic review of published clinical trials	Eligible studies were identified by searching MEDLINE (1966 to July 2006), EMBASE (1980 to July 2006), the Cochrane Library, the National Institutes of Health Clinical Trials Website, and relevant bibliographies.	Design: Trials based on double-blinding methods, with a random allocation of >100 patients and reporting adverse effects. Population: adults (age >18 years) with hyperlipidemia (defined uniquely within each study). Intervention a) Ezetimibe monotherapy b) Ezetimibe+ statin Comparator a) statin b) statin Outcome: adverse-event counts or %% as reported in the studies; AE are defined as myalgias, creatine kinase increases, rhabdomyolysis, transaminase increases, gastrointestinal adverse events, or discontinuations because of an adverse event Excluded: non-English language papers; Studies limited to specific patient populations	A combination of medical subject headings and text terms: ezetimibe, zetia, and vytorin was used. Quality assessment of the evidence and reporting was guided by the Quality of Reporting of Meta-analyses Statement and recommendations for assessing harm in randomized clinical trials. Three reviewers independently reviewed each eligible report. Results reflected adverse-event counts reported in the primary studies or, when studies reported event counts as a percentage, the calculated number of adverse events rounded to the nearest integer. Discrepancies in data extraction were resolved by consensus. The quality of method was scored by extracting information based on the Jadad score, which accounts for randomization, allocation of generation, double blinding, description of with-drawals, and dropouts. The authors used the Mantel-Haenszel statistical test and Galbraith plot to assess heterogeneity for each subgroup of adverse events and determine whether there was evidence of heterogeneity among studies. They used the random-effects modelling approach using the inverse variance to control heterogeneity, as recommended by DerSimonian and Laird. For binary outcomes, absolute risk difference and RR were calculated, and for continuous outcomes, standardized mean differences with 95% CI for both binary and continuous outcomes. Analyses were performed using Stata, version 9.0	Good quality review used the search terms that may not be comprehensive, but manual search was conducted as well. Studies in languages other than English were excluded, which risked language bias. Quality was assessed and its overall impact on the results was discussed. Data extraction and quality assessment were carried out by more than one reviewer, which helped to minimise bias. It is not clear whether the study selection, was also conducted by more than one reviewer. Publication bias was assessed using the adjusted rank correction test of Begg and Mazumdar and regression asymmetry test by Egger. Statistical assessment of degree of heterogeneity and meta-analysis techniques were used appropriately. There is a mismatch between the text of the abstract and the statistical results reported in Table 3, RD in AEs between the study arms, that makes interpretation of the RD results problematic.	18 studies met the inclusion/exclusion criteria and were assessed for quality. A total of 14,471 patients were evaluated: 503 were randomly assigned to ezetimibe monotherapy; 7,911, to ezetimibe-statin combination therapy; and 6,057, to statin monotherapy. The method quality of the studies included was high, with an average Jadad score of 4.6 points. For all models, p values for heterogeneity tests and publication bias were not significant (range 0.989 to 0.052 and 0.912 to 0.243, respectively). Compared with statin monotherapy, *ezetimibe monotherapy* [?? As in Table 3] did not result in significant absolute increases in risks of myalgias (risk difference -0.033, 95% confidence interval [CI] -0.06 to -0.01), creatine kinase increases (risk difference 0.011, 95% CI -0.02 to 0.04), rhabdomyolysis (risk difference -0.003, 95% CI -0.01 to 0.004), transaminase increases (risk difference -0.003, 95% CI -0.01 to 0.005), gastrointestinal adverse events (risk difference 0.005, 95% CI -0.03 to 0.04), or discontinuations because of an adverse event (risk difference-0.005, 95% CI -0.03 to 0.02). Based on this systematic review, the addition of ezetimibe to statin therapy does not significantly increase the incidence of adverse events.

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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.	To evaluate the evidence associated with the safety of co-administration of ezetimibe with statins.	Three electronic databases were searched (PubMed, EMBASE and Cochrane Library) from January 2002 to October 2014. using the following terms 'ezetimibe', 'zetia', 'ezetrol', 'statin', 'simvastatin', 'atorvastatin', 'rosuvastatin', 'lovastatin', 'pravastatin', 'cerivastatin', 'fluvastatin', 'hyperlipidaemia', 'dyslipidaemia' and 'hypercholesterolaemia'. The language was limited to English.	Design: double-blind RCT; treatment duration >4 weeks. Population: patients >18 years of age diagnosed with hypercholesterolaemia, whose low density lipoprotein cholesterol (LDL-C) levels were above NCEP ATP III guidelines Intervention. ezetimibe– statin combination therapy Comparator statin monotherapy. Outcomes numbers of serious adverse events, treatment discontinuations, allergic reactions or rashes, patients with alanine aminotransferase (ALT) >3 × upper limit of normal (ULN), patients with aspartate aminotransferase (AST) >3 × ULN, gastrointestinal adverse events and patients with creatine kinase (CK) >10 × ULN	Detailed information of whole articles was acquired by two reviewers independently. The detailed data were extracted as follows: study characteristics (first author's name, publication year, number of participants), invention and control measures (type and dosage of active drug, duration of follow up), individual characteristics (number of patients with hypertension or diabetes mellitus) and outcome indicators. The quality of RCTs were assessed with the Cochrane Risk of Bias tool. The results were presented separately by the type of AE and the ezetimibe+statin combination. The statistical analysis was performed by Software Review Manager 5.2 (Cochrane Collaboration, Oxford, UK). To assess heterogeneity for RCT, $\chi 2$ test and its results, P value and I^2 statistics were analysed to assess the incidence of adverse events. A fixed-effects model was used for meta-analysis to assess the safety of combination therapy.	Good quality review. The use of fixed- rather than random-effects model was not justified. P values were not adjusted for the repeated measures. Heterogeneity in the selected RCT was not explored beyond calculating I^2 statistic	A total of 20 RCTs met inclusion criteria, including 14,856 patients. Co-administration of ezetimibe and statins did not result in significant increases in total adverse events (30% vs 29%, P = 0.34), serious adverse events (2% vs 1.6%, P = 0.81), treatment discontinuations (3.5% vs 2.9%, P = 0.22), gastrointestinal adverse events (5% vs 4%, P = 0.08), allergic reactions or rashes (0.9% vs 1.3%, P = 0.33), creatine kinase > 10 × upper limit of normal (ULN) (0.2% vs 0.2%, P = 0.86), alanine aminotransferase > 3 × ULN (0.5% vs 0.4%, P = 0.96) and aspartate aminotransferase > 3 × ULN (0.4% vs 0.4%, P = 0.58). Conclusion: The incidence of adverse events was similar between ezetimibe–statin combination therapy and statin monotherapy; thus, we recommend combination therapy for patients with hypercholesterolaemia at high risk for cardiovascular and cerebrovascular disease.

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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.	The aim of this study was to determine the net effect of Ezetimibe and of the widely marketed combination, Ezetimibe+simvastatin, on mortality and morbidity outcomes.	Three electronic bibliographic data-bases: MEDLINE (PubMed) Central Controlled Trials Register of the Cochrane Collaboration; EMBASE, ClinicalTrials.gov, were searched; the online registers of trials compiled by Merck and Novartis and through personal communication with the authors of the trials to retrieve unpublished data. Manual search of the references was also conducted. Search terms Included a comprehensive list for Ezetimibe; Cochrane filters for RCT and Guidelines were used.	Design: RCT, observational studies were excluded Population: Participants were (adult?) males or females of all ages regardless of the clinical condition Intervention a) Ezetimibe monotherapy b) Ezetimibe+ another lipid-lowering drug c) Ezetimibe+simvastatin Comparator a)placebo b) placebo in combination with the same lipid-lowering drug at the same dosage c) placebo Outcomes: all-cause mortality; CV mortality; stroke; MI; cancer; SAEs (namely any adverse event that results in death, is life-threatening, or requires or prolongs hospital stay, or causes persistent or significant disability/ incapacity; any probably related congenital anomaly/birth defect or any other condition which investigators judge to represent significant hazards) *Excluded:* surrogate end-points as LDL-C variations or the mean change in CIMT	Two authors independently selected the trials fulfilling the inclusion criteria and a third resolved any disagreement. Two authors independently extracted the data using a standardized item-list. The quality of the trials was assessed using a Cochrane check-list for quality assessment. Meta-analysis was conducted using both the fixed effect- & the random effect- model. The results are expressed as pooled risk ratios (RR) with 95% CI. Publication bias was assessed using the Peters formal statistical test. A p value <0.10 suggested a publication bias. Formal test for effect modifier variables was undertaken using a meta-regression univariate model with the suspected modifier stratified as dummy variable; a cut-off of 0.05 defined the statistical significance for the coefficient test. The variable suspected as being an effect modifier in the E+ another drug versus the same drug analyses was the comparator/co-treatment. We calculated the statistical power of the meta-analysis for SAEs in scenarios of added sample size using the method described by Crowther which assumes effect sizes of future trials consistent with those observed previously. All analyses were done using the Stata12-SE	All major databases were searched. Search strategy is good. Independence in RCT selection, assessment of quality and data extraction was observed. Sensitivity analysis with respect to missing data was conducted A sophisticated statistical analysis was used of the pooled data of the very rare events. The use of univariate model and appropriate-ness of the meta-regression was not discussed. No qualitative assessment of the underlying heterogeneity was undertaken. Some of the studies (Collins, 2003; Barta 2007, Schwartz 2012) were not excluded but do not appear in the included list either. The results do not support the negative conclusion as none of the trials were powered to detect final outcomes, as according to the authors' own estimation the pooled sample size is too small to detect the difference in aggregated SAEs (assumed to be 45%, the only point estimate they quote)	No RCT of direct comparisons of E monotherapy against placebo was identified. 7 RCTs were selected in 5 of which the combination of Ezetimibe+another lipid-lowering drug was tested against the same lipid-lowering drug at the same dosage 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.

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Sando Karen R. Nonstatin Therapies for Management of Dyslipidemia: A Review. Clinical Therapeutics Volume 37, Issue 10, 1 October 2015, Pages 2153–2179	The purpose of this review is to summarize and interpret the evidence that evaluates non-statin drug classes in reducing cardiovascular events, to provide recommendations for use of non-statin therapies in clinical practice, and to review emerging non-statin therapies for management of dyslipidemia	PubMed, International Pharmaceutical Abstracts,Cochrane Database of Systematic Reviews (between 1970 and June 30, 2015), by using the terms niacin, omega-3 fatty acids (FAs), clofibrate, fibrate, fenofibrate, fenofibric acid, gemfibrozil, cholestyramine, colestipol, colesevelam,ezetimibe, proprotein convertase subtilisin/kexin 9 (PCSK9), cholesteryl ester transfer protein (CETP), and cardiovascular outcomes. Only English language, human clinical trials, meta-analyses, and systematic reviews were included. Additional references were identified from citations of published articles.	Population: not described Intervention. Non-statin therapies as monotherapies or in combination with statins Comparator not described Outcomes cardiovascular events, not otherwise identified	Not described, but apparently no assessment of the quality of the identified trials or data extraction and analysis was undertaken	Poor quality. Lilimited search strategy (no EMBASE) or Cochrane registry. Not limited to RCTs. Not clear how selection was conducted (two independent reviewers?) or how the data was extracted. Also no information on how the quality of the evidence was assessed. No comments on heterogeneity of included trials. Not clear what were the inclusion/ exclusion criteria. The review is not specific to ezetimibe	Ezetimibe–statin combination therapy can reduce cardiovascular outcomes in those with chronic kidney disease and following vascular surgery or acute coronary syndrome. A total of 7 RCTs and systematic reviews were identified that evaluated the effects of ezetimibe in combination with other lipid-lowering therapies on cardiovascular outcomes. In summary, ezetimibe is a safe and effective agent to lower LDL-C as monotherapy or in combination with statin therapy. Before 2014, only limited evidence showed benefit in cardiovascular outcomes for statin–ezetimibe combination therapy, particularly in the setting of postvascular surgery and CKD. The results of IMPROVE-IT support the use of ezetimibe in high-risk patients with ACS. Therefore, the most promising role of ezetimibe in clinical practice is in combination with statin therapy for patients with a high risk of cardiovascular events, specifically those with a history of ACS. Ezetimibe monotherapy should not be routinely recommended for the sole purpose of cardiovascular risk reduction.

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Ijioma, N. Robinson, J. G. Lipid-lowering effects of ezetimibe and simvastatin in combination Expert Review of Cardiovascular Therapy 2011; 9(2) 131-145	To review current information on the pharmacology, clinical efficacy and safety of ezetimibe/simvastatin combination therapy as a lipid-lowering pharmacologic option	PubMed was searched for English-language articles from January 2005 to 14 April 2010 using the keywords 'ezetimibe and simvastatin' and 'hyperlipidemia'. Manual References in the identified papers was conducted, and retrospective studies were excluded.	Design: prospective trials of ezetimibe and simvastatin (no further details were specified, but non-randomised trials were not excluded	Not outlined, however no formal assessment of the quality of the identified trials was carried out, no systematic analysis of the data (e.g. meta-analysis) was undertaken	Poor quality review; Only one database was searched with severely restricted selection of search terms; the selection criteria are not clearly defined; participation of the authors in the selection of the studies is not clear; not clear whether assessment of the quality of evidence was ever conducted. Apparently no statistical analysis of aggregated data was conducted.	Ezetimibe monotherapy lowers LDL-C by 19–23%. Co-administration of ezetimibe with simvastatin provides an additional approximately 15% reduction in LDL‐C compared with statin monotherapy. Ezetimibe/simvastatin co-administration results in LDL-C reductions of 34–61%, non-HDL-C reductions of 41–56%, 6–12% increases in HDL, 19–35% reductions in triglycerides, and 35–49% reductions in ApoB. Imaging studies with ezetimibe/simvastatin have been performed in different population groups to evaluate the efficacy of ezetimibe/simvastatin on carotid intima-media thickness (CIMT). CIMT reduction has been used as a surrogate cardiovascular clinical end point. Conflicting results have been obtained from these studies. Dose-comparison studies and pooled analyses have shown greater lipid-lowering efficacy of ezetimibe/simvastatin compared with other statin monotherapy doses or with up-titration of other statins. Two trials reported that LDL-C-lowering response of ezetimibe/simvastatin is not determined by baseline cholesterol status. Low-density lipoprotein-C and non-HDL-C are the primary and secondary targets of lipid-lowering therapy identified by NCEP ATP III. Many individuals will need a greater than 50% reduction in LDL-C and/or non-HDL-C to reach the targets of less than 100 and 130 mg/dl, respectively. Ezetimibe combined with simvastatin 20–80 mg provides an alternative to atorvastatin 80 mg and rosuvastatin 20–40 mg to achieve this level of cholesterol reduction. Unlike atorvastatin 80 mg (in the Treating to New Targets) and rosuvastatin 20 mg (in the Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin) ezetimibe/simvastatin has resulted in a less than expected reduction in ischemic CVEs in the sole clinical trial reported to date (SEAS). At the time of publication SHARP and IMPROVE-IT trials were on-going.

