National Institute for Health and Care Excellence

Final

Cardiovascular disease: risk assessment and reduction, including lipid modification

[D] Evidence review for escalation of lipid-lowering treatment for secondary prevention of CVD

NICE guideline NG238

Evidence review underpinning recommendations 1.7.1, 1.7.8 to 1.7.11, 1.10.1 and 1.10.2

December 2023

Final

Developed by National Institute for Health and Care Excellence

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ISBN: 978-1-4731-5638-8

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1.1 Review question

In adults with CVD requiring escalation of therapy beyond statins, what is the effectiveness of lipid-lowering therapy?

1.1.1 Introduction

Recommendations in NICE guideline CG181, to date, have included advice on follow-up for people started on statin treatment; recommending a percentage reduction of non-HDL cholesterol levels to aim for at 3 months follow-up and guidance on factors to consider if this is not achieved, such as adherence and dose of statin therapy. However, the recommendations do not address when to escalate treatment beyond statin therapy.

Recent evidence suggests that many people are not being prescribed lipid lowering medicines beyond high intensity statins, even after a CVD event. This partial update of CG181 intends to address this gap, specifically for secondary prevention of CVD where risk of further CVD events is greatest. An evidence review and economic analysis will be undertaken to inform escalation of lipid lowering therapy beyond statins, including consideration of a treatment target for secondary prevention.

1.1.2 Summary of the protocol

For full details see the review protocol in Appendix A.

Table 1: PICO characteristics of review question

Population	**Inclusion:** • Adults (aged 18 years and older) with CVD. • ≥50% of participants are receiving high or medium intensity statin therapy as background or randomised treatment. **Exclusion:** • Children aged under 18 years of age. • People who are intolerant of or have contraindications to statins. • People with familial hypercholesterolaemia. • People receiving renal replacement therapy. • People with familial clotting disorders that increase cardiovascular risk. • People with other monogenic disorders that increase cardiovascular risk. • People at high risk of CVD or abnormalities of lipid metabolism because of endocrine or other secondary disease processes other than diabetes.
Interventions	• Ezetimibe (+ high or medium intensity statin) • Inclisiran (+ high or medium intensity statin) • Alirocumab or evolocumab (+ high or medium intensity statin) - assuming a class effect for PCSK9 monoclonal antibodies • Combinations of the above interventions (for example, inclisiran + ezetimibe + high or medium intensity statin; or alirocumab/evolocumab + ezetimibe + high or medium intensity statin)
Comparisons	• Interventions compared with each other • Placebo / no treatment • High or medium intensity statin

	○ High intensity statins are defined as atorvastatin 20–80 mg or rosuvastatin 10–40 mg and medium intensity statins as atorvastatin 10 mg, fluvastatin 80 mg, rosuvastatin 5 mg or simvastatin 20–40 mg.
Outcomes	• LDL-C (change from baseline: absolute change and % change) • Non-HDL-C (change from baseline: absolute change and % change) • Combined major adverse cardiovascular events (CVD death, nonfatal MI, nonfatal ischaemic stroke) (time-to-event) • Quality of life, any validated measure (continuous) • Treatment-related adverse effects (dichotomous): ○ Myopathy/rhabdomyolysis ○ New-onset diabetes ○ Increased liver transaminases (>3-times upper-limit of normal) ○ Cancer ○ Gall-bladder related disease ○ Injection site reactions ○ Nausea ○ Influenza
Study design	RCT, systematic review of RCTs or individual participant data meta-analysis of RCT data.

1.1.3 Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in Appendix A and the methods document. The clinical review was conducted mainly to provide inputs for the model and neither the pairwise nor network meta-analysis estimates directly inform the recommendations, as they cannot give any information about a cholesterol target. Therefore, setting specific clinical importance thresholds was not prioritised, but the size of the effects in relation to risks and benefits for people with CVD was discussed.

Where studies reported lipid levels as mg/dl, these were converted to mmol/litre using a conversion factor of 0.02586.

An original network meta-analysis was conducted by the NICE Technical Support Unit for the outcomes of percentage and absolute change in both LDL cholesterol and non-HDL cholesterol. Details of this analysis are provided in a separate NMA results document.

Declarations of interest were recorded according to NICE's conflicts of interest policy.

1.1.4 Effectiveness evidence

Included studies

Thirty four RCT studies reported in 51 papers were included in the review;[1-27, 29-42, 44-53] these are summarised in Table 2 below. Evidence from these studies is summarised in the clinical evidence summaries below (Table 3 to Table 7).

See also the study selection flow chart in B.2, study evidence tables in Appendix D, forest plots in Appendix E and GRADE tables in Appendix G.

All included studies reported having at least 80% of participants with cardiovascular disease (CVD) at baseline. However, there were differences between the studies regarding statin treatment before randomisation and statin intensity during the trial, as well as in the dosing regimens of the PCSK9 monoclonal antibodies. Furthermore, not all of the trials were placebo controlled, with some using an active comparator or usual care with no blinding. These details are summarised in Table 2.

Of the 34 included trials:

- 15 (reported in 19 papers)[3-5, 7, 15-17, 21, 23-25, 35, 39, 46-48, 50-52] compared ezetimibe plus statin with statin alone. Of these:
  - 2 were placebo-controlled.[5, 16]
  - At randomisation 4 used medium-intensity statins,[3, 5, 25, 52] 8 used high-intensity[16, 17, 23, 24, 35, 39, 49, 50] and 2 used mixed or unclear statin intensities.[46, 48]
  - IMPROVE-IT was the largest trial, and it should be noted that 27% of participants in the statin arm were escalated from simvastatin 40 mg to simvastatin 80 mg.[5]
  - Only 1 trial exclusively included patients who had prior statin treatment;[49] 1 had 57% with statin pre-treatment,[3] 6 reported <50% with prior statin,[5, 25, 39, 46, 48, 52] and 2 included only statin-naïve patients.[16, 35]
  - Follow-up ranged from 12 weeks to 6 years.

- 14 (reported in 26 papers)[1, 2, 8, 9, 11, 12, 18-20, 26, 27, 29-34, 36, 38, 40-42, 44, 45, 49, 53] compared PCSK9 inhibitors (PCSK9i) with placebo or usual care in populations amongst whom the majority were taking background statin treatment. Of these:
  - The control group was usual care in 4 trials.[2, 11, 36, 38]
  - All except one[34] enrolled those with statin pre-treatment, which continued during trial.
  - Statin intensity definitions did not match those used in this guideline, but most participants were on maximum tolerated dose, which included high and medium intensity statins in varying proportions.
  - The largest trials were FOURIER[42] (N=27563) and ODYSSEY OUTCOMES[45] (N=18924).
  - The specific PCSK9 monoclonal antibody used was alirocumab in 9 trails reported in 8 papers[2, 11, 18, 19, 26, 34, 36, 45] and evolocumab in 4 trials,[12, 29, 31, 42] with 1 trial including both.[38]
  - Follow-up ranged from 12 weeks to >2 years.
  - The results for ODYSSEY LONG TERM,[26] ODYSSEY DM-DYSLIPIDEMIA[36] and ODYSSEY DM-INSULIN[36] do not represent the full trial cohort, which included <80% with CVD. Therefore, the CVD subgroup from individual participant data (IPD) meta-analysis has been reported in this review.
- 2 trials[6, 13] compared PCSK9i with ezetimibe in populations amongst whom the majority were taking background statin treatment.
- 1 trial[14] compared PCSK9i plus ezetimibe with ezetimibe in populations amongst whom the majority were taking background statin treatment.

- 2 trials (reported in 1 paper)[37] compared inclisiran with placebo (ORION 10 and 11) in populations amongst whom the majority were taking background statin treatment.

Cochrane reviews

Two Cochrane reviews[43, 54] were identified that partially matched the protocol and were included and used in the following ways:

- All included studies were cross-checked for inclusion in this review.
- Relevant outcome data for studies included in this review was cross-checked with the data extracted for this analysis as an additional measure of quality assurance.
- Risk of bias assessments for studies included in this review were used as a basis for critical appraisal considerations but were re-assessed per outcome and in line with NICE guideline methodology.

Evidence tables for the individual systematic reviews have not been included in the present review but the relevant information from them has been used to inform the analyses and cross-check data included in the evidence tables for the relevant studies.

Earlier versions of these reviews and their review protocols have not been included. See the excluded studies list in Appendix K.

1.1.5 Summary of studies included in the effectiveness evidence

Details of the included studies are summarised in Table 2.