Appendix 4: Description of the identified trials

Trial	Description of the trial	Inclusion Criteria (abridged)	Exclusion Criteria (abridged)	Patient characteristics/ risk assesment/ compartibility with General Statement for Lipid Lowering Drugs
Up-titrating statin dose+ ezetimibe vs up-titrating statin dose				
Cannon 2015 IMPROVE-IT SIM 40-80 Secondary prevention population with both first and second line therapies. Depending on dose-response the SIM dose could be doubled to 80mg	A DB RCT involving 18,144 patients who had been hospitalized for an acute coronary syndrome within the preceding 10 days were assigned either EZ 10+SIM 40 or PBO + SIM 40 (simvastatin monotherapy). The primary end point was a composite of cardiovascular death, nonfatal myocardial infarction, unstable angina requiring rehospitalization, coronary revascularization (≥30 days after randomization), or nonfatal stroke. The median follow-up was 6 years	Patients who had been hospitalized for an acute coronary syndrome within the preceding 10 days and had LDL cholesterol levels of 1.3 to 2.6 mmol/L if they were receiving lipid-lowering therapy or 1.3 to 3.2 mmol/L if they were not receiving lipid-lowering therapy. Subjects must have had a plasma triglyceride (TG) level ≤4.0 mmol/L.	On continous lipid-lowering therapy with LDL-C lowering potency greater than simvastatin 40 mg. a. Hemodynamic events: 1) Hypotension, defined as sustained systolic blood pressure of <90 mmHg; 2) Unstable or severe Pulmonary edema/decompensated CHF; 3) Acute mitral regurgitation; 4) Acute ventricular septal defect. b. Recurrent symptoms of cardiac ischemia: c. Stroke or transient ischemic attack (TIA); d. Arrhythmic events. Subject had active liver disease or persistent serum transaminase elevations (≥2 x ULN)	The patients are in the high risk category according to the GSLLD. *However, the patients do not meet the PBS eligibility criteria for EZ*, which requires 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. This is above the threshol of a maximum level of 2.6 mmol/L for the second line therapy patients enrolled in the trial. *Not a target population for the review*
Protocol 025 Ballantyne et al 2004 Mixed population first line of treatment Forced titration	A 28-week (4-week placebo/ diet run-in period and 24-week active treatment period) multicenter, active-controlled, double-blind study. Each group was force-titrated over four 6-week treatment periods: (1) 10 mg of atorvastatin as the initial dose was titrated to 20, 40, and 80 mg; (2) co-administration of 10 mg of ezetimibe and 10 mg of simvastatin (10/10 mg) was titrated to 10/20, 10/40, and 10/80 mg of ezetimibe simvastatin; and (3) co-administration of 10/20 mg of ezetimibe + simvastatin was titrated to 10/40 mg (for 2 treatment periods) and 10/80 mg of ezetimibe + simvastatin.	Men and women 18 to 79 years, with an LDL-Cholesterol level at or above drug treatment thresholds established by NCEP ATP III after a four week placebo/diet run-in period. The relevant NCEP ATP III thresholds are as follows:- Established CHD or CHD risk equivalent with an LDL-C> 130 mg/dL (3.36 mmol/L); No established CHD or CHD risk equivalent, with >2 risk factors conferring a 10 year risk for CHD of between 10 and 20% with an LDL-C level > 130 mg/dL NO established CHD or CHD risk equivalent with >2 risk factors conferring a 10 year risk for CHD < 10% with an LDL-C>160 mg/dL No established CHD or CHD risk equivalent with < 2 risk factors and LDL-C level > 190mg/dL.	Fasting serum triglyceride level ≥350mg/dL ALT, AST or CK levels more than 1.5 times ULN. Serum creatinine level ≥ 1.5 mg/dL Haemoglobin A1c≥9.0% in patients with diabetes.	*No selection criterion for uncontrolled hyperolesterolaemia while on the maximum dose of SIM was included* Secondary prevention population met the GSLLD criteria for high risk. Primary prevention population was identified a) at a 10 year risk for CHD of between 10 and 20% with an LDL-C level > 130 mg/dL (3.36 mmol/L); - overlaps with the definition of high risk population in NVDPA-2012 (except not necessarily at a 5 year risk); b) at a 10 year risk for CHD < 10% corresponds to the low level of risk in NVDPA-2012 classification, but may meet the GSLLD criteria depending on the nature of 2 risk factors. *Population in the RCT is overlapping with the target population for the review*
Protocol 693 Stein 2004 Atorvastatin Filter	A 14 week DB RCT where eligible subjects continued to receive atorvastatin (10 mg) and were	Adult subjects with Heterozygous Familial Hypercholesterolemia, or	N/A	*Uncontrolled hyperolesterolaemia while on ATOR 10, not necessarily the maximum dose of SIM.* Secondary prevention population met the GSLLD

Study Mixed prevention population, second line therapy, dose-response titration	randomized to receive blinded treatment with ezetimibe (10 mg/day; or an additional 10 mg/day of atorvastatin. The atorvastatin dose in both groups was doubled after 4 weeks, 9 weeks, or both when the LDL-C level was not at its goal <2.6 mmol/L, so that patients receiving combined therapy could reach 40 mg/day and patients receiving atorvastatin alone could reach 80 mg/day.	Coronary Heart Disease, or multiple cardiovascular risk factors (greater than or equal to 2) and primary hypercholesterolemia Plasma LDL-C greater than or equal to 3.37 mmol/L (130 mg/dl) and plasma triglycerides less than or equal to 3.99 mmol/L (350 mg/dl) while on a starting dose of atorvastatin 10 mg and diet for at least four weeks		criteria for high risk. Population was selected according to the NCEP ATP III thresholds. Participants were adults with heterozygous familial hypercholesterolemia (HeFH), CHD, or multiple (≥2) cardiovascular risk factors, and a LDL-C level ≥ 130 mg/dL (3.36 mmol/L); after a 6- to 10-week dietary stabilization and atorvastatin (10 mg/day) open-label run-in period. *Population in the RCT is overlapping with the target population for the review*
McKenney 2007 COMPELL Open label trial Mixed prevention population, first line therapy	Open-label, multicenter, 12-week study in patients (50% women) who qualified for drug therapy based on number of CHD risk factors. Patients were randomized to four parallel arms, titrated from low to moderate or high doses: atorvastatin/niacin ER, rosuvastatin/niacin ER, simvastatin/ezetimibe, or rosuvastatin alone. Only the relative results from the study arms that received in a first line treatment EZ+SIM 20 or ROSUV20 were used for the review	Men and women, aged 21 years or older The mean of the two consecutive determinations of LDL-C, following a minimum of 4 weeks drug washout period had to be ≥ 4.9 mmol/L for patients with 0-1 risk factors, ≥ 4.1 mmol/L for those with two or more risk factors or ≥3.4 mmol/L for patients with established CHD The two qualifying lipid determinations could not differ by more than 15% from each other Mean triglycerides were required to be ≤ 3.4 mmol/L	Major organ system disease Severe hypertension Diabetes Major CV event within the previous 12 months Severe heart failure History of myopathy Active gout Expected life expectancy <2 years Baseline creatine kinase > 3 times the ULN Liver transaminases > 1.3 times the ULN Creatinine ≥ 1.5 mg/dL Estimated creatinine clearance <30 ml/min Uric acid >1.3 times ULN Concomitant medications known to increase the risk of myopathy were excluded as were other lipid modifying drugs	Patients were eligible for treatment based on the NCEP III guidelines; Secondary prevention population met the GSLLD criteria for high risk. Low and moderate risk population according to NCEP III guidelines may not be eligible for subsidised statin treatment according to GSLLD criteria. *Population in the RCT, especially in the high risk end, is overlapping with the target population for the review, however the trial results (effect size) do not apply to the second line treatment population*
Fixed dose of statin +ezetimibe vs up-titrating of statin either in terms of dose or in terms of potency				
P090 Leiter 2008 ATOR 40 (run in) ATOR 80 or EZ + ATOR 40 Mixed prevention population Second line treatment	In this double-blind, parallel-group study, adult hypercholesterolemic patients using atorvastatin 40 mg/day during the run-in period were randomly assigned to atorvastatin 40 mg plus ezetimibe 10 mg or uptitration to atorvastatin 80 mg.	Subjects were men and women with hypercholesterolemia aged >18 and < 80 years. LDL cholesterol >1.8 mmol/L and ≤4.1 mmol/L at baseline; triglycerides ≤350 mg/dl, hemoglobin A1c <8.5%, liver transaminases (alanine aminotransferase and aspartate ami-notransferase) ≤1.5 times the ULN with no active liver disease, and creatinine kinase ≤2 times the ULN. High risk patients based on the NCEP III criteria included patients with CHD/CHD risk equivalent, including those who had ≥2 risk factors that conferred a 10-year risk of CHD > 20%,	Patients were excluded if they were using any lipid-lowering agents except those of equal or lower potency to atorvastatin 40 mg within 6 weeks or fibrates within 8 weeks of screening. Subjects using prescription and/or over-the-counter drugs with the potential for significant lipid effects (other than study drug) or with potential drug interactions with statins were also excluded from the study.	*Although uncontrolled (i.e not achieving the target of <2.6 mmol/L) hyperolesterolaemia needed to be established after ATOR 40 mg run-in, ATOR 40 is not neccessarily the maximum tolearted dose of statin.* *It is not clear what proportion of the RCT population would meet the GSLLD criteria for high risk, the population is overlapping with the target population for the review,*

		determined using the Framingham calculation.		
Teramoto 2012 ATOR 10 (run in) ATOR 20 or EZ + ATOR 10 Primary prevention first line treatment	An open-label, randomized, 3-parallel-group comparison tria in patients with high LDL cholesterol that had not reached the lipid management target value after 4 weeks on 10 mg atorvastatin monotherapy	Patients aged > 20 if their LDL cholesterol levels had not reached the lipid management target value in accordance with the Guidelines for Prevention of Atherosclerotic Diseases, and were treated with 10 mg atorvastatin for 4 weeks or longer before the start of the 4-week washout period. The patients were excluded from further analysis When the LDL cholesterol level measured at 4 weeks after the start of the atorvastatin 10 mg treatment period reached the lipid management target value; • When AST or ALT showed a value of ≥ 3 times the upper limit of the reference values on 2 consecutive measurements; and • When CPK showed a value exceeding 10 times the upper limit of the reference values and was accompanied by muscle symptoms (pain, tenderness, or weakness).	(1) a triglyceride level measured at the start of the washout period or the treatment period exceeding 400 mg/dL; (2) homozygous familial hypercholesterolemia; (3) creatine phosphokinase >2 times the ULN and/or glyco-sylated hemoglobin (HbA1c) > 8% measured at the start of the washout period or the treatment period; (4) severe hepatic function disorder or aspartate aminotransaminase or alanine aminotransferase >2 times the ULN measured at the start of the washout period or the treatment period; (5) a history of hypersensitivity to any of the ingredients in the ezetimibe tablets, atorvastatin calcium hydrate tablets; (6) discontinued use of 10 mg atorvastatin for<4 weeks at the start of the treatment period; (7) use of cyclosporine after the start of the washout period;	The relatively low risk population who did not achieve the targets according to the Guidelines for Prevention of Atherosclerotic Diseases *It is not clear what proportion of RCT population met the GSLLD criteria for high risk, the population is overlapping with the target population for the review, however the trial results (effect size) do not apply to the second line treatment population*
Protocol 079 Conard 2008 ATOR 20 (run in) ATOR 40 or EZ + ATOR 20 Primary prevention population, second line treatment	The aim of this study was to evaluate the efficacy and safety of ezetimibe 10 mg added toatorvastatin 20 mg compared with doubling atorvastatin to 40 mg in patients with hyper-cholesterolemia at moderately high risk for coronary heart disease who did not reach low-density lipoprotein (LDL) cholesterol levels <2.6 mmol/L with atorvastatin 20 mg. All patients received at least 4 weeks of A20 if previously on A20, and at least 5 weeks if statin naïve	Men and women aged 18 - 79 years with hypercholesterolaemia and moderately high risk for coronary heart disease (CHD). Patients with LDL > 2.5 mmol/L and < 4.1 mmol/L and on a stable dose of A20 and triglyceride levels less than or equal to 4 mmol/L were eligible for randomisation as they were defined as uncontrolled, since they did not reach their guideline LDL-C target of < 2.5 mmol/L while on ATOR 20 statin therapy.	Pregnant or lactating women or intending to become pregnant. Patients with insensitivity or intolerance to ezetimibe or atorvastatin. Patients with diabetes mellitus or coronary heart disease. High to very high risk patients particularly with diabetes mellitus and specific cardiovascular conditions were excluded.	Of the 196 patients randomised in the study, 190 (97%) had at least two CHD risk factors that conferred a 10-year risk for CHD of 10-20%. These patients are therefore classified as being at moderately high risk, which is a lower risk than most of the patients eligible for treatment according to the General Statement for Lipid Lowering Drugs for PBS subsidy. Ninety percent of these patients had hypertension, approximately one third of them were obese (i.e. BMI ≥ 30 kg/m2) and approximately one third had a fasting blood glucose level of ≥ 5.56 mmol/L. *It is not clear what proportion of RCT population met the GSLLD criteria or EZ eligibility criteria the population is overlapping with the target population for the review,*
Pesaro 2013 SIM 20 (run in) SIM 80 Secondary	Randomised controlled trial in high risk patients compared EZ + SIM 20 with SIM 80 over 6 weeks.	Patients aged between 18 and 80 years with stable coronary artery disease (CAD) documented by angio-graphically CAD defined as a coronary obstruction >50%, stable or no angina who received simvastatin treatment (20 mg/d) for	History of myocardial infarction or revascularization in the last 3 months, moderate/ severe left ventricular systolic dysfunction (ejection fraction <45%), warfarin treatment, malignancy, inflammatory diseases, creatinine	Mean baseline (i.e after SIM 20 run in) mean LDL-C values were about 2.7 mmol/L. *It is not clear what proportion of RCT population met the GSLLD criteria or EZ eligibility after run-in period*

prevention population, second line treatment		>4weeks, and had LDL-C >70 mg/dL (1.8 mmol/L).	>1.5 mg/d, active liver disease or known liver cirrhosis, and unexplained transaminase increase (>3-fold of normal).	*on SIM 20 therapy, the population is overlapping with the target population for the review,*
Protocol 021 Gaudiani 2005 subgroup T2D population, SIM 20 (run in) SIM 40 or EZ + SIM 20 mixed prevention secondary line treatment	A randomized, double-blind, parallel group, trial in T2DM patients, 30–75 years of age, who had been on a stable dose of a thiazolidinediones (TZD) for at least 3months and had LDL-C >2.6mmol/l (100 mg/dl) prior to study entry. Following 6 weeks of open-label simvastatin 20mg/ day, patients were randomized to the addition of either blinded ezetimibe 10mg/day or an additional blinded simvastatin 20mg/day (total simvastatin 40 mg/day) for 24 weeks.	Males and females age ≥30 and ≤75 Subjects with Type 2 Diabetes Subjects who took pioglitazone (15 to 45 mg/day) or rosiglitazone (2 to 8 mg/day) as monotherapy or in combination with other antidiabetic medications including insulin in accordance with TZD labels (at a stable dose for at least 3 months prior to entry) HbA1C ≤ 9.0% Plasma TG <6.8 mmmol/L LDL-C > 2.6 mg/dL prior to initiation of statin therapy ALT and AST ≤ 30% above ULN with no active liver disease, and CPK ≤ 50% above the ULN in the absence of an obvious non-pathological etiology for the CPK elevation Alcohol consumption typically ≤ 7 drinks/week Females surgically sterilised or highly unlikely to conceive	A diagnosis of Type I or Type V hyperlipidemia, or homozygous familial hypercholeterolemia A history of hyperlipidemic pancreatitis Subjects with atherosclerotic disease taking a daily statin dose greater than 40mg simvastatin Myocardial infarction, percutaneous coronary angioplasty, stent insertion, coronary bypass surgery, or stroke within 3 months prior to entry Bile acid sequestrants, fish oil, fibrates, nicotinic acid, and red yeast extract taken within 6 weeks. Subjects with fasting plasma C-peptide ≤ 0.5ng/mL at entry Subjects treated with sliding scale insulin Renal insufficiency as measured by serum creatinine > 1.8 mg/dL at entry Active liver disease Secondary hypercholesterolemia due to hypothyroidism or nephrotic syndrome Subjects with known Type 1 Diabetes Mellitus Females receiving cycical sex hormones Partial ileal bypass Subjects taking warfarin or warfarin-like anticoagulants	A second line treatment in patients who inadequately controlled on SIM 20 6 week run in therapy according to NCEP III guidelines; *The patients were not necessarily meeting GSLLD eligibility criteria, and unlikely meeting the PBS criteria for EZ treatment.. Not a target population for the review.*
P112 Zieve 2010 ATOR 10 (run-in dose) ATOR 20 then ATOR 40 or EZ + ATOR 20 Mixed prevention population, Second line treatment	After stabilization of atorvastatin 10-mg therapy, patients with LDL cholesterol level below a target level, were randomized to receive ezetimibe added to atorvastatin 10 mg for 12 weeks versus up titration to atorvastatin 20 mg for 6 weeks followed by up titration to atorvastatin 40mg for an additional 6 weeks.	Established coronary heart disease and other AVD and LDL cholesterol >1.8 mmol/L but <4.1 mmol/L no AVD but diabetes mellitus (type 1 or 2) or multiple risk factors and a 10-year risk of coronary heart disease of > 20% (as determined by the Framingham calculation) and LDL cholesterol >2.6 mmol/L but <4.9 mmol/L; triglycerides <350 mg/dl, alanine aminotransferase and aspartate aminotransferase ≤1.5 times the ULN with no active liver disease, creatine kinase ≤2 times the ULN, thyroid-stimulating hormone ≥0.3 or ≤5.0 IU/ ml, and hemoglobin A1c <8.5%. Patients >65 years old, at high risk of coronary heart disease, with and without atherosclerotic vascular disease and a LDL cholesterol level that was not <70 mg/dl (1.8 mmol/L) or <100 mg/dl (2.6	Patients were excluded from the study if they had uncontrolled hypertension (systolic blood pressure >160 mm Hg or diastolic blood pres-sure >100 mm Hg) or impaired renal function (creatinine ≥2.0 mg/day or a history of nephrotic range proteinuria), were taking lipid-lowering agents (except for simvastatin 10, 20, or 40 mg; atorvastatin 20 mg; pravastatin 10, 20, or 40 mg; fluvastatin 20, 40, or 80 mg; ezetimibe 10 mg; lovastatin 10, 20, or 40 mg; or rosuvastatin 5 mg) within 6 weeks or fibrates within 8 weeks of screening taking prescription and/or over-the-counter drugs with potential drug interactions with statins within 6 weeks of the study start.	*High risk population met the GSLLD criteria,* *The RCT population overlaps with the target population at the baseline, It is not clear what proportion of RCT population met EZ eligibility criteria; the population is overlapping with the target population for the review,*

		mmol/L), respectively after ATOR 10 run-in period		
Protocol 700 **Dobs 2003** SIM 20 (run in) SIM 40 or EZ + SIM 20 Dose-response titration Mixed prevention population; first line treatment	Following dietary stabilization, a 6-10 week drug washout, and open-label SIM 20 mg/d run-in, 100 patlents with baseline LDL-C ≥ 3.37 mmol/L and TG 450 mg/dL while on SIM 20 mg were randomized to EZE 10 mg or additional double-blind SIM 20 mg. SIM dose was doubled after 4 or 9 weeks if LDL-C was still ≥ 2.6 mmol/L (maximum of 80 mg with SIM alone and 40 mg with EZE+SIM).	Adult subjects with Heterozygous Familial Hypercholesterolemia, or Coronary Heart Disease, or multiple cardiovascular risk factors (greater than or equal to two) and primary hypercholesterolemia Plasma LDL-C greater than or equal to 3.37 mmol/L (130 mg/dl) and plasma triglycerides less than or equal to 3.99 mmol/L (350 mg/dl) while on a starting dose of simvastatin 20 mg and diet for at least four weeks	Not specified	*High risk population. An unknown proportion of RCT population would meet the GSLLD and the PBS RCT population overlaps with the target population.*
Lee 2013 subgroup T2D population ATOR 20 vs EZ + SIM 20 Primary prevention first line of treatment	An open-label, randomized, controlled 12 week study in Type 2 diabetes patients with high levels of LDL cholesterol (> 2.6 mmol/L) were randomized to receive ezetimibe/simvastatin 10/20 mg versus atorvastatin 20 mg once daily after 4 weeks wash-out period..	Men or women aged between 20 and 80 years who had been diagnosed with type 2 diabetes glycosylated hemoglobin (HbA1c) <8.5% and had been on stable oral hypoglycemic therapy for at least 3 months] and hypercholesterolemia (LDL cholesterol > 2.6 mmol/L).	A history of hyper-sensitivity to ezetimibe or statins, chronic renal failure (serum creatinine concentration [3.0 mg/dL); hepatic dysfunction [alanine aminotransferase (ALT) or aspartate aminotransferase (AST) levels C3 times the ULN]; an unexplained serum creatinine kinase (CK) elevation [2.5 times the ULN; congestive heart failure; stroke, myocardial infarction, or coronary revascularization within the preceding 3 months; uncontrolled thyroid disease; medical conditions that require drugs that were expected to have significant drug interactions with ezetimibe or statins, co-morbid conditions with life expectancy of <1 year, pregnant or breastfeeding women.	Low to medium risk population. No T2D –specific eligibility criteria for lipid-lowering drugs was used as a selection criteria. *It is not clear what proportion of RCT population met the GSLLD criteria for statin treatment. Study population overlaps with the target population for the review, however the trial results (effect size) do not apply to the second line treatment population as in the PBS restrictions.*
Protocol 807 **Constance 2007** subgroup T2D population ATOR 10 (run-in dose) ATOR 20 vs EZ + SIM 20 or EZ + SIM 40 Mixed prevention second line of treatment	A randomized, double-blind study evaluated the efficacy of switching from atorvastatin (ATV) 10 mg to ezetimibe/simvastatin (EZE/SIMVA) 10/20 mg, EZE/SIMVA 10/40 mg or doubling the dose of ATV from 10 to 20 mg in patients with type 2 diabetes (T2D).	Men and women greater than 18 years of age, diagnosed with Type 2 Diabetes with HbA1c ≤ 10%, ALT and/or AST levels ≤ 1.5 times the ULN and CK levels ≤ 1.5 times the ULN Patients were on Atorvastatin 10mg for >6 weeks prior to study entry and complete a 4 week, open label Atorva 10mg/day run-in baseline period Women of childbearing age were included if they had a negative pregnancy test and were considered highly unlikely to conceive.	CHF, MI, CABS or angioplasty within 3 months, uncontrolled hypertension, uncontrolled endocrine or metabolic disease known to influence serum lipids or lipoproteins, impaired renal function (creatinine ≥ 177 µmol/l), or nephrotic syndrome Alcohol consumption >14 drinks per week and treatment with excluded concomitant medications (immunosuppressants, corticosteroids, or potent inhibitors of cytochrome P450 3A4)	A second line treatment therapy in patients who were not necessarily inadequately controlled on the ATOR 10 run-in therapy (mean LDL-C at randomisation was 2.4-2.5 mmol/L) *It is not clear what proportion of RCT population met the GSLLD criteria for statin treatment or the PBS eligibility criteria for EZ treatment. Study population overlaps with the target population for the review.*

Cho 2011 ATOR 20 vs EZ + SIM 20 Secondary prevention population, first line treatment	The aim of this randomized, open-label study is to compare the effect of ezetimibe/simvastatin 10/20 mg and atorvastatin 20 mg on achieving a target LDL-C goal in very high risk patients.	Patients with coronary artery disease and documented hypercholesterolemia (LDL-C >1.8 mmol/L and ≤6.5 mmol/L) at screening were enrolled. Patients were 20 to 79 years of age. Very high risk patients were defined as those with the presence of established cardiovascular disease plus 1) multiple major risk factors (especially diabetes), 2) poorly controlled risk factors {especially continued cigarette smoking, uncontrolled blood pressur and low high density lipoprotein-cholesterol (HDL-C)}, 3) multiple risk factors of the metabolic syndrome {especially high triglycerides (TG) ≥200 mg/dL plus non HDL-C ≥130 mg/dL with low HDL-C (<40 mg/dL), impaired fasting glucose and central obesity} and 4) patients with acute coronary syndromes (ACS).	Exclusion criteria included conditions or medications that could have affected lipid levels, such as patients with congestive heart failure defined by the New York Heart Association class III or IV, as well as patients with poorly controlled hypertension (systolic blood pressure >180 mmHg or diastolic blood pressure >100 mmHg), evidence of uncontrolled endocrine or metabolic disease known to influence serum lipid profile, and concomitant excluded drug use (i.e. immunosuppressants, corticosteroids, or potent inhibitors of cytochrome P450 3A4).	Very high risk patients *would have met the GSLLD criteria for statin treatment. Study population overlaps with the target population for the review, however the trial results (effect size) do not apply to the second line treatment population as in the PBS restrictions.*
Protocol 806 **Barrios 2005** ATOR 10 (run-in dose) ATOR 20 vs EZ + SIM 20 Secondary prevention population, second line treatment	This randomised, double-blind study evaluated the efficacy and safety of ezetimibe/simvastatin (EZ+SIM 20 tablet compared to doubling the atorvastatin dose in hypercholesterolaemic patients with atherosclerotic or coronary heart disease (CHD) who had not achieved their LDL-C goal of <2.50 mmol/l while on a stable dose of ATV 10 mg for ≥ 6 weeks.	Men and women greater than 18 years of age with documented hypercholesterolemia and atherosclerotic or CHD Serum LDL-C between 2.5 mmol/L and 4.2 mmol/L while on a stable dose of Atorva 10mg for ≥ 6 weeks prior to randomisation Patients of childbearing age were eligible if they had a negative pregnancy test or considered by the investigator to be highly unlikely to conceive	CHF, MI, CABS, or angioplasty within the past 3 months, poorly controlled or newly diagnosed Type I or II diabetes; uncontrolled hypertension, uncontrolled endocrine or metabolic disease known to influence serum lipids; ALT and AST levels >1.5 times the ULN and CK levels >1.5 times ULN	Very high risk patients *would have met the GSLLD criteria for statin treatment prior to randomisation. It is not clear what proportion of RCT population met the PBS eligibility criteria for EZ. Study population overlaps with the target population for the review.*
P809 Farnier 2009 Run-in on background medication ROSU 10 vs EZ + SIM 20 Mixed prevention population, second line treatment	Randomised, double-blind study, in patients with documented hypercholesterolaemia (LDL-C ≥2.59 and ≤ 4.92 mmol/l) and with high cardiovascular risk who were taking a stable daily dose of one of several statin medications for ≥6 weeks prior to the study randomisation visit entered a 6-week open-label stabilisation/screening period during which they continued to receive their prestudy statin dose. patients were then randomised to EZ + SIM 20 mg or ROSUV 10 mg for 6 weeks	Patients at high cardiovascular risk if they met one or more of the following criteria: (i) history of CHD (i.e. stable and unstable angina, revascularisation procedure, myocar dial infarction, documented silent myocardial ischaemia), or with established vascular atherosclerotic disease (i.e. peripheral vascular disease, ischaemic stroke); (ii) type 2 diabetes without a history of vascular disease and with high cardiovascular risk {i.e. renal impairment [proteinuria > 300 mg/24 h or creatinine clearance (standardised for body surface area) < 1.002 ml/s] and/or at least two CHD risk factors }; (iii) CHD risk > 20% over 10 years as determined by the Framingham risk calculation. Fasting TG levels had to be ≤3.96 mmol/l at week–one before randomisation.	conditions or medications, that could have affected lipid levels; alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels > 1.5 ULN; active liver disease; creatine kinase (CK) levels > 3 · ULN; patients with congestive heart failure defined by New York Heart Association Class III or IV; patients with poorly controlled [haemoglobin A1c (HbA1c) > 8.5%] diabetes; uncontrolled hypertension (systolic > 160 mmHg or diastolic >100 mmHg); impaired renal function (creatinine >176.8 lmol/l) or history of nephrotic range proteinuria; partial ileal bypass surgery or other significant intestinal malabsorption; positive pregnancy test for female patients of child-bearing potential; and treatment with excluded concomitant meds.	Very high risk patients *would have met the GSLLD criteria for statin treatment prior to randomisation. It is not clear what proportion of RCT population met the PBS eligibility criteria for EZ treatment.* *Study population overlaps with the target population for the review.*