Table 2: Summary of studies included in the evidence review

Author, year (trial name)	Population	Baseline LDL-C/non-HDL-C	Intervention	Comparison	Background treatment	Outcomes (follow-up time)	Indirectness
Ezetimibe							
Arimura 2012[3]	People with stable angina and dyslipidaemia who were successfully implanted with a drug-eluting stent or a bare-metal stent. N=50 Mean age (SD): 69 (8.5) years. Previous CVD event: stable angina and coronary stent	Not reported	Ezetimibe 10 mg/day and atorvastatin 10 mg/day (medium intensity statin). N=25	Atorvastatin 10 mg/day N=25	All participants received aspirin and ticlopidine or clopidogrel throughout the study period.	LDL-C (mg/dl) At 6-8 months	None
Cannon 2015a,[5] Blazing 2014,[4] Cannon 2008[7] (study rationale and design), Oyama 2021[32] (contains data on subgroup analysis)	People (≥50 years) hospitalised for an ACS N=18,144 Mean age (SD): 63.6 (9.8) years	Mean (SD) in intervention vs comparison LDL-C: 93.8 (nr) vs 93.8 (nr) mg/dl Non-HDL-C: 120.5 (nr) vs 120.5 (nr)	Simvastatin 40mg/d plus ezetimibe 10mg/d as fixed dose combination tablet. Simvastatin dose increase to 80mg for	Simvastatin 40mg/d (medium intensity) plus placebo. Simvastatin increased to 80mg for LDL >79mg/dl in 27%. N=9077	Matched between groups: Aspirin: 97% Thienopyridine: 86% Beta-blocker: 87% ACE inhibitor or ARB: 76%	LDL-C and non-HDL-C at 1 year (mg/dl) MACE (death from cardiovascular causes, major coronary event or, nonfatal	Serious comparator indirectness: 27% in control group had the simvastatin dose increased to 80 mg

Author, year (trial name)	Population	Baseline LDL-C/non-HDL-C	Intervention	Comparison	Background treatment	Outcomes (follow-up time)	Indirectness
IMPROVE-IT	Qualifying ACS event: acute MI with or without ST-segment elevation on electrocardiography or high-risk UA	Subgroup data for baseline LDL-C 50-<70 mg/dl; 70-<100mg/dl; 100-125 mg/dl	LDL-C> 79mg/dl in 6% of patients N=9067			stroke). at 7 years Myopathy, rhabdomyolysis, ALT, AST or both, cancer, gall-bladder-related adverse events at 7 years	
Hougaard 2017[16] OCTIVUS	People with first STEMI, no prior treatment with statins or other lipid lowering drugs and a non-significant lesion in one of the two non-culprit coronary arteries. N=87 Mean age (SD): 56.3 (10.1) Previous CVD event: STEMI.	Mean (SD) in intervention vs comparison LDL-C: 3.7 (0.7) vs 4.1 (0.9) mmol/l	Ezetimibe: atorvastatin 80mg/d (high-intensity) and ezetimibe 10mg/d N=43	Placebo: atorvastatin 80mg/day and placebo N=44	No baseline statin use. Background treatment not specified.	LDL-C (mmol/l) At 1 year Adverse events: elevated liver enzymes At 3 months	None
Joshi 2017[17]	People with CAD N=80	Mean (SD) LDL cholesterol:	Ezetimibe 10mg/d plus rosuvastatin 10mg/d (high-intensity statin)	Rosuvastatin 10mg/d N=40	High intensity statins as part of study; unclear if at baseline.	LDL-C (mg/dl) Musculoskeletal side effects	None

Author, year (trial name)	Population	Baseline LDL-C/non-HDL-C	Intervention	Comparison	Background treatment	Outcomes (follow-up time)	Indirectness
	Mean age (SD): 60.1 (10.5) Previous CVD diagnosis: coronary artery disease (CAD)	162.68 (23.13) vs 153.38 (24.78) mg/dl Non-HDL-C: not reported	N=40		Advised to follow lifestyle modifications, stop smoking, exercise regularly, avoid alcohol and have a low-fat diet. Regular treatment of CAD including antiplatelets, beta-blockers, ACE inhibitors, nitrates was continued.	Gastrointestinal side effects At 24 weeks	
Kouvelos 2013[21]	People undergoing vascular surgery (peripheral artery disease) N=262 Mean age (range): 71 (41 to 89) years Previous CVD diagnosis: CAD or cardiac failure	Mean (SD) in intervention vs comparison LDL-C: 148 (58.1) vs 143 (54.1) mg/dl	Ezetimibe 10mg/d + rosuvastatin 10mg/d Starting 2 weeks prior to vascular surgery N=126	Rosuvastatin 10mg/d (high-intensity statin) N=136	For people already on statin, there was an 8-week washout period. All participants were under antiplatelet therapy for at least 3 weeks prior to the procedure. People who were enrolled and were already receiving beta-blocker therapy continued their medication. For those not already on a beta - blocker, bisoprolol (2.5 mg once daily) was initiated	LDL-C mg/dl At 1 year (after surgery) Composite of death from cardiac causes, nonfatal acute MI, ischemic stroke and UA (also reported individually) From month 1 to 12 of the follow-up The same outcome was also reported for different	None

Author, year (trial name)	Population	Baseline LDL-C/non-HDL-C	Intervention	Comparison	Background treatment	Outcomes (follow-up time)	Indirectness
					at the screening visit.	time-points as follows: Major adverse CV event (death from cardiac causes, nonfatal myocardial infarction, ischemic stroke, and unstable angina) during 1 year follow-up	
Luo 2014[23]	Elderly hypercholesterolemic people with abnormal LDL-C levels despite undergoing lipid-lowering therapy for 3 months. Mean age (SD): 66.7 (6.12) years Previous CVD diagnosis: 83.3% coronary heart disease	Mean (SD) in intervention vs comparison LDL-C: 3.27 (0.36) vs 3.31 (0.46) mmol/l Non-HDL not reported	Ezetimibe + atorvastatin (10mg/d) N=40	Atorvastatin 20mg once per night N=44	No information	LDL-C (mmol/l) Combined major cardiovascular events (MI or cardiovascular death) At 12 months	None

Author, year (trial name)	Population	Baseline LDL-C/non-HDL-C	Intervention	Comparison	Background treatment	Outcomes (follow-up time)	Indirectness
Luo 2016[24]	People with coronary heart disease confirmed by coronary angiography receiving lipid-lowering therapy for 3 months but not achieving standard goals for LDL-C levels <2.6mmol/l N=148 Mean age (SD): 61.2 (10.7) Previous CVD event/diagnosis: stroke or CHD	Mean (SD) in intervention vs comparison LDL-C: 3.57 (0.38) vs 3.52 (0.46) mmol/l HDL-C not reported.	Ezetimibe 10mg/d plus atorvastatin (20mg/d) N=74	Atorvastatin 20mg/d N=74	Secondary prevention drugs, such as aspirin, angiotensin II receptor antagonists, and hypoglycaemic drugs were routinely administered to both groups. Statins and other LLTs not reported.	LDL-C (mmol/l) Combined major cardiovascular events. (cardiac death, hospitalization for unstable angina, nonfatal myocardial infarction, coronary revascularization, and stroke) Myopathy/rhabdomyolysis At 12 months	None
Masuda 2015[25]	People aged 20 to 80 years old with clinically stable angina pectoris PCI; LDL-C level higher than 100 mg/dl mmol/l at entry, regardless to prior	Mean (SD) in intervention vs comparison LDL-C: 131.8 (25.6) vs 123 (27) mg/dl Non HDL-C: 151.4 (29.4) vs 146.2 (35.6)	Ezetimibe 10mg/d + rosuvastatin 5mg/d (medium intensity statin) N=19	Rosuvastatin 5mg/d (medium intensity statin) N=21	At baseline: **Ezetimibe and rosuvastatin group:** Beta-blocker: 9 (42.9%) ARB: 9 (42.9%) ACE inhibitor: 2 (9.8%)	LDL-C (mg/dl) Non-HDL (mg/dl) Rhabdomyolysis Creatine kinase >5x ULN	None

Author, year (trial name)	Population	Baseline LDL-C/non-HDL-C	Intervention	Comparison	Background treatment	Outcomes (follow-up time)	Indirectness
	administration of statins. Mean age (SD): 67 (8.35) years Previous CVD diagnosis: CAD				Oral glycaemic agent: 8 (38.1%) Insulin:1 (4.8%) Current smoking: 9 (42.9%) Hypertension: 13 (61.9%) **Rosuvastatin group** Beta-blocker: 9 (47.4%) ARB: 10 (52.6%) ACE inhibitor: 3 (15.8%) Oral glycaemic agent: 7 (36.8%) Insulin: 0 (0%) Current smoking: 4 (21.1%) Hypertension: 17 (89.5%) **Baseline statin use:** 42.9% vs 36.8% in intervention vs comparison	AST or ALT >3x upper limit of normal Myalgia At 6 months	
Ran 2017[35] NSTE-ACS	People undergoing percutaneous coronary intervention for non-ST-	Mean (SD) in intervention vs comparison LDL-C: 141 (27) vs 141 (33) mg/dl	Ezetimibe 10mg/d + rosuvastatin 10mg (high-intensity statin)	Rosuvastatin 10mg/d N=42	All participants were treated with standard non-ST-elevation acute coronary syndrome drugs	LDL-C (mg/dl) non-HDL-C (mg/dl)	None

Author, year (trial name)	Population	Baseline LDL-C/non-HDL-C	Intervention	Comparison	Background treatment	Outcomes (follow-up time)	Indirectness
	elevation acute coronary syndrome (NSTE-ACS) N=125 (analysed 84) Mean age (SD): 60.5 (7.5) Previous CV event: non-STEMI, UA or stroke	Non-HDL-C: 166 (30) vs 165 (35) mg/dl	N=42		including aspirin, clopidogrel, B-blocker and angiotensin-converting enzyme inhibitors/angiotensin II receptor antagonists. Lipid lowering therapies started the day after percutaneous coronary intervention within 24 hours.	Muscle pain Rhabdomyolysis GI discomfort Liver enzyme elevation At 12 weeks	
Ren 2017[39]	People hospitalised within preceding 24 hours with acute myocardial infarction (including STEMI and non-STEMI) N=113 Mean age (SD): 59 (2.2) years Previous CVD event: Acute MI	Mean (SD) in intervention vs comparison LDL-C: 3(0.96) vs 2.93 (1.02) mmol/l	Ezetimibe (10mg/d) + rosuvastatin (10mg/d) N=55	Rosuvastatin 10mg/d (high intensity statin) N=58	Participants received treatment according to common guidelines, including appropriate use of antiplatelet agents, anticoagulants, statins, B-blockers and revascularization. **Baseline statin** in 9.1% and 10.5% in each group	LDL-C (mmol/l) At 1 year	None