Protocol 051 **Ballantyne 2005** A dose-comparison study EZ+SIM (10,20,40, 80mg) vs ATOR (10,20,40, 80mg) Mixed population first line treatment	A double-blind, (10 weeks, with 4-week placebo/diet run-in period followed by 6 weeks of active treatment) parallel-group study RCT in patients with LDL-C above ATP III goal randomised to atorvastatin (10, 20, 40, or 80 mg) or to ezetimibe/simvastatin (10/10, 10/20, 10/40, or 10/80 mg).	Males or females age ≥18 and ≤79 LDL-C levels ≥ NCEP adult treatment threshold Patients with CHD or CHD risk equivalent or have +2 risk factors that confer a 10-year risk for CHD >20%, LDL-C ≥3.4 mmol/L Patients without CHD or CHD risk equivalent with ≥2 risk factors that confer a 10-year risk for CHD of 10-20%, LDL-C ≥3.4 mmol/L Patients without CHD or CHD risk equivalent with + 2 risk factors that confer a 10-year risk for CHD of < 10%, LDL-C ≥4.1 mmol/L Patients without CHD or CHD risk equivalent with < risk factors, LDL-C ≥4.9 mmol/L TG ≤4.0 mmol/L ALT, AST ≤ 1.5 ULN with no active liver disease Women of childbearing age were included if they were considered unlikely to conceive due to use of a medically approved method of contraception or surgical sterilisation. Women on a stable HRT regimen as long as this was maintained throughout the study	Weight < 45kg Hypersensitivity to HMG-CoA reductase inhibitors Patients already on lipid lowering therapy Women pregnant or lactating Congestive heart failure defined by the new York Heart Association (Class III or IV) Myocardial infarction, coronary artery bypass surgery or angioplasty within 3 months prior to Week-4 of the study; Uncontrolled cardiac arrhythmia; Unstable angina pectoris Partial ileal bypass; Uncontrolled endocrine or metabolic disease known to influence serum lipids; Type 1 or 2 Diabetes that is poorly controlled (HbA1C >9%) or newly diagnosed, or change in antidiabetic therapy within 3 months of screening; Disorders of the hematologic, digestive or central nervous systems Patients positive for HIV; Uncontrolled hypertension (treated or untreated) with systolic blood pressure typically >160 mm Hg or diastolic >100 mm Hg; Patients taking drugs that are potent cytochrome P450 3A4 inhibitors. Patients on amiodarone hydrochloride or verapamil. Bile acid sequestrants, fish oil, nicotinic acid, and red yeast extract taken within 6 weeks prior to Week-1 or fibrates within 8 weeks prior to Week-1	High and very high risk population *would have met the GSLLD criteria for statin treatment prior to randomisation. It is not clear what proportion of RCT population met the PBS eligibility criteria for EZ treatment after run-in period on background medication.* *Study population overlaps with the target population for the review, however the trial results (effect size) do not apply to the second line treatment population as in the PBS restrictions.*
Protocol 077 **Goldberg 2006** **VYTAL** subgroup T2D population ATOR 20 or ATOR 40 vs EZ + SIM 20 Mixed prevention first line treatment	A double-blind RCT consisted of adult patients who after wash out period of 3-5 weeks and placebo run-in period of 4 weeks were randomized to the recommended usual starting (ezetimibe/simvastatin, 10/20 mg/d, vs atorvastatin, 10 or 20 mg/d) or next highest (ezetimibe/simvastatin, 10/40 mg/d, vs atorvastatin, 40 mg/d) doses.	Men and women greater than 18 years of age with a confirmed diagnosis of Type 2 diabetes. Patients discontinued fibrates 8 weeks prior and discontinued other lipid-lowering therapies 6 weeks prior to study Patients were required to have LDL-C ≥ 2.6 mmol/L and TG ≤ 4.5 mmol./L	Patients with CHF, uncontrolled cardiac arrhythmias, uncontrolled hypertension, and MI or CABS within 3 months of study entry Type 1 diabetes Poorly controlled type 2 diabetes Serious hematologic, digestive or central nervous system disorders	*It is not clear what proportion of RCT population met the GSLLD criteria for statin treatment or the PBS eligibility criteria for EZ treatment. Study population overlaps with the target population for the review. However the trial results (effect size) do not apply to the second line treatment population as in the PBS restrictions*
Protocol 058 **Catapano 2006** ROSUV 10, 20, 40 vs EZ+SIM 20	A double-blind, 10 weeks (4-week placebo/diet run-in period, followed by 6 weeks of active treatment) parallel-group RCT in	Men and women greater than 18 years of age with primary hypercholesterolemia Willing to follow a low cholesterol diet during the run in period and the study Baseline LDL-Cholesterol levels of >3.3 mmol/L	Congestive heart failure defined by the new York Heart Association (Class III or IV) Myocardial infarction, coronary artery bypass surgery or angioplasty within 3 months prior to Week-4 of the study; Uncontrolled cardiac	*It is not clear what proportion of high to low risk RCT population would have met the GSLLD criteria for statin treatment or the PBS eligibility criteria for EZ treatment. Study population overlaps with the target*

Primary prevention population first line treatment	hypercholesterolemic patients randomized based on stratification LDL-C levels to ezetimibe/simvastatin or rosuvastatin, respectively, at the usual starting (10/20 or 10 mg/day), the next highest (10/40 or 20 mg/day), and maximum doses (10/80 or 40 mg/day).	and <6.40mmol/L and triglycerides <3.96 mmol/L during placebo run in period Women of childbearing age were included if they were considered unlikely to conceive due to use of a medically approved method of contraception or surgical sterilisation. Postmenopausal women on a stable HRT regimen as long as this was maintained throughout the study; Hepatic transaminases and creatine kinase < 1.5 x ULN; HbA1c<9% in patients with diabetes	arrhythmia; Unstable angina pectoris Partial ileal bypass Unstable or severe peripheral artery disease within 3 months prior to Week-4 of the study; Uncontrolled hypertension (treated or untreated) with systolic blood pressure typically >160 mm Hg or diastolic >100 mm Hg Impaired renal function (creatinine ≥ 2.0 mg/dL) or nephritic syndrome at week -4 of the study Women pregnant or lactating Type 1 or Type 2 diabetes where HbA1C >9% Patients taking drugs that are potent cytochrome P450 3A4 inhibitors. Bile acid sequestrants, fish oil, nicotinic acid, and red yeast extract taken within 6 weeks prior to Week-1 or fibrates within 8 weeks prior to Week-1; Treatment with psyllium, other fibre based laxatives, orlistat, and/or other OTC therapies known to affect serum lipids; phytosterol margarines. Warfarin therapy accompanied by unstable INR within 4 weeks prior to week -1.	*population for the review. However the trial results (effect size) do not apply to the second line treatment population as in the PBS restrictions*
Garcia 2016 SIM 80 vs EZ + SIM 10 Primary prevention, first line therapy	Randomized 8 weeks clinical trial with two groups of lipid-lowering and one placebo group. The two active groups were designed to promote a similar degree of reduction in LDL-c the first used statin at a high dose (80 mg, simvastatin 80 group) and the second used statin at a low dose (10 mg) associated with ezetimibe (10 mg, simvastatin 10/ezetimibe group) to optimize the hypolipidemic effect.	Statin naïve women attending the clinic were consecutively selected based on the following inclusion criteria: age above 18 years, body mass index (BMI) > 25 kg/m², and LDL-cholesterol > 100 mg/dL (2.6 mmol/L).	Use of statin, ezetimibe, fibrate, or hormone replacement therapy within the previous 3 months; triglyceride level > 400 mg/dL; serum creatinine above 2.0 mg/dL; hepatic enzymes levels at least 1.5 times above ULN; serum creatine kinase (CPK) level higher than three times the ULN; pregnancy or lactation; and occurrence of cardiac insufficiency, collagenosis, acute inflammatory conditions, or psychiatric disease. patients who had started beta-blockers, angiotensin-conversion inhibitors, or calcium-channel blockers within the prior 4 weeks and those with a brachial artery diameter below 2.5 mm	Small size, likely underpowered trial in low- to medium risk with fairly high LDL-c at the baseline (3.4 – 3.8 mmol/L). *It is not clear what proportion of RCT population would meet GSLLD at baseline. Study population overlaps with the target population for the review. However the trial results (effect size) do not apply to the second line treatment population as in the PBS restrictions.*
Ostad 2009 ATOR 80 vs EZ + ATOR 10 Secondary prevention	Patients with coronary artery disease (CAD)were randomly assigned to double-blind treatment for 8 weeks with atorvastatin 80mg per day (A80) or atorvastatin 10mg+ezetimibe 10mg per day (A10E10), respectively. Flow-mediated vasodilation (FMD) of the	Statin and ezetimibe-naïve patients with CAD (defined as at least one coronary stenosis >50% or general wall irregularities), an LDL-cholesterol of >2.6mmol/L and endothelial dysfunction of the brachial artery (defined as flow-mediated dilation <6%) were included in the study.	The most relevant exclusion criteria were the presence of an acute coronary syndrome, pre-treatment with ezetimibe, statins, fibrates or colestipol within the previous 3 months, initiation of ACE inhibitor-, AT1-receptorblocker- or calcium channel blocker therapy within the previous 4weeks, serum creatinine >2.0 mg/dl, elevated liver enzymes >1.5 times the upper	Small size trial in very high risk patients who *would have met the GSLLD criteria for statin treatment prior to randomisation. It is not clear what proportion of RCT population met the PBS eligibility criteria for EZ treatment*. *Study population overlaps with the target population for the review. However the trial results (effect size)*

population **first** line treatment	brachial artery, nitroglycerin-mediated endothelium-independent vasodilation (NMD), lipid, C-reactive protein (CRP) plasma concentrations and urinary 8-iso-prostaglandin F2alpha excretion were measured before and after treatment.		normal limit, elevated creatine kinase >3 times upper normal limit or overt heart failure with an left ventricular ejection fraction of <30%.	*do not apply to the second line treatment population as in the PBS restrictions.*
McCormack 2010 IN-PRACTICE SIM 40 run-in ATOR 40 ROSUV 5 or 10 vs EZ + SIM 40 Secondary prevention population **second** line treatment	a prospective, double-blind study in patients with established CVD, diabetes or high risk of CVD who had been taking simvastatin 40 mg for ≥6 weeks were screened and those with fasting LDL-C ≥2.0 mmol/l (and < 4.2 mmol/l) at screening and after a further 6-week run-in period on simvastatin 40 mg were randomised to ezetimibe/simvastatin 10/40 mg, atorvastatin 40 mg or rosuvastatin 5 or 10 mg once daily for 6 weeks.	Patients eligible for inclusion were > 18 years of age, had established CVD or diabetes, or were at high risk of CVD (> 20% 10- year risk according to the Framingham scale), and had been taking simvastatin 40 mg for at least 6 weeks. Patients had to have a fasting LDL-C level between 2.0 and 4.2 mmol/l (77 and 162 mg/dl) at screening (visit 1) and at the end of the 6-week simvastatin 40 mg run-in period (visit 2). Patients also had to have a fasting triglyceride level < 3.7 mmol/l (< 328 mg/dl) and, for those with diabetes, haemoglobin A1C ≤ 9% at visit 1, and show≥75% compliance with simvastatin medication (assessed by tablet count) during the run-in period	known hypersensitivity to study medications, a history of liver disease, severe renal impairment (estimated creatinine clearance < 30 ml/min), uncontrolled endocrine or metabolic disease known to affect serum lipids or lipoproteins, previous or current alcohol abuse, elevated creatine kinase (> 10· upper limit of normal). Female patients were also excluded if they were pregnant, breastfeeding or not using adequate contraception	High risk patients with established CVD, diabetes or high risk of CVD and *would have met the GSLLD criteria for statin treatment prior to randomisation. it is not clear what proportion of RCT population met the PBS eligibility criteria for EZ treatment if the dose of statin would be up-tirated even further* *Study population overlaps with the target population for the review.*
Fixed dose statin +ezetimibe vs matching fixed dose of statin				
Protocol 692 Ballantyne 2003 Atorvastatin Factorial Study ATOR (10, 20, 40, 80) or EZ + ATOR (10, 20, 40, 80) Primary prevention first line therapy	Patients enrolled in this RCT had a 2 to 12 week screening phase which included washout of previous lipid lowering therapies and dietary advise. Patients were then randomised to one of ten treatments: placebo, EZ, ATOR (10, 20, 40 or 80mg strengths) or EZ co-administered with ATOR (10, 20, 40, or 80mg). Patients were followed up for 12 weeks.	Male and female adult subjects (18 years or more) Subjects with primary hypercholesterolemia defined as calculated LDL-C ≥ 3.75 mmol/L and ≤6.48 mmol/L and TG ≤ 3.99 mmol/L. Willing to follow NCEP Step 1 diet or stricter. Fertile females using adequate contraception during the study. Postmenopausal women on stable HRT or raloxifen regimen	congestive heart failure (defined as New York Heart Association class III or IV heart failure); uncontrolled cardiac arrhythmias; myocardial infarction, coronary bypass surgery, or angioplasty within 6 months of study entry; history of unstable or severe peripheral artery disease within 3 months of study entry; unstable angina pectoris; uncontrolled or newly diagnosed (within 1 month of study entry) diabetes mellitus; unstable endocrine or metabolic diseases known to influence serum lipids and lipoproteins; known impairment of renal function; active or chronic hepatic or hepatobiliary disease; and known coagulopathy	91% of population did not have CHD diagnosis. >70% had one risk factor, and a third of the patients had hypertension. Mean LDL-C at randomisation was 4.53 to 4.6 mmol/L across the arms. *Study population overlaps with the target population for the review. However the trial results (effect size) do not apply to the second line treatment population as in the PBS restrictions.*
Protocol 038 Bays 2004 Simvastatin factorial study	A randomized, multicenter, double-blind, placebo-controlled, factorial design study. After a 6- to 7 week washout period and 4-week, single-blind, placebo run in,	Men or Women ≤80 and ≥18 years old Willing to comply with the NCEP step I or similar diet for the duration of the study Women that are highly unlikely to conceive (i.e. surgically sterilised or using an acceptable method	Individuals were excluded from participating in the study if they met the following criteria: <50% of ideal body weight according to the 1983 Metropolitan Height and Weight tables (or body weight <100 lb), hypersensitivity to	The distribution of patients by the degree of CHD risk was not reported. The mean LDL-C at randomisation was 4.5 to 4.65 mmol/L across the arms. *It is not clear what proportion of RCT population would meet GSLLD at baseline. Study*

SIM (10, 20, 40, 80) or EZ + SIM (10, 20, 40, 80) Primary prevention, first line therapy	hypercholesterolemic patients were randomized equally to 1 of 10 daily treatments for 12 weeks: EZ+SIM 10/10, 10/20, 10/40, or 10/80 mg; SIM 10, 20, 40, or 80 mg; EZ 10 mg; or placebo.	of birth control Patients must have a plasma LDL-C ≥3.7mmol/L but ≤6.4 mmol/L Triglyceride level ≤3.96 mmol/L Liver transaminases (ALT,AST) ≤1.5 x upper limit of normal with no active liver disease and CPK ≤1.5 ULN Female patients who received hormone therapy (including HRT, any oestrogen antagonist/agonist, or oral contraceptives) if maintained on a stable dose and regimen for alt least 8 weeks prior to visit 3 and who were willing to continue the same regimen throughout the study	statins, or alcohol consumption >14 drinks per week. Pregnant or lactating females were also excluded. Patients of childbearing age were eligible to participate in the study if they were surgically sterilized or considered highly unlikely to conceive due to use of an acceptable method of birth control. Patients with stable/controlled cardiovascular disease, hypertension, or diabetes mellitus were also allowed to participate in this study.	*population overlaps with the target population for the review. However the trial results (effect size) do not apply to the second line treatment population as in the PBS restrictions.*
Protocol 068 **Davidson 2002** Simvastatin factorial study SIM (10, 20, 40, 80) or EZ + SIM (10, 20, 40, 80) Primary prevention, first line therapy	A randomized, multicenter, double-blind, placebo-controlled, factorial design study After dietary stabilization, a 2- to 12-week washout period, and a 4-week, single-blind, placebo lead-in period, were randomized to one of the following 10 groups administered daily for 12 consecutive weeks: ezetimibe 10 mg; simvastatin 10, 20, 40, or 80 mg; ezetimibe 10 mg plus simvastatin 10, 20, 40, or 80 mg; or placebo.	Adults 18 years or older Males and females with primary hypercholesterolemia Calculated plasma LDL-C ≥3.75 and ≤6.5 mmol/L Triglycerides<350 mg/dl (3.95mmol/L) Willing to comply with the NCEP Step 1 diet or stricter; Adequate washout of previous lipid lowering medication. Fertile females using adequate contraception during the study Postmenopausal women on stable HRT or raloxifen regimen	Prohibited concomitant illnesses and procedures included congestive heart failure (defined as New York Heart Association class III or IV heart failure) (13); uncontrolled cardiac arrhythmias; history of unstable or severe peripheral artery disease within three months of study entry; unstable angina pectoris; myocardial infarction, coronary bypass surgery, or angioplasty within six months of study entry; uncontrolled or newly diagnosed (within one month of study entry) diabetes mellitus; active or chronic hepatic or hepatobiliary disease; known impairment of renal function; known coagulopathy; and unstable endocrine disease.	Low-to medium risk population with high LDL-c at the baseline. Fifty-five percent of subjects had cardiovascular risk factors or history of cardiovascular disease. Overall approximately 43% of subjects had a known family history of coronary artery disease, 29% had a history of hypertension, 7% had known coronary heart disease and 4% had diabetes mellitus. *It is not clear what proportion of RCT population would meet GSLLD at baseline. Study population overlaps with the target population for the review. However the trial results (effect size) do not apply to the second line treatment population as in the PBS restrictions.*
Protocol 005 **Goldberg 2004** Simvastatin factorial study SIM (10, 20, 40, 80) or EZ + SIM (10, 20, 40, 80) Primary prevention, first line therapy	A randomized, double-blind, placebo-controlled, factorial design study After a 6 to 8-week washout period, and a 4-week, single-blind, placebo lead-in period, were randomized to one 10 groups administered daily for 12 consecutive weeks: ezetimibe 10 mg; simvastatin 10, 20, 40, or 80 mg; ezetimibe 10 mg plus simvastatin 10, 20, 40, or 80 mg; or placebo.	Men or Women ≤80 and ≥18 years old Patients must have a plasma LDL-C ≥3.7mmol/L but ≤6.4 mmol/L; Triglyceride level ≤3.96 mmol/L Women that are highly unlikely to conceive. Alcohol consumption ≤14 drinks per week Liver transaminases (ALT and AST)≤2 times the ULN with no active liver disease and creatine phosphokinase ≤1.5 times the ULN Willing to comply with the NCEP step I or similar diet for the duration of the study	congestive heart failure (defined as New York Heart Association class III or IV heart failure) (13); uncontrolled cardiac arrhythmias; history of unstable or severe peripheral artery disease within three months of study entry; unstable angina pectoris; myocardial infarction, coronary bypass surgery, or angioplasty within six months of study entry; uncontrolled or newly diagnosed (within 3 months of study entry) diabetes mellitus; uncontrolled hypertension	Low- to medium risk population (only 7% of patients had CHD diagnosis) with high LDL-c at the baseline. *It is not clear what proportion of RCT population would meet GSLLD at baseline. Study population overlaps with the target population for the review. However the trial results (effect size) do not apply to the second line treatment population as in the PBS restrictions.*
Kastelein 2008 subgroup of population with heterozygous familial hypercolestero-	A double-blind, randomized, 6 weeks placebo run-in, 24-month trial comparing the effects of daily therapy with 80 mg of simvastatin either with placebo or with 10 mg of ezetimibe in	Patients were enrolled regardless of their previous treatment with lipid-lowering drugs. Un-treated levels of LDL cholesterol had to be 210 mg per deciliter (5.43 mmol per liter) or more. Patients who were receiving lipid-lowering therapy and who	Major exclusion criteria included high-grade stenosis or occlusion of the carotid artery, a his-tory of carotid endarterectomy or carotid stenting, homozygous familial hypercholesterolemia, New	Low- to medium risk population (only 7% of patients had a MI) with high LDL-c at the baseline. *It is not clear what proportion of RCT population would meet GSLLD at baseline. Study population overlaps with the target population for the review.*

laemia (HeFH) SIM 80 vs EZ + SIM 80 Primary prevention, first line therapy	patients with familial hypercholesterolemia	had an LDL cholesterol level of less than 210 mg per deciliter at the time of screening were permitted to undergo randomization if their LDL cholesterol level was 210 mg per deciliter (5.43 mmol per liter) or more after the placebo run-in period.	York Heart Association class III or IV congestive heart failure, cardiac arrhythmia, angina pectoris, or recent cardiovascular events.	*However the trial results (effect size) do not apply to the second line treatment population as in the PBS restrictions.*
Chirinos 2010 subgroup of overweight or obese population SIM 20 vs EZ + SIM 20 Primary prevention, first line therapy	A DB RCT in overweight or obese subjects who had 4 week wash out period and were instructed to restrict carbohydrate intake. Patients were randomized to simvastatin (20 mg) or simvastatin (20 mg) plus ezetimibe (10 mg) for 8 weeks.	Patients who were overweight or obese (body mass index 25-45 kg/m^2) and had a moderately elevated LDL-C (3.4-4.9 mg/dL).Subjects demonstrating adequate adherence to a low-carbohydrate diet of <30 g/day in the a 4-week diet run-in period.	The major exclusion criteria for the study were triglyceride levels ≥400 mg/dL, serum creatinine ≥1.6 mg/dL, hepatic transaminases >2 times the ULN, hospitalization within the prior 6 months for an unstable pulmonary or cardiac condition, and uncontrolled hypertension.	Low- to medium risk with fairly high LDL-c at the baseline. *It is not clear what proportion of RCT population would meet GSLLD at baseline. Study population overlaps with the target population for the review. However the trial results (effect size) do not apply to the second line treatment population as in the PBS restrictions.*
Shankar 2007 SIM 10 vs EZ + SIM 10 Primary prevention, first line therapy	A double-blind, comparative, RCT in patients with hypercholesterolemia, who underwent 4 weeks wash-out and diet period and were randomly assigned to receive either simvastatin (10 mg/day) or simvastatin (10 mg) plus ezetimibe (10 mg) FDC for 12 weeks	Male and female patients 18 years of age or older were screened for primary hypercholesterolemia, defined as LDL-C >3.5 mmol/L in drug naïve patients and >3.1 mmol/L on previous hypolipidaemic drugs.	Unstable angina within 3 months prior to study, uncontrolled diabetes, hypertension, active hepatitis or hepatic dysfunction defined by elevation of aspartate aminotransferase/alanine aminotransferase >1.5 times the upper limit of normal, renal failure, hypothyroidism, history of known hypersensitivity to statins, pregnant and lactating women.	Low- to medium risk with fairly high LDL-c at the baseline (3.2 – 3.4 mmol/L). *It is not clear what proportion of RCT population would meet GSLLD at baseline. Study population overlaps with the target population for the review. However the trial results (effect size) do not apply to the second line treatment population as in the PBS restrictions.*
Protocol 023 Feldman et al 2004 SIM 20 vs EZ + SIM 20 Ezetimibe + Simvastatin Titration Study Mixed prevention population first line treatment	A 23-week RCT, 4-week placebo diet run-in period, eligible patients were randomized to 1 of 4 treatment groups: SIM 20 mg, EZ+SIM 10 mg, EZ+ simvastatin 20 mg, and EZ+ simvastatin 40 mg. Patients remained on their initial doses of simvastatin for the first 6 weeks of the study. Patients returned at week 5 of each subsequent 6-week period for the assessment of goal attainment. In all groups, the simvastatin doses were doubled at weeks 6, 12, and/or 18 up to a maximal dose of 80 mg/day in patients who did not achieve the target LDL cholesterol goal of <2.6 mmol/L. Patients who had 2 consecutive LDL cholesterol values <1.3mmol/L had their doses of	Males and females aged ≥18 and ≤80 Subjects with a diagnosis (defined by the NCEP ATP III guidelines) of CHD, a CHD risk equivalent of more than or equal to 2 multiple risk factors that confer a 10 year risk for CHD >20% as determined by the Framingham calculation LDL-C ≥3.4 mmol/L following a placebo/diet run in period TG level ≤350 mg/dL ALT and AST ≤50% above the ULN with no active liver disease CPK ≤50% above the ULN at visit 2 Able to maintain an NCEP Step 1 or similar diet for the duration of the study Females surgically sterilised or highly unlikely to conceive	Weight <50% of ideal body weight Subjects already on lipid lowering therapy in whom withholding lipid lowering treatment during the placebo run-in would be inappropriate Alcohol consumption >14 drinks/week Myocardial infarction, coronary artery bypass surgery, or angioplasty within 3 months of visit 1 Uncontrolled diabetes (HbA1c>9.0%) or a diagnosis of diabetes within 3 months of visit 1 Secondary hypercholesterolemia due to hypothyroidism (unless on a stable dose of T4 for 6 weeks with normalised T4 and TSH) Partial ileal bypass Uncontrolled hypertension (SBP >160 mmHg or DBP >100 mmHg) at visit 1 Lipid lowering agents including fish oil, cholestin, bile acid sequestrants, HMG-CoA reductase inhibitors and niacin, taken within 6 weeks, and fibrates, taken within 8 weeks, or visit 1	High- to medium risk with high LDL-c at the baseline (4.2 – 4.5 mmol/L). *It is likely that the study population would meet GSLLD at baseline. Study population overlaps with the target population for the review. However the trial results (effect size) do not apply to the second line treatment population as in the PBS restrictions.*

	simvastatin back-titrated to the next lower dose or were discontinued if they were at the lowest		Subjects who received LDL apheresis	

Appendix 5

Mean per cent change in TC in RCTs of ezetimibe in combination with statin

Table A.5.1 mean per cent change in TC in RCTs of ezetimibe in combination with statin