Author, year (trial name)	Population	Baseline LDL-C/non-HDL-C	Intervention	Comparison	Background treatment	Outcomes (follow-up time)	Indirectness
Tsujita 2015;[46, 47] PRECISE-IVUS	People aged 30-85 years diagnosed with ACS or stable CHD, undergoing coronary angiography or PCI under intravascular ultrasound guidance with LDL-C ≥ 100mg/dl N=246 (analysed 202) Mean age (SD):66.5 (10) years Previous CVD event/diagnosis: PCI, MI, stroke or PAD.	Mean (SD) interventions vs comparison LDL-C: 109.8 (25.4) vs 108.3 (26.3) mg/dl	Atorvastatin dose titration with a treatment goal of LDL-C <70mg/dl Plus Ezetimibe 10mg/d N=100	Atorvastatin: dose titration with a treatment goal of LDL-C <70mg/dl N=102	**Atorvastatin + ezetimibe group** Aspirin= 100% Thienopyridines= 100% Cilostazol= 1% Sarpogrelate hydrochlorine= 2% Warfarin= 5% Nitrates= 6% Beta-blockers= 41% Calcium blockers= 44% ACE inhibitors= 25% Angiotensin II receptor blocker= 48% Hypoglycaemic agents= 25% **Atorvastatin monotherapy group** Aspirin= 100% Thienopyridines= 99% Cilostazol= 0%	LDL-C (mg/dl) CVD events (defined as cardiac death, myocardial infarction, target vessel revascularization (PCI or coronary artery bypass grafting)) Increased liver transaminases At 10 months	

Author, year (trial name)	Population	Baseline LDL-C/non-HDL-C	Intervention	Comparison	Background treatment	Outcomes (follow-up time)	Indirectness
					Sarpogrelate hydrochlorine= 2% Warfarin= 1% Nitrates= 14% Beta-blockers= 50% Calcium blockers= 34% ACE inhibitors= 27% Angiotensin II receptor blocker= 36% Hypoglycaemic agents= 25% **Baseline statin use:** 46% vs 48%		
Ueda 2017;[48] Hiro 2014[15] (protocol) ZIPANGU	People 20-80 with elective PCI with at least 1 yellow plaque of grade≥2 in the non-PCI target coronary artery segments and hypercholesterolemia (LDL-C >100mg/dl) N=131	Mean (SD) intervention vs comparison LDL-C: 101 (27) vs 100 (27) mg/dl	Ezetimibe 10mg/d plus atorvastatin 10mg/d (medium intensity) increased to 20mg (high intensity) if LDL-C >70mg/dl after 3 months N=65	Atorvastatin 10mg/d increased to 20mg if LDL-C >100mg/dl at 3 months N=66	Participants had counselling on lifestyle improvement. Diet and medical treatments for their complications or atherosclerosis prevention other than lipid management were administered comprehensively for all enrolled patients based on	LDL-C (mg/dl) At 9 months	Possible intervention indirectness: statin dose titration unlikely to be matched between arms.

Author, year (trial name)	Population	Baseline LDL-C/non-HDL-C	Intervention	Comparison	Background treatment	Outcomes (follow-up time)	Indirectness
	Mean age (SD): 69.5 (9.7) Previous CV event/diagnosis: MI, angina pectoris, stroke, or PAD.				the individualised strategies of their doctors.		
Wang 2016[50]	People with one or more atherosclerotic lesions near the middle of the coronary arteries; total cholesterol ≥5.2 mmol/l and/or LDL≥3.6 mmol/l N=106 Mean age (SD): 48.9 (64.1) years Previous CVD diagnosis: coronary artery disease	Mean (SD) intervention vs comparison LDL-C: 3.62 (1.18) vs 3.48 (1.26) mmol/l	Ezetimibe plus rosuvastatin: both 10mg/night N=50	Rosuvastatin 10mg/night N=48	**Ezetimibe + rosuvastatin group** Nitrate ester= 84% Antiplatelet= 100% Beta-receptor blocker= 78% Calcium channel blocker= 30% Low weight molecular heparin= 80% Angiotensin-converting enzyme inhibitor/angiotensin receptor blocker= 36% **Rosuvastatin group** Nitrate ester= 81%	LDL-C (mmol/l) Rhabdomyolysis Increased liver transaminases Major adverse cardiac events (MI, cardiac death or stroke) At 12 months	None

Author, year (trial name)	Population	Baseline LDL-C/non-HDL-C	Intervention	Comparison	Background treatment	Outcomes (follow-up time)	Indirectness
					Antiplatelet= 100% Beta-receptor blocker= 73% Calcium channel blocker= 27% Low weight molecular heparin= 81% Angiotensin-converting enzyme inhibitor/angiotensin receptor blocker= 33%		
Wang 2017[49]	People with carotid atherosclerosis, type 2 diabetes and CHD with LDL-C ≥2.6mmol/l after 3 months of statin treatment N=100 Mean age (SD): 58 (9.5) Previous CVD diagnosis: coronary artery disease	Mean (SD) intervention vs comparison LDL-C: 3.53 (0.87) vs 3.45 (0.75) mmol/l	Ezetimibe 10mg/d plus atorvastatin 20mg/d N=51	Atorvastatin 20mg/d N=49	Other drugs for hypertension and arterial sclerosis such as aspirin, β-blockers, angiotensin converting enzyme inhibitors, angiotensin II receptor antagonist and hypoglycaemic drugs were routinely used in both groups.	LDL-C (mmol/l) At 12 months	None

Author, year (trial name)	Population	Baseline LDL-C/non-HDL-C	Intervention	Comparison	Background treatment	Outcomes (follow-up time)	Indirectness
West 2011/2011a[51, 52]	People with PAD aged between 30 and 85 years with symptoms of intermittent claudication and an ankle-branchial index between 0.4 and 0.9; statin-naïve regardless of baseline LDL-C N=44 Mean age (SD): 60.5 (9.2) years Previous CVD diagnosis: PAD and 50% also CAD	Mean (SD) intervention vs comparison LDL-C: 118 (41) vs 118 (34) mg/dl	Simvastatin 40mg/d plus ezetimibe 10mg/d N=22	Simvastatin 40mg/d (medium-intensity statin) N=22	Baseline treatment below but unclear if this was continued during the study: Intervention vs comparison: Aspirin 72% vs 69% ACE inhibitor 28% vs 50% ARB 22% vs 13% B-blocker 33% vs 38%	LDL-C (mg/dl) At 1 year MACE (death, MI, stroke and transient ischemic attack) At 2 years	None
PCSK9i versus placebo or usual care							
Ako 2019[2]; Ako 2018[1] (rationale and design) ODYSSEY J-IVUS	People with ACS and LDL-C ≥2.59mmol/l despite stable statin therapy, or who were not on statins with LDL-C levels above target	Mean (SD) in intervention vs comparison Calculated LDL-C: 2.54 (0.60) vs 2.48 (0.57) mmol/l	Alirocumab: 75mg every two weeks every 2 weeks; at week 14 the study allowed alirocumab dose increase to 150mg every 2 weeks if week	Usual care: atorvastatin ≥10mg/day or rosuvastatin ≥5mg/day; i.e. stable dose statin therapy, with optional dose adjustment. Non-statin, non-	Stable dose statin therapy (atorvastatin or rosuvastatin) with/without other LLTs (added as seen fit by investigators to meet LDL-C targets)	LDL-C (mmol/l & mg/dl) Non-HDL-C (mmol/l & mg/dl) TEAEs (leading to death or discontinuation)	None

Author, year (trial name)	Population	Baseline LDL-C/non-HDL-C	Intervention	Comparison	Background treatment	Outcomes (follow-up time)	Indirectness
	after statin initiation. ACS was defined as STEMI, non-STEMI, and unstable angina. N=206 Mean age (SD): 61.2 (10.9) years Index ACS event: STEMI, NSTEMI, UA.	Non-HDL-C: 3.21 (0.65) vs 3.22 (070) mmol/l	12 LDL-C was ≥2.59mmol/l N=93	PCSK9 inhibitor LLTs could be added by investigators if LDL-C goal <2.59mmol/l (<100mg/dl) could not be achieved. N=89		Injection-site reactions Type 2 diabetes Treatment emergent SAEs Treatment emergent CVD events confirmed by adjudication (MI, Ischemic stroke, ischemia driven coronary revascularisation) At 36 weeks	
Gao 2021[11]	People 18-80 years with stable CAD or ACS N=61 Mean age (SD): 61.3 (9.4) years Previous CVD event: MI, stroke, or ACS	Mean (SD) in intervention vs comparison. LDL-C: 3.04 (0.78) vs 3.18 (0.97) mmol/l	Alirocumab 75mg every 2 weeks + high-intensity statin (atorvastatin 20mg/d or rosuvastatin 10mg/d) N=30	Usual care: atorvastatin 20mg/d or rosuvastatin 10 mg/d N=31 15/31 people received ezetimibe and statin combination therapy	Statin dose escalation or the addition of other concomitant non-statin lipid lowering therapies could be considered by physicians responsible for achieving the target LDL-C levels; Antithrombotic	LDL-C (mmol/l) At 36 weeks Adverse cardiac events (Cardiac death, MI, ischemia driven target lesion revascularisation) Injection site reactions	None

Author, year (trial name)	Population	Baseline LDL-C/non-HDL-C	Intervention	Comparison	Background treatment	Outcomes (follow-up time)	Indirectness
					therapy and other concomitant medications were decided by their responsible physicians; all were prescribed antiplatelet therapy, and approximately 90% were treated with beta blockers. Angiotensin converting enzyme inhibitors/angiotensin receptor blockers: 60% vs 64.5%	Within 36-week follow-up	
Giugliano 2012;[12] Kohli 2012[20] (protocol & rationale) LAPLACE-TIMI-57	People aged 18-80 years with history of hypercholesterolaemia and fasting LDL-C concentration greater than 2.2 mmol/l while on a stable dose of statin (with or without ezetimibe) for at least 4 weeks.	Mean (SD) in intervention vs comparison every 2 weeks vs intervention vs comparison every 4 weeks LDL-C: 3.1 (0.6) vs 3.2(0.7) vs 3.1 (0.7) vs 3.2 (0.8) mmol/l	Evolocumab: AMG 145 (human monoclonal IgG2 antibody against PCSK9) 140mg every 2 weeks (n=78) Or 420mg every 4 weeks (n=80)	Placebo every 2 weeks (n=78) or every 4 weeks (n=79)	Baseline statin use: 100% across groups except 97% in placebo every 4 weeks; high-intensity statin in 32% vs 24% vs 36% vs 25% in each group (intervention vs comparison every 2 weeks vs intervention vs	LDL-C (mmol/l) non-HDL-C (mmol/l) % change in LDL-C in subgroup analysis for LDL-C <3.4mmol/l available vs LDL-C <2.6mmol/l vs 2.6 to <3.4 mmol/l vs ≥3.4 mmol/l and	29% were on high-intensity statins but that included simvastatin 80mg; statin intensity for 71% of participants randomised to arms extracted in the present review was not specified and approximately 10% in each comparison group