Study Drug dose (mg)	**Statin arm**			**Statin + ezetimibe arm**				**Percentage reduction**		
	N (total randomised) n (arms)	TC baseline (mmol/L)	TC endpoint (mmol/L)	Drug dose (mg)	N (total randomised) n (arms)	TC baseline (mmol/L)	TC 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	4.20	3.75	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	4.21	3.25	NR	NR	NR
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	6.9	NR	EZ +SIM 10 (start dose) Week 7-12 EZ +SIM 20 Week 13-18 EZ +SIM 40 Week 19-24 EZ +SIM 80 EZ +SIM 20 (start dose) Week 7-12 EZ +SIM 40 Week 13-18 EZ +SIM 40 Week 19-24 EZ +SIM 80	263 263	6.9 6.8	NR NR	Week 6 -28.1 (0.6) Week 12 -33.1 (0.6) Week 18 -37.0 (0.7) Week 24 -40.2 (0.7)	Week 6 -33.9 (0.6) Week 12 -35.6(0.6) Week 18 -40.5(0.5)# Week 24 -43.3(0.5)# Week 6 -36.2(0.6) Week 12 -39.2 (0.6) Week 18 -40.5(0.5)# Week 24 -43.3(0.5)#	NR NR NR NR 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%)	6.78	NR	 Week 4 EZ+ ATOR 10 Week 8 EZ + ATOR 20 Week 14 EZ + ATOR 40	305 (all) 293(96%) NR 84 (60%)	6.83	NR	 -6.1 (0.6) -16.0 (0.7)	 -17.3 (0.6) -26.1 (0.7)	 -11.3** -12.9
McKenney 2007[1] Week 1-4 ROSUV 10 Week 5-8 ROSUV 20 Week 9-12 ROSUV 40	76	NR	NR	Week 1 EZ +SIM 20 Week 4 EZ +SIM 20 Week 8 EZ +SIM 40	77	NR	NR	NR NR	NR NR	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	7.71	NR	EZ+ATOR 10	47	7.88	NR	-10.3 (-13.0, -7.6)	-17.9 (-20.6, -15.2)	-7.6 (-11.4, -3.8)*
P079 Conard 2008[2] ATOR 20 (run in) ATOR 40	98^	5.20	NR	EZ+ATOR 20	98^	5.25	NR	-7(-10, -5)	-20(-22, -5)	-12 (-16, -9)***
Lee 2013[1] ATOR 20	63	5.60	1.22	EZ+SIM 20	62	5.75	1.32	-33.4 (10.4)	-32.3 (14.5)	NR (NS)
Constance 2007[2] ATOR 10 (run in) ATOR 20	219	4.55	NR	EZ + SIM 20 EZ + SIM 40	220 222	4.45 4.57	NR NR	-5.47 (17.49)	-14.15 (17.49) -16.83 (17.54)	NR***
Garcia 2016[1] SIM 80	16	5.30	4.29	EZ+SIM 10	16	5.82	4.55	NR	NR	NR
Secondary prevention population										
Pesaro 2013[2] SIM 20 (run in) SIM 80	31	4.55	NR	EZ+SIM 20	37	4.78	NR	-17 (12)	-20 (12)	NR

P021 Gaudiani 2005[2] SIM 20 (run in) SIM 40	107	4.34	NR	EZ + SIM 20	103	4.45	NR	-1.5 (15.5)	-14.5 (15.2)	NR***
Cho 2011[1] ATOR 20	43	5.13	3.54	EZ +SIM 20	42	5.17	3.65	-29.9 (13.4)	-28.3 (14.6)	NR
Barrios 2005[2] ATOR 10 (run in) ATOR 20	214	5.39	NR	EZ+ SIM 20	221	5.31	NR	-13.0 (0.9)	-20.3 (0.8)	-7.2 (1.2)***
Ostad 2009[2] ATOR 80	24	6.03	3.44	EZ+ATOR 10	25	6.13	3.85	-43 (9)	-36 (17)	NR (NS)
Mixed (both primary and secondary) prevention population										
P090 Leiter 2008[2] ATOR 40 (run in) ATOR 80	291^	4.27	NR	EZ+ATOR 40	288^	4.27	NR	-7 (-8, -5)	-17 (-18, -15)	-10 (-12, -8)*
P112 Zieve 2010[2] ATOR 10 (run-in dose) Week 1-6 ATOR 20 Week 7-12 ATOR 40	 526 515 509	4.71	NR	 Week 6 EZ + ATOR 10 Week 12 EZ + ATOR 10	 527 516 516	4.73	NR	 -8 (-9, -7) -12 (-13, -10)	 -16 (-17, -15) -14 (-15, -12)	 -8 (-9, -7)*** -2 (-4, -0.2)*
McCormack 2010[2] SIM 40 (run in) ATOR 40 ROSU 5/10##	259 262	4.7 4.7	NR NR	EZ+SIM 40	255	4.7	NR	-8.3 (-10.2, -6.5) -2.5 (-4.4, -0.7)	-16.3 (-18.2, -14.5)	NR*** NR***

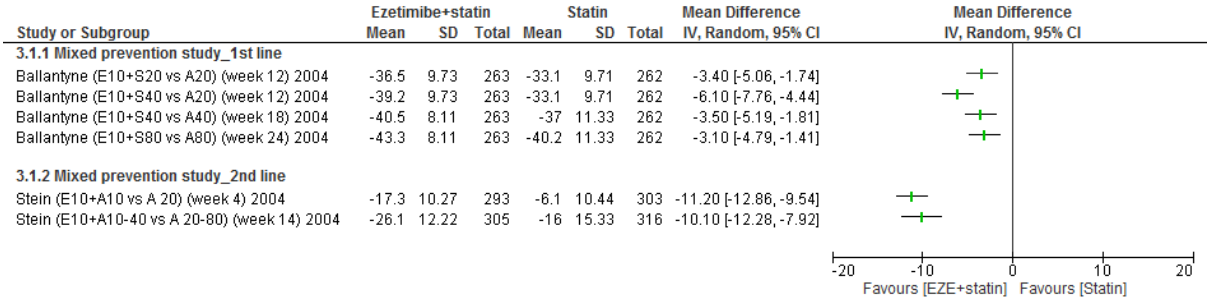
P051 Ballantyne 2005[1]	927				923					
ATOR 10 mg	235	6.75	NR	EZ +SIM 10	230	6.83	NR	-21.3(NR)	-25.5(NR)	NR
ATOR 20 mg	230	6.96	NR	EZ +SIM 20	233	6.84	NR	-24.8(NR)	-25.4 (NR)	NR
ATOR 40 mg	232	6.85	NR	EZ +SIM 40	236	6.85	NR	-23.6(NR)	-27.3 (NR)	NR
ATOR 80 mg	230	6.89	NR	EZ +SIM 80	224	6.80	NR	-32.1(NR)	-30.8 (NR)	NR
P077Goldberg 2006[1] VYTAL										
ATOR 10 mg	237	5.96	NR					-27.8 (NR)		-9.7***
ATOR 20 mg	240	5.97	NR	EZ +SIM 20	247	5.89	NR	-32.5 (NR)	-37.5 (NR)	-5.0***
ATOR 40 mg	241	5.95	NR	EZ +SIM 40	247	5.92	NR	-37.0 (NR)	-40.5 (NR)	-3.5***
P058 Catapano 2006[1]										
ROSU 10	492	6.7	NR	EZ +SIM 20	492	6.6	NR	-32.3 (0.4)	-36.6 (0.4)	-4.3 (0.6)***
ROSU 20	495	6.7	NR	EZ +SIM 40	493	6.7	NR	-37.3 (0.4)	-39.2 (0.4)	-2.0 (0.6)***
ROSU 40	494	6.7	NR	EZ +SIM 80	493	6.6	NR	-40.6 (0.4)	-44.0 (0.4)	-3.4 (0.6)***
Fixed dose statin +ezetimibe vs matching fixed dose of statin										
Primary prevention population										
P692 Ballantyne 2003[1]	248				255					
ATOR 10	60	7.00	NR	EZ + ATOR 10	65	6.79	NR	-25.78 (12.34)	-37.97 (11.85)	-9.07 (-11.14, -6.99)**
ATOR 20	60	6.89	NR	EZ + ATOR 20	62	6.95	NR	-29.85 (12.05)	-39.21 (11.81)	-12.19 (-16.34, -8.03)**
ATOR 40	66	6.89	NR	EZ + ATOR 40	65	7.01	NR	-32.47 (12.02)	-41.86 (11.93)	-9.36 (-13.56, -5.16)**
ATOR 80	62	6.99	NR	EZ + ATOR 80	63	6.90	NR	-40.15 (11.81)	-45.66 (11.91)	-5.51 (-9.68,-1.35)**
P038 Bays 2004[1]	612^				604^					
SIM 10	155	6.77	5.19	EZ +SIM 10	151	6.78	4.64	-23.1 (-24.9,-21.4)	-31.4 (-33.2,-29.6)	-8.3(-10.8,-5.8)***
SIM 20	147	6.86	5.21	EZ +SIM 20	153	6.69	4.25	-24 (-25.7, --22.2)	-36.3(-38.0,-27.2)	-12.3(-14.8,-9.8)***
SIM 40	154	6.66	4.72	EZ +SIM 40	146	6.72	4.07	-28.9 (-30.7, -27.2)	-39.2(-41.0,-37.4)	-10.3(-12.8,-7.8)***
SIM 80	156	6.82	4.45	EZ +SIM 80	154	6.79	3.83	-34.7 (-36.4,-32.9)	-43.4(-45.2,-41.7)	-8.8(-11.2,-6.3)***

P068 Davidson 2002[1]	263				274					
SIM 10	70	6.72	5.48	EZ +SIM 10	67	6.80	4.58	-25.81(0.7)	-32.48 (1.37)	-14.08(-17.85,-10.3)***
SIM 20	61	6.94	5.11	EZ +SIM 20	69	6.87	4.64	-18.4(1.34)	-32.66(1.36)	-6.62(-10.51, -2.72)***--
SIM 40	65	6.82	4.93	EZ +SIM 40	73	6.79	4.09	-26.05 (1.44)	-39.67(1.32)	12.45(-16.24,-8.66)***
SIM 80	67	6.92	4.74	EZ +SIM 80	65	6.80	3.98	-27.22(1.41)	-41.43(1.43)	-9.87(-13.78,-5.97)***
P005 Goldberg 2004[1]	349^				353^					
SIM 10	81	6.69	5.27	EZ +SIM 10	87	6.70	4.58	-20.7(-23.1,-18.2)	-31.5(-33.8,-29.1)	-10.8(-14.2,-7.4)***
SIM 20	90	6.66	5.05	EZ +SIM 20	86	6.88	4.36	-24.1(-26.4,-21.8)	-36.5(-38.9,-34.2)	-12.4(-15.7,-9.1)***
SIM 40	91	6.71	4.77	EZ +SIM 40	89	6.71	4.03	-28.7(-31.0,-26.3)	-39.5(-41.8,-37.1)	-10.8(-14.1, -7.5)***
SIM 80	87	6.72	4.56	EZ +SIM 80	91	6.64	3.77	-31.7(-34.0,-29.3)	-43.0(-45.3,-40.7)	-11.3(-14.6,-8.0)***
Kastelein 2008[1] SIM 80	363	10.34	7.00	EZ+SIM 80	357	10.34	5.62	-31.9(0.8)	-45.3(0.8)	NR
Chirinos 2010[1] SIM 20	30	5.33	NR	EZ+SIM 20	28	5.79	NR	-16.2(-20.9,-11.5)	-27.2(-33.6,-20.8)	NR
Shankar 2007[1] SIM 10	116	6.70	4.80	EZ+SIM 10	114	6.83	4.73	-28.0(18.5)	-30.8(18.9)	NR
Secondary prevention population										
P023 Feldman 2004[1] SIM 20	246	6.64	N/R	EZ +SIM 10 EZ +SIM 20 EZ +SIM 40	242 108 96	6.40 6.43 6.52	NR NR NR	-27(0.7)	-33(0.6) -38(0.9) -42(1.0)	N/R N/R N/R

*p<0.05; **<p<0.01;***p<0.001

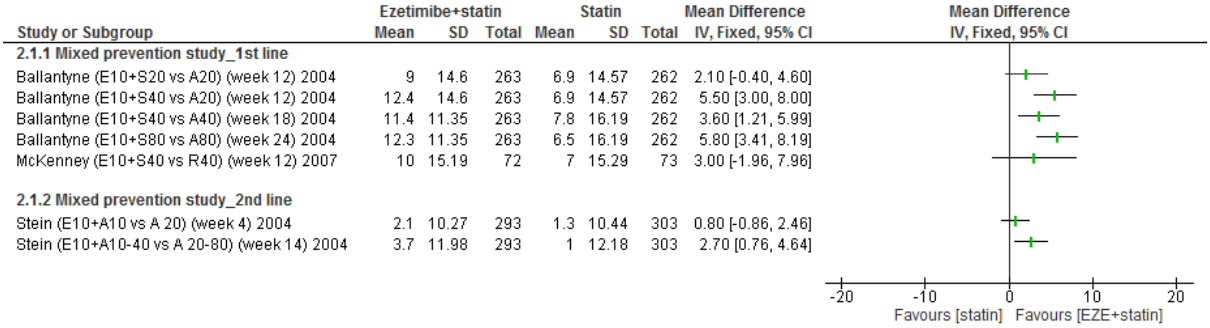
NR: not reported; NS: non-significant;

Figure A5.2 Comparison 1. Up-titrating statin dose+ ezetimibe vs up-titrating statin (TC)



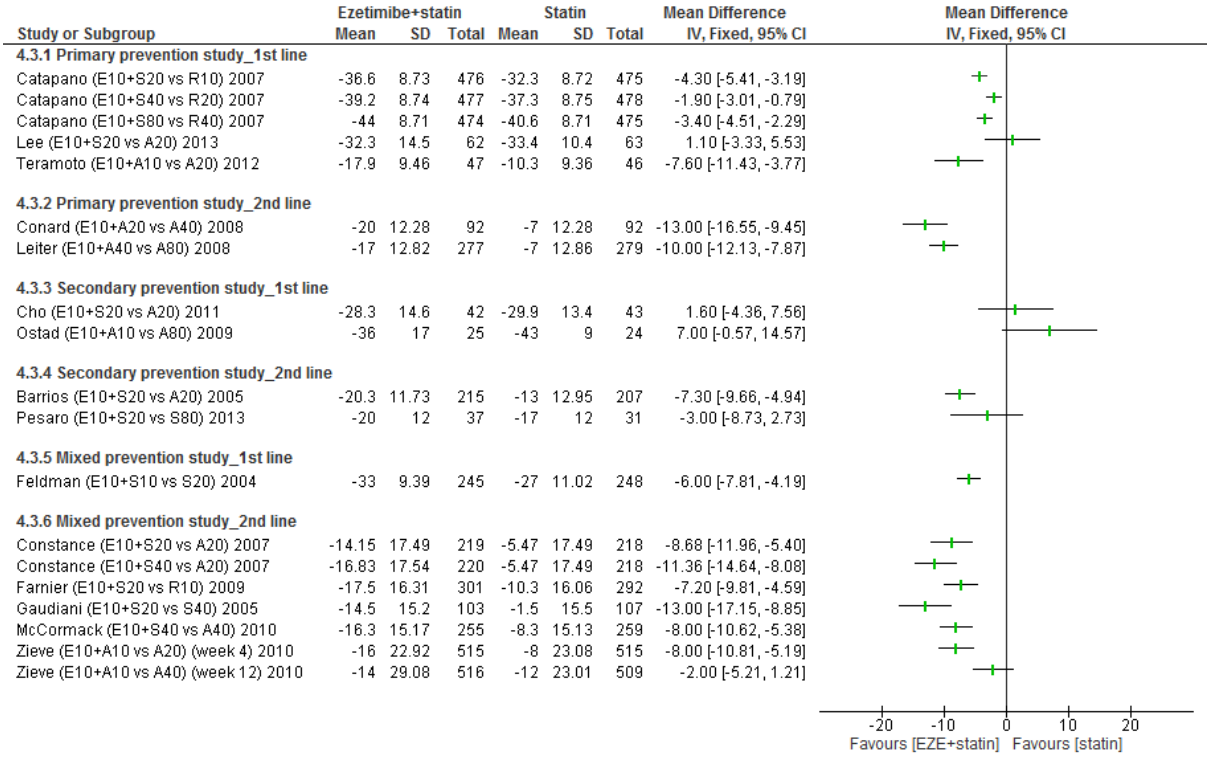
Study or Subgroup	Ezetimibe+statin Mean	SD	Total	Statin Mean	SD	Total	Mean Difference IV, Random, 95% CI
3.1.1 Mixed prevention study_1st line							
Ballantyne (E10+S20 vs A20) (week 12) 2004	-36.5	9.73	263	-33.1	9.71	262	-3.40 [-5.06, -1.74]
Ballantyne (E10+S40 vs A20) (week 12) 2004	-39.2	9.73	263	-33.1	9.71	262	-6.10 [-7.76, -4.44]
Ballantyne (E10+S40 vs A40) (week 18) 2004	-40.5	8.11	263	-37	11.33	262	-3.50 [-5.19, -1.81]
Ballantyne (E10+S80 vs A80) (week 24) 2004	-43.3	8.11	263	-40.2	11.33	262	-3.10 [-4.79, -1.41]
3.1.2 Mixed prevention study_2nd line							
Stein (E10+A10 vs A 20) (week 4) 2004	-17.3	10.27	293	-6.1	10.44	303	-11.20 [-12.86, -9.54]
Stein (E10+A10-40 vs A 20-80) (week 14) 2004	-26.1	12.22	305	-16	15.33	316	-10.10 [-12.28, -7.92]

Figure A5.3 Comparison 1. Up-titrating statin dose+ ezetimibe vs up-titrating statin (HDL-C)



Study or Subgroup	Ezetimibe+statin Mean	SD	Total	Statin Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
2.1.1 Mixed prevention study_1st line							
Ballantyne (E10+S20 vs A20) (week 12) 2004	9	14.6	263	6.9	14.57	262	2.10 [-0.40, 4.60]
Ballantyne (E10+S40 vs A20) (week 12) 2004	12.4	14.6	263	6.9	14.57	262	5.50 [3.00, 8.00]
Ballantyne (E10+S40 vs A40) (week 18) 2004	11.4	11.35	263	7.8	16.19	262	3.60 [1.21, 5.99]
Ballantyne (E10+S80 vs A80) (week 24) 2004	12.3	11.35	263	6.5	16.19	262	5.80 [3.41, 8.19]
McKenney (E10+S40 vs R40) (week 12) 2007	10	15.19	72	7	15.29	73	3.00 [-1.96, 7.96]
2.1.2 Mixed prevention study_2nd line							
Stein (E10+A10 vs A 20) (week 4) 2004	2.1	10.27	293	1.3	10.44	303	0.80 [-0.86, 2.46]
Stein (E10+A10-40 vs A 20-80) (week 14) 2004	3.7	11.98	293	1	12.18	303	2.70 [0.76, 4.64]

Figure A5.4 Comparison 2. Fixed dose of statin+ ezetimibe vs up-titrating statin (TC)



Study or Subgroup	Ezetimibe+statin Mean	SD	Total	Statin Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
4.3.1 Primary prevention study_1st line							
Catapano (E10+S20 vs R10) 2007	-36.6	8.73	476	-32.3	8.72	475	-4.30 [-5.41, -3.19]
Catapano (E10+S40 vs R20) 2007	-39.2	8.74	477	-37.3	8.75	478	-1.90 [-3.01, -0.79]
Catapano (E10+S80 vs R40) 2007	-44	8.71	474	-40.6	8.71	475	-3.40 [-4.51, -2.29]
Lee (E10+S20 vs A20) 2013	-32.3	14.5	62	-33.4	10.4	63	1.10 [-3.33, 5.53]
Teramoto (E10+A10 vs A20) 2012	-17.9	9.46	47	-10.3	9.36	46	-7.60 [-11.43, -3.77]
4.3.2 Primary prevention study_2nd line							
Conard (E10+A20 vs A40) 2008	-20	12.28	92	-7	12.28	92	-13.00 [-16.55, -9.45]
Leiter (E10+A40 vs A80) 2008	-17	12.82	277	-7	12.86	279	-10.00 [-12.13, -7.87]
4.3.3 Secondary prevention study_1st line							
Cho (E10+S20 vs A20) 2011	-28.3	14.6	42	-29.9	13.4	43	1.60 [-4.36, 7.56]
Ostad (E10+A10 vs A80) 2009	-36	17	25	-43	9	24	7.00 [-0.57, 14.57]
4.3.4 Secondary prevention study_2nd line							
Barrios (E10+S20 vs A20) 2005	-20.3	11.73	215	-13	12.95	207	-7.30 [-9.66, -4.94]
Pesaro (E10+S20 vs S80) 2013	-20	12	37	-17	12	31	-3.00 [-8.73, 2.73]
4.3.5 Mixed prevention study_1st line							
Feldman (E10+S10 vs S20) 2004	-33	9.39	245	-27	11.02	248	-6.00 [-7.81, -4.19]
4.3.6 Mixed prevention study_2nd line							
Constance (E10+S20 vs A20) 2007	-14.15	17.49	219	-5.47	17.49	218	-8.68 [-11.96, -5.40]
Constance (E10+S40 vs A20) 2007	-16.83	17.54	220	-5.47	17.49	218	-11.36 [-14.64, -8.08]
Farnier (E10+S20 vs R10) 2009	-17.5	16.31	301	-10.3	16.06	292	-7.20 [-9.81, -4.59]
Gaudiani (E10+S20 vs S40) 2005	-14.5	15.2	103	-1.5	15.5	107	-13.00 [-17.15, -8.85]
McCormack (E10+S40 vs A40) 2010	-16.3	15.17	255	-8.3	15.13	259	-8.00 [-10.62, -5.38]
Zieve (E10+A10 vs A20) (week 4) 2010	-16	22.92	515	-8	23.08	515	-8.00 [-10.81, -5.19]
Zieve (E10+A10 vs A40) (week 12) 2010	-14	29.08	516	-12	23.01	509	-2.00 [-5.21, 1.21]

Figure A5.5 Comparison 2. Fixed dose of statin+ ezetimibe vs up-titrating statin (HDL-C)

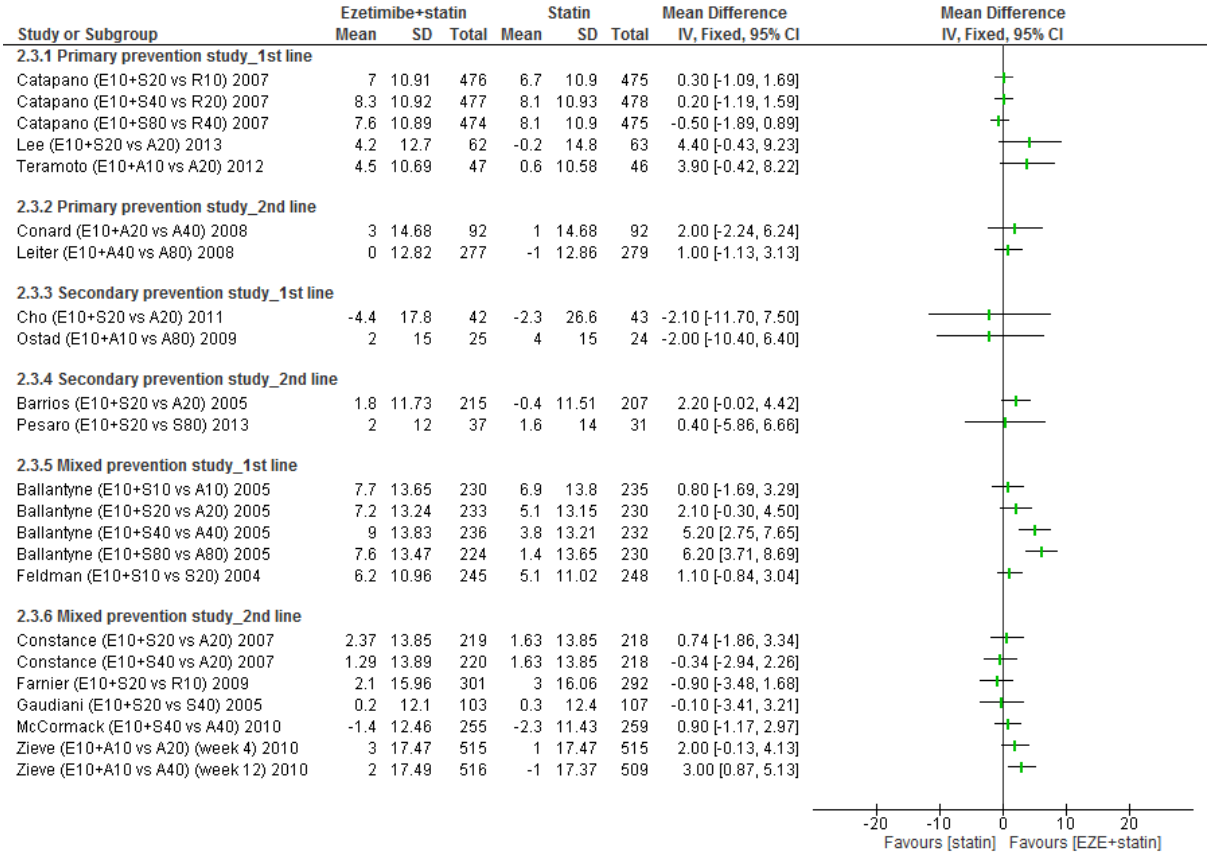


Figure A5.6 Comparison 3. Fixed dose of statin+ ezetimibe vs matching fixed statin dose (TC)

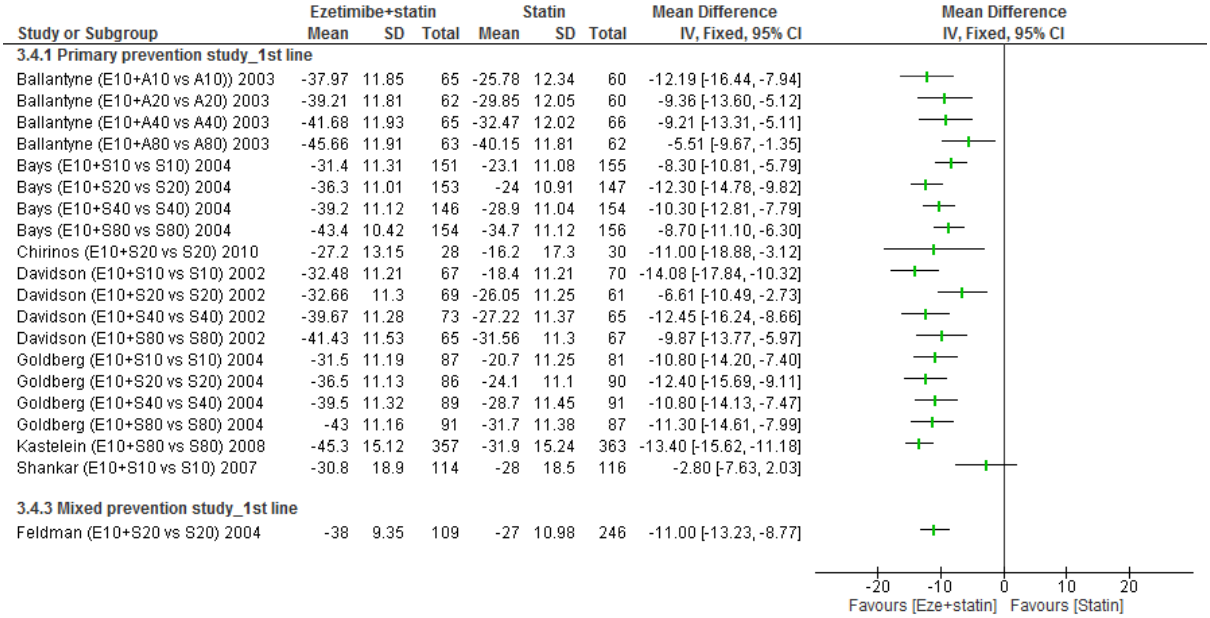


Table A5.2 Mean percentage reduction in LDL-C in ezetimibe monotherapy trials

Study	**Placebo arm**			**Ezetimibe arm**			**Percentage reduction**		
Drug dose (mg)	N (total randomised)	LDL-c baseline (mmol/L)	LDL-c endpoint (mmol/L)	N (total randomised)	LDL-c baseline (mmol/L)	LDL-c endpoint (mmol/L)	Mean %P (SD; SE)	Mean %E (SD; SE)	Mean % further reduction (%E - %PBO) (95%CI)
P692 Ballantyne 2003	60	4.60	NR	65	4.53	NR	5.9(1.92) SE SD=14.87	-18.4(1.85) SD=14.92	NR p-value not reported
P005 Goldberg 2004	93	4.50	NR	92	4.55	NR	2.7 (13.3) SD	-19.8 (10.5) SD	NR p-value not reported
P038 Bays 2004	140-146	4.60	NR	143-148	4.65	NR	-2.2 (1.2) SE SD=14.20	-18.9 (1.2) SE SD=14.35	NR p-value not reported
P680 Davidson 2002	65-69	4.59	4.53	55-60	4.69	3.83	-1.3 (1.7) SE SD=13.71	-18.1 (1.9) SE SD=14.09	NR p-value not reported
Farnier 2005	64	4.2	NR	187	4.1	NR	0.2 (no SE/SD)	-13.4 (no SE/SD)	NR p-value not reported
P474 Dujovne 2002	226	4.34	NR	666	4.34	NR	0.36 (0.83) SE SD=12.48	-16.86 (0.55) SE SD=14.19	p<0.01
P475 Knopp 2003	204 (205)	4.25	NR	621 (622)	4.27	NR	0.79 (0.87) SD=12.43	-17.69 (0.59) SD=14.70	p<0.01