Author, year (trial name)	Population	Baseline LDL-C/non-HDL-C	Intervention	Comparison	Background treatment	Outcomes (follow-up time)	Indirectness
	N=315 (in groups relevant to the present review) Mean age (range): 63 (55-69) years Previous CVD event/diagnosis: 81% CVD: CAD, MI, coronary artery bypass graft percutaneous coronary intervention, cerebrovascular or peripheral arterial disease.	Non-HDL-C: 3.8 (0.7) vs 3.8 (0.8) vs 3.7 (0.8) vs 3.9 (0.9) mmol/lEE			comparison every 4 weeks) Ezetimibe in 9% across groups except 10% in placebo every 4 weeks	subgroup with non-intensive statin regimen vs intensive statin regimen Injection site reactions Positively adjudicated clinical cardiovascular events (Acute coronary syndrome, coronary revascularisation, transient ischaemic attack, congestive heart failure requiring) At week 12	were on statins not relevant to the review protocol (lovastatin, pitavastatin, or pravastatin low dose)
Kereiakes 2015;[18] Colhoun 2014[8] (rationale) ODYSSEY COMBO I	Adults with established CVD (coronary heart disease) and LDL-C ≥70 mg/dl or coronary heart disease risk equivalents	Mean (SD) in intervention vs comparison LDL-C: 100.2 (29.5) vs 106 (35.3) mg/dl	Alirocumab 75mg every 2 weeks with potential dose increase to 150mgv if LDL-C >70mg/dl at week 8	Placebo injection N=107	All participants were receiving a stable, maximally tolerated statin dose: atorvastatin, 40-80 mg; rosuvastatin, 20-40 mg;	LDL-C (mg/dl) Non-HDL-C At 24 weeks Major adverse CVD events	None

Author, year (trial name)	Population	Baseline LDL-C/non-HDL-C	Intervention	Comparison	Background treatment	Outcomes (follow-up time)	Indirectness
	(e.g. diabetes with other risk factors or chronic kidney disease); N=316 Mean age (SD): 63 (9.3) years CHD history: 78%	Non-HDL-C: 130 (34) vs 133.4 (39.8) mg/dl	N=209		simvastatin, 80 mg daily; or lower doses in cases of intolerance Other lipid-lowering therapy also permitted: bile acid sequestrant, ezetimibe, niacin or omega-3 ≥1000 mg/day with stable dose ≥4 weeks; or fenofibrate with stable dose ≥6 weeks before enrolment. **99.5% statin use at baseline;** 61.7% vs 64.5% high-intensity statin at baseline. **Other LLT at baseline:** 38.2% vs 49.5%; ezetimibe: 7.2% vs 10.3%	(CHD death, non-fatal MI or fatal/non-fatal stroke) Injection-site reaction Nausea Influenza At 52 weeks	
Koh 2017[19] ODYSSEY KT	Adults (aged ≥18 years) with high CV risk who had inadequately	Mean (SD) in intervention vs comparison	Alirocumab 75mg every 2 weeks, increased to 150mg at week	Placebo plus maximally tolerated statin N=102	Maximally tolerated statins: atorvastatin 40 to 80 mg daily, rosuvastatin 20	LDL-C (mg/dl) At 24 weeks	None

Author, year (trial name)	Population	Baseline LDL-C/non-HDL-C	Intervention	Comparison	Background treatment	Outcomes (follow-up time)	Indirectness
	controlled hypercholesterolemia on maximally tolerated statin therapy at a stable dose for at least 4 weeks before screening. N=199 Mean age (SD): 60.6 (9.8) years Previous CVD diagnosis: Coronary heart disease: 99% vs 93.1% in each group	Calculated LDL-C: 97 (27.8) vs 99.3 (25.2) mg/dl Non-HDL-C: 123.9 (29) vs 128.4 (30.3) mg/dl	12 if LDL-C >70mg/dl at week 8, plus maximally tolerated statin N=97		mg daily, or simvastatin 40 mg daily. Patients were also eligible if they were receiving a daily dose of atorvastatin, rosuvastatin, or simvastatin considered appropriate by the investigator. Background treatment with LLTs other than statins was allowed for all patients, provided that they had been on a stable dose for at least 4 weeks before the screening visit. **Baseline statin use** 100% (>70% high-intensity) **Other baseline LLT** (e.g. ezetimibe, nutraceuticals) in 23%	Injection site reactions From first to last injection plus 70 days Positively adjudicated CVD events (non-fatal MI, fatal/non-fatal ischemic stroke, ischemia driven coronary revascularisation procedure) From first to last injection plus 70 days New onset diabetes at 52 weeks	

Author, year (trial name)	Population	Baseline LDL-C/non-HDL-C	Intervention	Comparison	Background treatment	Outcomes (follow-up time)	Indirectness
McCullough 2018[26] ODYSSEY Long Term	IPD analysis of subgroup of people with clinical ASVCD from ODYSSEY Long Term and ODYSSEY HIGH FH. ASCVD defined as: coronary heart disease, stroke and peripheral arterial disease, all of presumed atherosclerotic origin. N= 1,853 (1827 analysed) Mean age (SD): 61.3 (9.8) years Previous CVD event/diagnosis: ACS, coronary revascularisation procedure, PAD, ischaemic stroke.	Mean (SD) in intervention vs comparison: LDL-C: 120.1 (41.3) vs 122.8 (44.5) mg/dl Non-HDL-C: 149.4 (45) vs 152.2 (48.9)	Alirocumab 150 mg every 2 weeks N=1201	Placebo N=626	Maximally tolerated statin with or without additional lipid lowering therapy; no further details given. Baseline statin use: 56.3% vs 59% high intensity and 29.2% vs 27.2% moderate intensity in intervention vs comparison groups.	LDL-C (mg/dl) At 24 weeks	Analysis extracted includes data from the ASCVD subgroup of ODYSSEY LONG TERM (97%) and ODYSSEY HIGH FH (3%)
Nicholls 2016;[31] Puri 2016[33] (protocol)	Adults with at least 1 epicardial coronary	Mean (95% CI) in intervention vs comparison	Evolocumab 420mg monthly (subcutaneous injection)	Placebo N=484	Baseline statin use: 98%; high-intensity : 57.9% vs 59.9%;	LDL-C & HDL-C (mg/dl)	Lipid outcomes assessed over 18 months - protocol

Author, year (trial name)	Population	Baseline LDL-C/non-HDL-C	Intervention	Comparison	Background treatment	Outcomes (follow-up time)	Indirectness
GLAGOV	stenosis of 20% or greater on clinically indicated coronary angiography and had a target vessel suitable for imaging with 50% or less visual obstruction; treated with a stable statin dose for at least 4 weeks and with LDL-C level of 80 mg/dl or higher or between 60 and 80 mg/dl with 1 major or 3 minor cardiovascular risk factors. N=968 Mean age (SD): 59.8 (9.2) years Previous CVD event/diagnosis: PCI or MI.	LDL-C: 92.6 (90.1 to 95%) vs 92.4 (90 to 94.6%) mg/dl Non-HDL-C: 119.4 (116.5 to 122.3%) vs 120.8 (117.9 to 123.7%) mg/dl	N=484		moderate intensity: 40.5% vs 38.2%; low intensity: 0.4 vs 0.2% Baseline ezetimibe: 2.1%	Combined major cardiovascular events (first major adverse CV event) New onset diabetes Increased liver transaminases Injection site reactions At 18 months	specified 12 months.

Author, year (trial name)	Population	Baseline LDL-C/non-HDL-C	Intervention	Comparison	Background treatment	Outcomes (follow-up time)	Indirectness
Nicholls 2022;[29] 2021[30] (protocol) HUYGENS	People with NSTEMI with at least 1 non-culprit epicardial coronary stenosis ≥20% on angiography during NSTEMI N=161 Mean age (SD): 60.5 (9.6) years Previous CVD event/diagnosis: all had NSTEMI, some also had MI and percutaneous coronary intervention.	Mean (SD) in intervention vs comparison LDL-C: 140 (34) vs 142.1 (32.3) mg/dl Non-HDL-C: 130.9 (36.6) vs 133.4 (38.7)	Evolocumab420 mg monthly (via subcutaneous injection) N=80	Placebo N=81	Statins: overall 95% of study population taking statins at baseline; 80.7% high intensity statins, 13.7% moderate intensity and 0.6% low intensity statins. High-intensity statins: atorvastatin ≥40 mg, rosuvastatin ≥20 mg, simvastatin ≥80 mg daily. Moderate-intensity: atorvastatin 10 to <40 mg, rosuvastatin 5 to <20 mg, simvastatin 20 to <80 mg daily. Low-intensity statins: atorvastatin <10 mg, rosuvastatin <5 mg, simvastatin <20 mg daily. 4.9% treated with Ezetimibe at time of screening; 99%	LDL-C (mg/dl) Non-HDL-C (mg/dl) At week 50	Population indirectness as some participants (unclear how many) were receiving simvastatin 80 mg/d as part of being on high-intensity statins.

Author, year (trial name)	Population	Baseline LDL-C/non-HDL-C	Intervention	Comparison	Background treatment	Outcomes (follow-up time)	Indirectness
					on antiplatelet therapy; 84% on beta-blockers; 72.7% on ACE inhibitor; 14.2% on angiotensin receptor blocker		
Raber 2022;[34] Zachin 2021[53] (rationale and design) PACMAN-AMI	People undergoing PCI for Acute myocardial infarction (AMI: STEMI or non-STEMI) N=300 Mean age (SD) 58.5 (9.7) years NSTEMI: 47%; STEMI: 53%	Mean (SD) intervention vs comparison. LDL-C: 154.8 (30.9) vs 150.9 (36.3) mg/dl Non-HDL: 165.7 (34.5) vs 162.9 (35.3)	Alirocumab 150mg (biweekly via subcutaneous injection) + high-intensity statin (rosuvastatin 20mg/d)	Placebo (biweekly via subcutaneous injection) + rosuvastatin 20mg/d	Baseline statin use in 11.5% vs 13.2%; high-intensity: 7.4% vs 5.9% in intervention and comparison. Other baseline lipid lowering treatments: 0% vs 0.7%	LDL-C (mg/dl) Non-HDL-C (mg/dl) Injection site reactions At 52 weeks	None
Ray 2019;[36] Muller-Wieland 2017[27] (secondary publication) ODYSSEY DM-DYSLIPIDEMIA & DM-INSULIN	People with established ASCVD receiving maximally tolerated statin who were enrolled in the DM-DYSLIPIDEMIA and DM-INSULIN studies. ASCVD	Mean (SD) in alirocumab DM-DYSLIPIDEMIA vs usual care; alirocumab DM-INSULIN vs placebo LDL-C: 108.3 (46.3) vs 109.4 (44); 107.2 (35.1) vs 111.9 (46.4) mg/dl	Alirocumab DM-DYSLEPIDIMIA: 75mg (with blinded dose increase to 150mg at week 12 if week 8 non-HDL-C was ≥100 mg/dl) N=95	Usual care (DM-DYSLEPIDIMIA): every 2 weeks; with UC options selected before stratified randomization based on the investigator's preference for each participant. The following five UC options were	DM-DYSLIPIDEMIA: stable maximally tolerated statin dose for ≥4 weeks prior to screening visit, without other lipid-lowering therapies (LLTs), DM-INSULIN: Statins and other LLTs remained	LDL-C (mg/dl) Non-HDL-C (% change from baseline) At 24 weeks Influenza Nausea	Low % (less than 10% in each group) was on low-intensity statins.

Author, year (trial name)	Population	Baseline LDL-C/non-HDL-C	Intervention	Comparison	Background treatment	Outcomes (follow-up time)	Indirectness
	was defined as CHD; acute and silent MI, and unstable angina, ischemic stroke, or PAD. N=142 from the DM-DYSLIPIDEMIA trial; Mean age (SD): 65.1 (8.8) years N=177 from the DM INSULIN trial (all with ASCVD and T2DM) Mean age (SD) 65.8 (8.8) years Previous CVD diagnosis: CHD approximately 90% in each group including MI, and coronary revascularisation.	Non-HDL-C: 156.5 (48.4) vs 156.8 (43.3); 142.8 (41.5) vs 147 (54.9)	Alirocumab DM-INSULIN: 75mg every 2 weeks (with blinded dose increase to 150mg every 2 weeks at week 12 if week 8 LDL-C was ≥70mg/dl. N=119	included: continued use of maximally tolerated statin therapy with no additional LLT, fenofibrate, ezetimibe, omega-3 fatty acid, and nicotinic acid, reflecting variability in regional practice and therapeutic options available at the time the study was conducted. N=47 Placebo DM-INSULIN N=58	stable throughout the duration of the study. Baseline statin use: 84.8%, 87.2%, 77.3%, 72.4% in each group (majority of which was high intensity in DM-DYSLIPIDEMIA and moderate intensity in DM-INSLUIN)	From first to last dose plus 70 days or day 225 (in alirocumab vs usual care)	

Author, year (trial name)	Population	Baseline LDL-C/non-HDL-C	Intervention	Comparison	Background treatment	Outcomes (follow-up time)	Indirectness
Rehberger 2022[38]	People ages 18-65 years with clinically stable CAD of at least 6 months after MI (with mean age <55 years at first coronary event). N=100 Mean age (SD): 50.2 (9.1) years Previous CVD diagnosis: coronary artery disease	Mean (SD) in alirocumab vs ezetimibe vs control groups LDL-C: 2.3 (0.7) vs 2.4 (0.8) vs 2.4 (0.9) mmol/l	Alirocumab: 150mg subcutaneously every 2 weeks N=35 Evolocumab: 140mg subcutaneously every 2 weeks N=34	Control: standard lipid-lowering therapy with no PCSK9 inhibitors N=31	All participants were treated with statins at the highest tolerated doses with or without ezetimibe, and all were treated with angiotensin-converting enzyme inhibitors, beta blockers and acetylsalicylic acid. One in each group received a calcium channel blocker.	LDL-C (mmol/l) At 6 months	Type of statin received was not specified.
Sabatine 2017;[42] Sabatine 2016[41] (protocol) FOURIER	People aged 40-85 with clinically evidence CVD (history of MI, non-haemorrhagic stroke or symptomatic PAD) N=27,564 Mean age (SD): 62.5(9) years	Median (IQR) in intervention vs comparison LDL-C: 92 (80-109) vs 92 (80 to 109) mg/dl	Evolocumab 140mg subcutaneously every 2 weeks or 40mg monthly (based on patient preference) N=13784	Matching placebo injections N=13780	Optimised stable lipid-lowering therapy (at least atorvastatin 20 mg daily or equivalent), with or without ezetimibe. At baseline, 69.3% of the patients were taking high-intensity statin therapy (defined as atorvastatin	LDL-C Non-HDL-C At 48 weeks MACE (CVD death, MI or stroke) At 36 months Subgroup analysis based on baseline	None

Author, year (trial name)	Population	Baseline LDL-C/non-HDL-C	Intervention	Comparison	Background treatment	Outcomes (follow-up time)	Indirectness
	Previous CVD diagnosis: MI, non-haemorrhagic stroke or PAD.				≥40 mg, rosuvastatin ≥20 mg or simvastatin 80 mg)	LDL-C (<80mg/dl vs 80-<92 mg/dl vs 92-109 mg/dl vs >109 mg/dl) and statin intensity (high vs not high) available Rhabdomyolysis New-onset diabetes Increase liver transaminases Injection site reaction At 36 months	
Schwartz 2018;[45] Diaz 2022[9] (subgroup), Schwartz 2014[44] (protocol) ODYSSEY OUTCOMES	People hospitalised with acute coronary syndrome (myocardial infarction or unstable angina) 1-12 months earlier, LDL-C at least 70 mg/dl, non-HDL-C at least	Mean (SD) in intervention vs comparison. LDL-C: 92(31) mg/dl in both groups Non-HDL: 122 (35) vs 123(36) mg/dl	Alirocumab: 75mg subcutaneously every 2 weeks increased to 150mg if LDL-C remains ≥50mg/dl after 1 month N=9462	Placebo N=9462	Atorvastatin 40 or 80mg or rosuvastatin 20 or 40mg or maximal tolerated dose of one of the statins with or without lipid lowering therapies; National Cholesterol Education Program Adult	LDL-C (mg/dl) At 12 months MACE (composite of death from CHD, nonfatal MI, fatal or nonfatal ischemic stroke or UA requiring hospitalisation)	None

Author, year (trial name)	Population	Baseline LDL-C/non-HDL-C	Intervention	Comparison	Background treatment	Outcomes (follow-up time)	Indirectness
	100mg/dl or Apo B level at least 80mg per dL, receiving statins at high-intensity dose or maximum tolerated dose N=18,924 Mean age (SD): 58.5 (9.3) years Previous CVD event/diagnosis: MI: 19% PCI: 17% Coronary artery bypass grafting: 5.5% Stroke: 3.2% PAD: 4% Index ACS event: 34% STEMI; 48% NSTEMI; 17% UA				Treatment Panel-III therapeutic lifestyle changes or equivalent throughout the study.	At 4 years Myopathy New onset diabetes Increased liver transaminases Injection site reactions At 4 years	
PCSK9i versus ezetimibe							
Cannon 2015;[6] Colhoun 2014[8] (rationale); EI	People with hypercholesterolaemia and	Mean (SD) in intervention vs comparison	Alirocumab: 75mg every 2 weeks with	Ezetimibe plus subcutaneous placebo (for	Background statin: % in	LDL-C (mmol/l)	None

Author, year (trial name)	Population	Baseline LDL-C/non-HDL-C	Intervention	Comparison	Background treatment	Outcomes (follow-up time)	Indirectness
Shahawy 2017[10] (104 week data); Leiter 2017[22] (influenza outcome) ODYSSEY COMBO II	established CHD or CHD risk equivalents with LDL-C poorly controlled with a maximally tolerated daily dose of statin at stable dose for ≥4 weeks before screening LDL-C ≥ 1.8 mmol/l (≥ 70 mg/dl) with history CHD LDL-C ≥ 2.6 mmol/l (≥ 100 mg/dl) without history CHD N=720 Mean age (SD): 61.5 (9.3) years Previous CVD event/diagnosis: Documented history of CHD (acute MI Silent MI Unstable angina or	LDL-C: 2.8 (0.9) vs 2.7 (0.9) mmol/l Non-HDL-C: 3.6 (1.0) vs 3.5 (1.0) mmol/l	increase to 150mg at week 12 (if week 8LDL-C was ≥1.8 mmol/l) plus oral placebo for ezetimibe daily N=479	alirocumab) every 2 weeks N=241	intervention vs comparison Any statin: 99.8% vs 100%; high-intensity (40-80mg/d atorvastatin or 20-40mg/d rosuvastatin): 66.8 vs 66.4%; atorvastatin: 49.5% vs 66.4%; simvastatin: 21.9 vs 20.3%	Non-HDL-C (mmol/l) At week 24 Adjudicated cardiovascular events (CHD death, nonfatal MI, fatal/nonfatal ischemic stroke, UA hospitalisation, HF hospitalisation, ischemia driven coronary revascularisation) at 52 weeks MACE (CHD death, nonfatal MI, ischemic stroke or unstable angina requiring hospitalisation at 104 weeks Increased liver transaminases at 104 weeks	