Study	Placebo arm			Ezetimibe arm			Percentage reduction		
Drug dose (mg)	N (total randomised)	LDL-c baseline (mmol/L)	LDL-c endpoint (mmol/L)	N (total randomised)	LDL-c baseline (mmol/L)	LDL-c endpoint (mmol/L)	Mean %P (SD; SE)	Mean %E (SD; SE)	Mean % further reduction (%E - %PBO) (95%CI)
Kerzner 2003	64	4.6	NR	72	4.6	NR	0.0 (16.0)	-19.00 (16.97)	NR p-value not reported
Melani 2003	65	4.6	4.6	64	4.6	3.7	1.3 (12.9)	-18.7 (12.80)	NR p-value not reported

Appendix 6

Table A.6.1 Summary of clinical adverse events (any, serious, withdrawals, hospitalisations, death) reported in the RCTs of ezetimibe in combination with statin

Trial ID Dose group	N	Any adverse event n (%)	Serious event (e.g. increase CPK or muscle-related symptoms) n (%)	Adverse event leading to withdrawal n (%)	Hospitalisations n (%)	Death n (%)
PROTOCOL 807 **CONSTANCE 2007**	*Source: Constance et al. 2007, Table 2. page 23*					
EZ+SIM 20	220	51 (23.3)	1 (0.5)	3 (1.4)	NR	0 (0.0)
ATOR 20	219	42 (19.2)	5 (2.3)	2 (0.9)	NR	1 (<0.1)
CANNON 2015 **IMPROVE-IT**	*Table 3, Cannon 2015*					
EZ+SIM 40	9067	746 (8.2)	748 (10.2)	10.6%	NR	From cancer 280 (3.8)
SIM 20/40	9077	777 (8.6)	732 (10.2)	10.1%	NR	From cancer 272 (3.6)
PROTOCOL 806 **BARRIOS 2005**	*Source: Barrios et al. 2005, Table 3. page 23*					
EZ+SIM 20	221	44 (19.9)	5 (2.3)	5 (2.3)	NR	NR
ATOR 20	214	51 (23.8)	2 (0.9)	8 (3.7)	NR	NR
PROTOCOL 025 **BALLANTYNE 2004**						
EZ+SIM 10	263	184 (70)	NR	15 (5.7)	NR	NR
EZ+SIM 20	263	165 (62.7)	NR	15 (5.7)	NR	NR
ATOR 10	262	187 (71.4)	NR	10 (3.8)	NR	NR
PROTOCOL 051	*Source: Trial report – Protocol 051: Section 8.2.1, Tables 8-2 & 8-3.*					

Trial ID Dose group	N	Any adverse event n (%)	Serious event (e.g. increase CPK or muscle-related symptoms) n (%)	Adverse event leading to withdrawal n (%)	Hospitalisations n (%)	Death n (%)
BALLANTYNE 2005						
ATOR 20	237	73 (30.8)	5 (2.1)	4 (1.7)	NR	1 (0.4)
EZ+SIM 20	237	74 (31.2)	4 (1.7)	3 (1.3)	NR	0 (0.0)
ATOR 40	235	77 (32.8)	4 (1.7)	2 (0.9)	NR	0 (0.0)
PROTOCOL692 BALLANTYNE 2003	*November 2006 submission*					
ALL EZ+ATOR	255	58%	2%	6%	NR	NR
ALL ATOR	248	59%	3%	5%	NR	NR
PROTOCOL 038 BAYS 2005	*November 2006 submission*					
ALL EZ+SIM	609	350 (57.5)	9 (1.5)	25 (4.1)	NR	1 (0.002)
ALL SIM	622	332 (53.4)	11 (1.8)	27 (4.3)	NR	0
PROTOCOL 700 DOBS 2003	*Source: Trial report- Protocol 700: p 69752 and 69769*					
ALL EZ+SIM (20, 40 mg)	66	45 (68.0)	3 (4.5)	6 (9.1)	2 (3.0)	0 (0.0)
All SIM (20, 40 mg)	34	24 (71.0)	0 (0.0)	1 (2.9)	0 (0.0)	0 (0.0)
PROTOCOL 021 GAUDIANI 2005	*Source: Trial report- Protocol 021: Section 8.2.1, Table 34; Section 8.2.4.2*					
EZ+SIM 20	104	68 (65.4%)	5 (4.8)	1 (1.0)	6 (5.8)	0 (0.0)
SIM 40	110	66 (60.0%)	1 (0.9)	4 (3.6)	1 (1.0)	0 (0.0)
PROTOCOL079 CONARD 2008						
EZ +ATOR 20	98	11 (11)	0	0	NR	0

Trial ID Dose group	N	Any adverse event n (%)	Serious event (e.g. increase CPK or muscle-related symptoms) n (%)	Adverse event leading to withdrawal n (%)	Hospitalisations n (%)	Death n (%)
ATOR 40	98	18 (18)	0	2(2)	NR	0
PROTOCOL 077 GOLDBERG 2006 VYTAL	*Source: Goldberg et al. 2006, Section: Safety and tolerability, Page 1584 and Table 3, Page 1586*					
All EZ+SIM (20 40 mg)	495	98 (19.8)	3 (0.6)	4 (0.8)	NR	0
All ATOR (10, 20 40 mg)	731	166 (22.7)	10 (1.4)	11 (1.5)	NR	1 (0.01)
MCKENNEY 2007 COMPELL	*Source: McKenney et al, 2007: Results Section, page 434*					
All EZ+SIM	77	NR	NR	NR	NR	NR
All ROSUV	76	NR	NR	NR	NR	NR
PROTOCOL 058 CATAPANO 2006	*Source: Section 8.2.1, Table 8.2; Section 11.2.*					
EZ+SIM 20	489	140 (28.6)	9 (1.8)	7 (1.4)	8 (1.6)	0 (0.0)
ROSUV 20	493	158 (32.0)	3 (0.6)	9 (1.8)	2 (0.4)	0 (0.0)
PROTOCOL 068 DAVIDSON 2002						
All EZ+SIM	274	54 (20)	7 (2.6)	20 (7.3)	NR	Two unrelated deaths were reported, one pre-randomisation and one post-randomisation
All SIM	263	50 (19)	2 (0.8)	14 (5.3)	NR	
PROTOCOL 005 GOLDBERG 2004						
All EZ+SIM	353	214 (60.6)	3 (0.8)	11 (3.1)	NR	0 (0.0)
All SIM	349	219 (62.8)	4 (1.1)	6 (1.7)	NR	0 (0.0)
PROTOCOL 809	*Table 4, Farnier 2009*					

Trial ID Dose group	N	Any adverse event n (%)	Serious event (e.g. increase CPK or muscle-related symptoms) n (%)	Adverse event leading to withdrawal n (%)	Hospitalisations n (%)	Death n (%)
FARNIER 2009						
EZ + SIM 20	314	22 (7.1)	3 (1)	9 (2.9)	NR	1 (0.3)
ROSUV 10	304	34 (11.2)	5 (1.6)	6 (2.0)	NR	0
PROTOCOL 023 **FELDMAN 2004**	*Table 92 November 2006 submission, Table 4 Feldman 2004*					
EZ + SIM 10	251	140 (56)	33 (13)	11 (4.4)	NR	0
EZ + SIM 20	109	74 (68)	12 (11)	7 (6.4)	NR	0
EZ + SIM 40	97	63 (65)	10 (10)	5 (5.2)	NR	1 (1)
SIM 20	253	168 (66)	22 (8)	14 (5.5)	NR	0
PROTOCOL 693 **STEIN 2004**	*Table 92 November 2006 submission*					
EZ +ATOR 10	305	24%	13 (4)	13(4)	NR	0
ATOR 20	316	22%	8 (3)	14(4)	NR	1 (0.3)
PROTOCOL 090 **LEITER 2008**	*Table 3, Leiter 2008*					
EZ +ATOR 40	288	63 (22)	9(3)	3 (1)	NR	0
ATOR 80	291	61 (21)	5(2)	3 (1)	NR	0
TERAMOTO 2012	*Table VIII, Teramoto 2012*					
EZ +ATOR 10	47	8.5%	0	NR	NR	0
ATOR 20	46	10%	0	NR	NR	0
PESARO 2013						

Trial ID Dose group	N	Any adverse event n (%)	Serious event (e.g. increase CPK or muscle-related symptoms) n (%)	Adverse event leading to withdrawal n (%)	Hospitalisations n (%)	Death n (%)
EZ + SIM 20	37	Not reported. A short term small size trial designed to assess different cholesterol-independent pleiotropic effects on inflammation and platelets.				
SIM 80	31					
LEE 2013						
EZ + SIM 20	66	15 (24.2)	0	NR	NR	0
ATOR 20	66	22 (34.9)	0	NR	NR	0
CHO 2011						
EZ + SIM 20	42	2.8%	0	NR	NR	0
ATOR 20	43	5.3%	0	NR	NR	0
MCCORMAC 2013						
EZ + SIM 40	259	89 (34.4)	4 (1.5)	7 (2.7)	0	0
ATOR 40	260	93 (35.8)	2 (0.8)	5 (1.9)	0	0
GARCIA 2016						
EZ + SIM 10	29	Not reported. A short term small size trial designed to assess the endothelial function by comparing the degree of arterial flow-mediated vasodilation (FMV) between the arms				
SIM 80	31					
OSTAD 2009						
EZ + ATOR 10	25	NR	2 (8)	2 (8)	NR	1
ATOR 80	24	NR	4 (16)	5 (21)	NR	0
CHIRINOS						
EZ + SIM 20	28	0	0	1 (3.6)	0	0
SIM 20	30	0	0	0	0	0
KASTELEIN						

Trial ID Dose group	N	Any adverse event n (%)	Serious event (e.g. increase CPK or muscle-related symptoms) n (%)	Adverse event leading to withdrawal n (%)	Hospitalisations n (%)	Death n (%)
EZ + SIM 80	357	122 (34.2)	12 (2.8)	29 (8.1)	10 patients in the combined-therapy group (including 2 deaths from cardiovascular causes, 3 nonfatal myocardial infarctions, 1 non-fatal stroke, and 6 coronary revascularizations)	
SIM 80	363	107 (29.5)	10	34 (9.4)	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)	
SHANKAR						
EZ + SIM 10	114	39 (35)	0	0	0	0
SIM 10	116	38 (34)	0	9	0	9

CPK= creatinine phosphokinase

Table A.6.2. Summary of adverse events reported in the selected RTS of ezetimibe monotherapy

	Ballantyne *et al.* 2003		**Bays *et al.* 2004**		**Davidson *et al.* 2002**		**Dujovne *et al.* 2002**		**Goldberg *et al.* 2004**		**Kerzner *et al.* 2003**		**Knopp *et al.* 2003**		**Melani *et al.* 2003**		**Farnier 2005**	
	EZE	PBO	EZE	PBO	EZE	PBO	EZE	PBO	EZE	PBO	EZE	PBO	EZE	PBO	EZE	PBO	EZE	PBO
	N=65	N=60	N=149	N=148	N=61	N=70	N=666	N=226	N=92	N=93	N=72	N=64	N=622	N=205	N=64	N=65	N=187	N=64
All adverse events	41	34	79	80	45	49	-	-	52	61	46	46	-	-	45	37	84	30
	(63%)	(57%)	(53%)	(54%)	(74%)	(70%)			(57%)	(66%)	(64%)	(72%)			(70%)	(57%)	(44.9%)	(46.9%)
Treatment-related adverse events	12	12	19	12	11	17	-	-	8	8	12	11	-	-	6	7	12	5
	(18%)	(20%)	(13%)	(8%)	(18%)	(24%)			(9%)	(9%)	(17%)	(17%)			(9%)	(11%)	(6.4%)	(7.8%)
Gastrointestinal adverse events	4	6	-	-	3	7	-	-	-	-	6	5	10	9	-	-	-	-
	(6%)	(10%)			(5%)	(10%)					(8%)	(8%)	(2%)	(4%)				
Musculoskeletal system disorder	3	3	-	-	1	3	31	9	-	-	-	-	19	9	-	-	-	-
	(5%)	(5%)			(2%)	(4%)	(5%)	(4%)					(3%)	(4%)				
Discontinuations due to any adverse events	3	3	2	2	5	3	29	6	3	2	3	5	22	5	2	5	4	0
	(5%)	(5%)	(1%)	(1%)	(8%)	(4%)	(4%)	(3%)	(3%)	(2%)	(4%)	(8%)	(4%)	(2%)	(3%)	(8%)	(2.1%)	(0%)
Treatment-related discontinuations	-	-	1	2	-	-	-	-	2	0	-	-	-	-	-	-	1	0
			(<1%)	(1%)					(2%)								(0.5%)	(0%)
Serious adverse events	-	-	2	2	-	-	-	-	0	1	-	-	-	-	-	-	0	0
			(1%)	(1%)						(1%)							(0%)	(0%)
Treatment-related serious adverse events	-	-	0	0	-	-	-	-	0	0	-	-	-	-	-	-	0	0
Liver function tests ULN, 2 consecutive times																		
ALT	0	0	1 (<1%)	1 (<1%)	0	0	3 (<1%)	1 (<1%)	0a	0 a	0	0	4	0	0	0	1 (1.6%)	1 (<1%)
AST	0	0	NA	NA														
Creatine phosphokinase ≥10×ULN	0	0	0	1 (<1%)	0	0	3 (<1%)	1 (<1%)	0	1 (1%)	0	0	0	0	0	0	0	0

Source: Table 2, Pandor 2009 completed with the data from Farnier 2005