Author, year (trial name)	Population	Baseline LDL-C/non-HDL-C	Intervention	Comparison	Background treatment	Outcomes (follow-up time)	Indirectness
	Coronary revascularisation procedure): 91.2% and 88% in intervention and comparison.					Local injection-site reactions at 104 weeks Diabetes mellitus/Type 2 diabetes onset at 104 weeks Influenza at 104 weeks	
Han 2020[13] ODYSSEY EAST	People with hypercholesterolemia and established CHD (97%) or CHD risk equivalents who were inadequately controlled with stable maximally tolerated statin therapy for at least 4 weeks N=615 Mean age (SD): 58.6 (10.9) years	Mean (SD) in intervention vs comparison LDL-C: 2.86 (1.25) vs 2.88 (1.29) mmol/l Non-HDL-C: 3.58 (1.31) vs 3.63 (1.36) mmol/l	Alirocumab (subcutaneous): 75mg every 2 weeks with dose increase to 150mg every 2 weeks at week 12 if week 8 LDL-C was >1.81 mmol/l N=407	Ezetimibe: 10mg daily (orally) N=208	Maximally tolerated statins: atorvastatin 40 to 80 mg daily, rosuvastatin 20 to 40 mg daily, simvastatin 40 mg daily, or lower doses of these if there was a documented reason. High-intensity statins in 68% at baseline	LDL-C Non-HDL-C. Injection site reactions Positively adjudicated CVD events (CHD death, non-fatal MI, fatal or non-fatal ischemic stroke, UA requiring hospitalisation, congestive heart failure requiring hospitalisation, ischemia driven coronary	None

Author, year (trial name)	Population	Baseline LDL-C/non-HDL-C	Intervention	Comparison	Background treatment	Outcomes (follow-up time)	Indirectness
						revascularisation) New onset diabetes/ Type 2 diabetes At week 24	
PCSK9i plus ezetimibe versus ezetimibe							
Hao 2022[14]	People with extremely high-risk CHD diagnosed with ACS and receiving PCI treatment and LDL-C ≥ 3.0 mmol/l after statin therapy N=136 Mean age (SD): 62.2 (11.9) years Index ACS event in intervention vs comparison: STEMI 39.7% vs 41.18%; NSTEMI 50% vs 45.59%; UA	Mean (SD) in intervention vs comparison LDL-C 3.54 (0.58) vs 3.52 (0.41) mmol/l	Evolocumab: 140mg every 2 weeks (subcutaneously within 48 hours after PCI) plus atorvastatin 40mg/d and ezetimibe 10mg/d N=68	Control: atorvastatin 40mg/d and ezetimibe 10mg/d N=61	All participants received standard PCI treatment and were implanted with drug-eluting stents. Both control and evolocumab groups received atorvastatin 40 mg/day and ezetimibe 10 mg/day to lower lipids after PCI. The rest of the treatment drugs were used in accordance with the current guidelines.	LDL-C mmol/l At 3-months	none

Author, year (trial name)	Population	Baseline LDL-C/non-HDL-C	Intervention	Comparison	Background treatment	Outcomes (follow-up time)	Indirectness
	10.29% vs 13.24%						
Inclisiran							
Ray 2020[37] ORION 10 and 11	People aged ≥18 years with history of ASCVD (CHD, CVD or PAD) or ASCVD risk equivalents (type 2 diabetes, familiar hypercholesterolemia and 10-year risk of a CV event) and elevated LDL cholesterol levels at screening despite maximum tolerated statin. Previous CVD diagnosis: >80% ASCVD across both trials N=3,178 Mean age (SD): 65.4 (8.7) years	Mean (SD) in ORION 10 inclisiran vs placebo; ORION-11 inclisiran vs placebo LDL-C: 104.5 (39.6) vs 104.8 (37); 107.2 (41.8) vs 103.7 (36.4) mg/dl Non-HDL-C: 134 (44.5) vs 134.7 (43.5); 137.6 (46.9) vs 133.9 (41) mg/dl	ORION-10/11: inclisiran: 284mg as a 1.5ml subcutaneous injection (4 injections: day 1, 90, 270 and 450) N=1,591	ORION 10/11: matching placebo ORION 11: placebo N=1,587	ORION-10: 89% on statins and 10% ezetimibe ORION-11: 95% on statins and 7% ezetimibe	LDL-C Non-HDL-C: Days 510 and 540 MACE (non-adjudicated terms, including those classified within cardiac death, and any signs or symptoms of cardiac arrest, nonfatal myocardial infarction, or stroke) Injection-site reaction Increased liver transaminases At day 540	None

Author, year (trial name)	Population	Baseline LDL-C/non-HDL-C	Intervention	Comparison	Background treatment	Outcomes (follow-up time)	Indirectness
ACS: acute coronary syndrome; AMI: acute myocardial infarction; CAD: coronary artery disease; CHD: coronary heart disease; LDL-C: low-density lipoprotein cholesterol; LLT: Lipid-lowering therapy; MI: myocardial infarction; PCI: percutaneous coronary intervention; SAEs: serious adverse events; STEMI: ST elevation myocardial infarction; TEAEs: treatment emergent adverse events; every 2 weeks: every two weeks; UA: unstable angina							

See Appendix D for full evidence tables.

1.1.6 Summary of the effectiveness evidence

Primary analyses

Table 3: Clinical evidence summary: ezetimibe plus statin versus statin

Outcomes	№ of participants (studies)	Certainty (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with statins	Risk difference with ezetimibe plus statins
LDL-C; (% change) follow-up: 6-12 months	322 (3 RCTs)	⊕⊕⊕◯ Moderate[a,b]	-	The mean LDL-C (% change) ranged from -29 to -52.4%	MD 11.5% lower (15.66 lower to 7.33 lower)
LDL-C; mmol/l (combined final value and absolute change) follow-up: 12 weeks - 1 year	15270 (15 RCTs)	⊕◯◯◯ Very low[a,b,c,d]	-	The range in mean change in LDL-C was -0.75 to -2.2 mmol/l and the range in mean final LDL-C value was 1.85 to 2.75 mmol/l	MD 0.41 mmol/l lower (0.47 lower to 0.34 lower)
non-HDL-C; (% change) follow-up: 6 months	40 (1 RCT)	⊕◯◯◯ Very low[a,b,e]	-	The mean % change in non-HDL-C; was -34.8%	MD 15.5% lower (26.61 lower to 4.39 lower)
non-HDL-C; mmol/l (combined final value and absolute change) follow-up: 12 weeks to 1 year	12954 (3 RCTs)	⊕◯◯◯ Very low[a,b,f]	-	The mean final value non-HDL-C was 2.4-2.8 mmol/l	MD 0.67 mmol/l lower (1 lower to 0.33 lower)
MACE follow-up: 6 months to 7 years	19067 (8 RCTs)	⊕⊕⊕◯ Moderate[g]	RR 0.94 (0.90 to 0.98)	293 per 1,000	18 fewer per 1,000 (29 fewer to 6 fewer)
MACE - follow up > 2 years follow-up: 7 years	18144 (1 study)	⊕⊕⊕◯ Moderate[g]	RR 0.94 (0.90 to 0.98)	302 per 1,000	18 fewer per 1,000 (30 fewer to 6 fewer)
MACE - follow up ≤ 2 years	923 (7 studies)	⊕⊕◯◯ Low[a,h]	RR 0.91 (0.63 to 1.31)	111 per 1,000	13 fewer per 1,000 (43 fewer to 32 more)

Outcomes	№ of participants (studies)	Certainty (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with statins	Risk difference with ezetimibe plus statins
follow-up: 6 months to 2 years					
MACE: HR follow-up: 7 years	18144 (1 RCT)	⊕⊕⊕◯ Moderate[g]	HR 0.94 (0.89 to 0.98)		)
Adverse events - myopathy or rhabdomyolysis follow-up: 6 months to 6 years	18514 (5 RCTs)	⊕◯◯◯ Very low[a,g]	OR 0.97 (0.57 to 1.64)	3 per 1,000	0 fewer per 1,000 (0 fewer to 0 more)[i]
Adverse events - raised liver transaminases follow-up: 6 months to 6 years	18696 (6 RCTs)	⊕⊕⊕◯ Moderate[a]	RR 1.08 (0.90 to 1.30)	23 per 1,000	2 more per 1,000 (2 fewer to 7 more)
Adverse events - cancer follow-up: 6 years	18144 (1 RCT)	⊕⊕⊕⊕ High	RR 1.02 (0.93 to 1.13)	81 per 1,000	2 more per 1,000 (6 fewer to 10 more)
Adverse events - gallbladder-related AE follow-up: 6 years	18144 (1 RCT)	⊕⊕⊕◯ Moderate[a]	RR 0.88 (0.75 to 1.03)	35 per 1,000	4 fewer per 1,000 (9 fewer to 1 more)

*a. Downgraded by 1 increment if the confidence interval crossed one MID and by 2 increments if the confidence interval crossed two MIDs (0.8 and 1.25 for dichotomous outcomes; 0.5 * median of baseline SD of the intervention and control group for continuous outcomes).*
b. Continuous MIDs: % change LDL-C: 9.45; absolute change LDL-C:0.35; % change non-HDL-C: 8.85; absolute change non-HDL-C: 0.455
c. Majority of evidence at high risk of bias (random effects study weighting). Reasons included such as high rates of missing data, imbalance in age between groups, insufficient information about randomisation procedures and potential deviation from randomised intervention in unblinded studies.
d. I^2 >50%; random effects model was used for the analysis due to heterogeneity unexplained by subgroup analysis
e. Very serious risk of bias due to between-group differences in age at baseline and high rate of missing outcome data.
f. I^2 >75%; random effects model was used for the analysis due to heterogeneity unexplained by subgroup analysis
g. All or the majority of evidence has serious intervention indirectness due to the proportion having the simvastatin dose increased from 40 to 80 mg being unbalanced between groups.
h. Follow-up <12 months in the majority of evidence based on weight in the meta-analysis.
i. Absolute effect calculated from risk difference.

Table 4: Clinical evidence summary: PCSK9i versus placebo or usual care

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo or usual care	Risk difference with PCSK9
% change LDL-C follow-up: 12-52 weeks	30644 (8 RCTs)	⊕⊕◯◯ Low[a,b]	-	The mean % change LDL-C ranged from -13.4 to 6.3%	MD 54.62% lower (59.28 lower to 49.97 lower)
LDL-C absolute change or final value follow-up: 12-52 weeks (one using time-weighted average from baseline to 18 months)	30054 (10 RCTs)	⊕⊕◯◯ Low[a,b]	-	The mean LDL-C absolute change ranged from -0.2 to -1.98 mmol/l	MD 1.43 mmol/l lower (1.56 lower to 1.3 lower)
non-HDL-C % change follow-up: 12-52 weeks	3090 (7 RCTs)	⊕⊕◯◯ Low[a,b]	-	The mean non-HDL-C % change ranged from -14.4 to 4.3%	MD 42.47% lower (48.45 lower to 36.5 lower)
non-HDL-C absolute change or final value (mmol/l) follow-up: 36-52 weeks (one using time-weighted average from baseline to 18 months)	1825 (5 RCTs)	⊕⊕◯◯ Low[a]	-	The mean non HDL-C absolute change (mmol/l) ranged from 0.028 to -1.77 mmol/l	MD 1.45 mmol/l lower (1.67 lower to 1.22 lower)
Major adverse CVD events/MACE (at 6 months to 4 years)	48232 (7 RCTs)	⊕⊕⊕◯ Moderate[c]	RR 0.83 (0.78 to 0.88)	89 per 1,000	15 fewer per 1,000 (20 fewer to 11 fewer)
Major adverse CVD events/MACE - follow up > 2 years	46488 (2 RCTs)	⊕⊕⊕◯ Moderate[c]	RR 0.83 (0.78 to 0.88)	89 per 1,000	15 fewer per 1,000 (20 fewer to 11 fewer)
Major adverse CVD events/MACE - follow up ≤ 2 years	1744 (5 RCTs)	⊕⊕⊕◯ Moderate[c]	RR 0.85 (0.63 to 1.14)	103 per 1,000	15 fewer per 1,000 (38 fewer to 14 more)

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo or usual care	Risk difference with PCSK9
MACE (at 36 months to 4 years)	46488 (2 RCTs)	⨁⨁⨁◯ Moderate[c]	HR 0.83 (0.78 to 0.88)		
Myopathy/rhabdomyolysis	46271 (2 RCTs)	⨁◯◯◯ Very low[c,d]	RR 0.91 (0.63 to 1.32)	3 per 1,000	0 fewer per 1,000 (1 fewer to 1 more)
New-onset diabetes (at 52 weeks to 4 years)	31302 (4 RCTs)	⨁⨁⨁⨁ High	RR 1.00 (0.93 to 1.07)	86 per 1,000	0 fewer per 1,000 (6 fewer to 6 more)
Increased liver transaminases (at 18-36 months)	28532 (2 RCTs)	⨁⨁⨁⨁ High	RR 0.99 (0.83 to 1.18)	17 per 1,000	0 fewer per 1,000 (3 fewer to 3 more)
Injection-site reactions (at 12 weeks to 4 years)	48638 (7 RCTs)	⨁⨁⨁⨁ High	RR 1.57 (1.40 to 1.77)	18 per 1,000	10 more per 1,000 (7 more to 14 more)
Nausea	317 (2 RCTs)	⨁⨁◯◯ Low[c]	RR 0.65 (0.15 to 2.85)	29 per 1,000	10 fewer per 1,000 (25 fewer to 53 more)

a. I^2 >75%; random effects model was used for the analysis due to heterogeneity unexplained by subgroup analysis
b. Continuous outcome MIDs: % change LDL-C = 13.85; absolute LDL-C: 0.37; % change non-HDL-C: 12.5; absolute non-HDL-C: 0.32.
c. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs (standard MIDs for dichotomous outcomes: 0.8 and 1.25)
d. Downgraded by 1 increment because the majority of the evidence was at high risk of bias (due to event rate for outcome being similar to number lost to follow-up)

Table 5: Clinical evidence summary: PCSK9i versus ezetimibe

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with ezetimibe	Risk difference with PCSK9i
% change LDL-C follow-up: range 24 weeks to 52 weeks	1318 (2 RCTs)	⨁⨁⨁⨁ High[a]	-	The mean % change LDL-C ranged from -18.3 to -20.3%	MD 33.5% lower (37.9 lower to 29.09 lower)

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with ezetimibe	Risk difference with PCSK9i
Final LDL-C follow-up: 24 weeks	707 (1 RCT)	⨁⨁⨁⨁ High	-	The mean final LDL-C was 2.1 mmol/l	MD 0.8 mmol/l lower (0.94 lower to 0.66 lower)
% change non-HDL-C follow-up: range 24 weeks to 52 weeks	1318 (2 RCTs)	⨁⨁⨁◯ Moderate[a,b]	-	The mean % change non-HDL-C ranged from -19.2 to -19.4%	MD 25.25% lower (29.86 lower to 20.64 lower)
MACE/ Positively adjudicated CVD events (at 24 to 104 weeks)	1332 (2 RCTs)	⨁◯◯◯ Very low[c,d]	RR 1.01 (0.58 to 1.76)	40 per 1,000	0 fewer per 1,000 (17 fewer to 31 more)
New-onset diabetes (at 24 to 104 weeks)	938 (2 RCTs)	⨁◯◯◯ Very low[d,e]	RR 0.92 (0.47 to 1.80)	40 per 1,000	3 fewer per 1,000 (21 fewer to 32 more)
Increased liver transaminases-alanine aminotransferase >3 x ULN follow-up: 104 weeks	720 (1 RCT)	⨁⨁◯◯ Low[d]	RR 2.52 (0.56 to 11.39)	8 per 1,000	13 more per 1,000 (4 fewer to 86 more)
Increased liver transaminases-aspartate aminotransferase >3 x ULN follow-up: 104 weeks	720 (1 RCT)	⨁⨁◯◯ Low[d]	RR 5.53 (0.72 to 42.62)	4 per 1,000	19 more per 1,000 (1 fewer to 173 more)

a. Continuous outcome MIDs: % change LDL-C: 15.34; final LDL-C value: 4.5 mmol/l; % change non-HDL-C: 12.61
b. I^2 >50%
c. Downgraded by 1 increment for serious indirectness due to one of 1/2 studies reporting outcome at 24 weeks
d. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs (standard MIDs for dichotomous outcomes: 0.8 and 1.25)
e. Unclear if diabetes referred to new onset in one of the studies with the higher weight in the meta-analysis.
f. Downgraded by 1 increment as the evidence was at high risk of bias, due to it being unclear if the outcome was consistently recorded.

Table 6: Clinical evidence summary: PCSK9i plus ezetimibe versus ezetimibe

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with ezetimibe	Risk difference with PCSK9i + ezetimibe
Final LDL-C (mmol/l) follow-up: 3 months	129 (1 RCT)	⨁⨁◯◯ Low[a,b]	-	The mean final LDL-C was 1.27 mmol/l	MD 0.69 mmol/l lower (0.84 lower to 0.54 lower)

a. Very high risk of bias due to recruitment and randomisation method not being specified (leading to potential selection bias), and treatment being adjusted according to lipid control during follow-up in combination with lack of blinding.
b. Continuous MID: final LDL-C: 0.25

Table 7: Clinical evidence summary: inclisiran versus placebo

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with Inclisiran
LDL-C % change follow-up: weighted average between 90 and 540 days	3178 (2 RCTs)	⨁⨁⨁◯ Moderate[a,b]	-	NR	MD 51.49% lower (56.00 lower to 46.99 lower)
LDL-C absolute change (mmol/l) follow-up: weighted average between 90 and 540 days	3178 (2 RCTs)	⨁⨁⨁◯ Moderate[c]	-	NR	MD 1.32 mmol/l lower (1.37 lower to 1.28 lower)
MACE (non-adjudicated terms) follow-up: 540 days	3174 (2 RCTs)	⨁⨁⨁◯ Moderate[d]	RR 0.74 (0.59 to 0.93)	102 per 1,000	27 fewer per 1,000 (42 fewer to 7 fewer)
Increased liver transaminases - ALT >3xULN follow-up: 540 days	3174 (2 RCTs)	⨁◯◯◯ Very low[d,e]	RR 0.99 (0.32 to 3.07)	4 per 1,000	0 fewer per 1,000 (3 fewer to 8 more)
Increased liver transaminases - AST	3174 (2 RCTs)	⨁◯◯◯ Very low[d,e]	RR 0.66 (0.24 to 1.86)	6 per 1,000	2 fewer per 1,000 (4 fewer to 5 more)

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with Inclisiran
>3xULN follow-up: 540 days					
Injection-site reactions follow-up: 540 days	3174 (2 RCTs)	⨁⨁◯◯ Low[e,f]	RR 5.01 (1.52 to 16.54)	7 per 1,000	28 more per 1,000 (4 more to 108 more)

a. I^2 = 86%; random effects model was used for the analysis due to heterogeneity unexplained by subgroup analysis.
b. Continuous MIDs: % change LDL-C; 12.3; absolute change LDL-C: 0.495
c. I^2= 84%; random effects model was used for the analysis due to heterogeneity unexplained by subgroup analysis.
*d. Downgraded by 1 increment if the confidence interval crossed one MID and by 2 increments if the confidence interval crossed two MIDs (0.8 and 1.25 for dichotomous outcomes; 0.5 * median of baseline SD of the intervention and control group for continuous outcomes).*
e. Event rate less than number lost to follow-up.
f. I^2 = 69%; random effects model was used for the analysis due to heterogeneity unexplained by subgroup analysis.

See Appendix G for full GRADE tables.

Sensitivity analyses

Forest plots showing the data stratified according to the prespecified subgroups (baseline LDL cholesterol, and non-HDL cholesterol and statin intensity) are provided in Appendix F where sufficient data were available.

These were discussed at the guideline committee meeting and the committee agreed that, while there was often insufficient outcome data to test robustly, the sensitivity analyses results did not show a consistent signal of any difference in LDL cholesterol, non-HDL cholesterol or MACE reductions achieved by any of the interventions according to baseline LDL cholesterol or non-HDL cholesterol or by statin intensity. Thus, decision making was based on the primary analysis using the total population and GRADE tables are not presented for the sensitivity analyses.

1.1.7 Economic evidence

The purpose of this review question was to identify key inputs for an economic model comparing the cost effectiveness of different cholesterol targets – see separate economic analysis report. Economic evaluations of lipid modification therapy were not systematically reviewed.

1.1.8 Evidence statements

Effectiveness/Qualitative

- Not applicable.

Economic

- Not applicable.

1.1.9 The committee's discussion and interpretation of the evidence

The outcomes that matter most

The committee agreed that LDL cholesterol, non-HDL cholesterol, combined major adverse cardiovascular events (CVD death, non-fatal MI, non-fatal ischemic stroke), quality of life and specific treatment-related adverse events (myopathy/rhabdomyolysis, new-onset diabetes, increased liver transaminases, cancer, gall-bladder related diseases, injection-site reactions, nausea and influenza) were all required for this evidence review. For the purposes of decision making, all outcomes were considered equally important and were therefore rated as critical.

The quality of the evidence

There were 34 RCTs included in the clinical evidence. The quality of the evidence varied across comparisons ranging from very low to high for different outcomes.

Pairwise analyses

Ezetimibe plus statin versus statin alone

There were 15 RCTs comparing ezetimibe plus statin versus statin alone, 10 of which were open-label unblinded studies. The majority of the outcomes available for this comparison were rated as moderate quality, including percentage change in LDL cholesterol from baseline, MACE outcomes and raised liver transaminases and gallbladder-related adverse events. These were downgraded for either imprecision where the confidence interval around the effect estimated crossed an MID, or for concerns over intervention indirectness due to imbalance in statin dose between intervention and comparator groups. Evidence for cancer was rated as high quality. Evidence for LDL cholesterol and non-HDL cholesterol reported as final values or absolute changes and percentage change in non-HDL cholesterol was of very low quality because of imprecision and further downgrading for risk of bias (such as high rates of missing data, imbalance in age between groups, insufficient information about randomisation procedures and potential deviation from randomised intervention in unblinded studies). Evidence for myopathy/rhabdomyolysis was also of very low quality, downgraded for imprecision and the aforementioned concerns over indirectness related to the intervention received, which was particularly important for this outcome because simvastatin 80 mg is known to be associated with an increased incidence of muscle adverse events.

The committee discussed the characteristics of the trial participants, including statin use before and during the study period. For this comparison only 1 trial exclusively included people who had prior statin treatment, 1 had 57% with statin pre-treatment, 6 reported <50% with prior statin, 3 included only statin naïve participants, while the remaining 4 did not provide information on prior statin use. Regarding the starting dose of statin at randomisation, 4 used medium intensity statins, 9 used high intensity and 2 were mixed or unclear. Statin dose titration was permitted if targets were not met in at least 3 trials that did

not start participants on high-intensity statins. This included the IMPROVE-IT trial, in which 27% in the statin alone arm were escalated to simvastatin 80 mg compared to 6% in the ezetimibe arm. The committee noted that this is likely to dilute the relative benefit of adding ezetimibe to statin but agreed that this does not limit the usefulness of the data as it reflects real-world practice. Other studies did not specify if dose escalation was permitted.

PCSK9i (alirocumab or evolocumab) versus placebo or usual care

Evidence for PCSK9i (alirocumab and evolocumab) compared to placebo or usual care was available from 14 RCTs. The quality of the evidence for the majority of outcomes including LDL cholesterol and non-HDL cholesterol and nausea was low due to imprecision around the effect estimates and inconsistency due to heterogeneity in the results of the studies contributing to the lipid outcomes that was unexplained by subgroup analysis. The quality of the evidence for MACE was moderate, only downgraded due to imprecision. The quality of the evidence for the adverse events of new-onset diabetes, increased liver transaminases and injection-site reactions was high, with no concerns lowering confidence in the evidence.

All except 1 trial enrolled people who were already receiving statins, which they continued alongside the randomised interventions. In most cases statins were administered at the maximally tolerated dose, which included high and medium intensity in varying proportions. A small proportion of participants (ranging from 1 to 14%) were also receiving ezetimibe as part of lipid-lowering therapy in 9 trials. The committee agreed that this was similar to current UK practice for those receiving PCSK9 inhibitors.

PCSK9i versus ezetimibe

The quality of the evidence for PCSK9i vs ezetimibe, available from 2 RCTs, was mostly of very low or low quality as it was downgraded for imprecision around the effect estimates and in some cases indirectness related to the outcome reporting (time-point being shorter than 12 months for MACE in one of the two contributing studies). For influenza, there was also risk of bias as it was unclear whether the outcome was consistently reported. The quality of the evidence for lipid outcomes was higher. Specifically, evidence was considered high quality for LDL cholesterol and moderate for percentage change in non-HDL cholesterol from baseline, the latter being downgraded for concerns over inconsistency due to heterogeneity in the results of the two studies contributing to the pooled estimate. Participants were receiving stable maximally tolerated statin therapy, which continued alongside the randomised interventions, which is directly applicable.

PCSK9i plus ezetimibe versus ezetimibe alone

Evidence for PCSK9i plus ezetimibe compared to ezetimibe alone, available from one RCT, was of low quality, downgraded for risk of bias due to the recruitment and randomisation methods not being specified (leading to potential selection bias), and treatment being adjusted according to lipid control during follow-up in combination with lack of blinding.

Inclisiran versus placebo

Evidence for inclisiran versus placebo, available from 2 studies was of moderate quality for LDL cholesterol and MACE and of low quality for injection site reactions and very low quality for increased liver transaminases. The quality of the evidence was mostly downgraded for imprecision and for inconsistency in the cases of LDL cholesterol and injection-site reactions due to heterogeneity in the results reported between the studies contributing to the pooled estimates for those outcomes. Increased liver transaminases and injection-site reactions were further downgraded for risk of bias due to the event rate being lower than the number lost to follow-up meaning that if any events had occurred in those who were not available for the analysis the effect estimate may have changed significantly.

Summary

Overall, the committee were confident that the evidence for LDL and non-HDL cholesterol were of sufficient quality to reliably inform the network meta-analyses and health economic model.

Network meta-analyses

For absolute and percentage change in LDL cholesterol and non-HDL cholesterol, the risk of bias and indirectness was as described for the pairwise analyses because the same studies were included.

The credible intervals around the effect estimates for each intervention relative to placebo varied. For absolute and percentage change in LDL cholesterol, there was little uncertainty for most of the estimates for active treatments compared to placebo. However, there was moderate uncertainty for percentage change in LDL cholesterol for inclisiran compared to placebo, with credible intervals spanning around 20% and for evolocumab plus ezetimibe there was considerable uncertainty for absolute change in LDL cholesterol with credible intervals spanning 0.8 mmol/litre.

For percentage change in non-HDL cholesterol there was considerable uncertainty for ezetimibe and inclisiran, with the credible intervals spanning an interval of more than 20% and moderate uncertainty for PCSK9i with the credible interval spanning around 15%. For absolute change in non-HDL cholesterol, which was not available for inclisiran, the credible intervals spanned more than 1.0 mmol/litre for ezetimibe and more than 0.8 mmol/litre for PCSK9i, again showing considerable uncertainty.

Inconsistency was minimal for all of the modelled datasets, and there was good agreement between the direct and indirect treatment effect estimates.

The committee were confident that these results were a good reflection of the true effects and could therefore be used to inform the economic model.

Benefits and harms

Pairwise analyses

Ezetimibe plus statin versus statin alone

Absolute LDL cholesterol change from baseline or final score was more commonly reported than other lipid outcomes. The committee noted variability between studies in the change and final scores. Overall, adding ezetimibe had a clear benefit for additional lipid lowering compared with statin alone. There was limited evidence to demonstrate whether this benefit translated into a reduction in MACE and the absolute risk difference was modest. However, the committee discussed that the majority of studies had a follow-up of 1 year or less, and that in the largest study with the longest follow-up the benefit of ezetimibe was likely to have been diluted by the simvastatin dose being increased in a larger proportion of the control group than the experimental group. Therefore, they agreed that the evidence was likely to be an underestimate of the true benefit of ezetimibe for this outcome.

The occurrence of protocol-reported adverse events (including myopathy/rhabdomyolysis, liver transaminases, cancer or gallbladder-related adverse events) was rare overall making the estimates imprecise, but the committee agreed that there were no clinically important differences for any reported adverse events. This was in line with the committee's opinion that the adverse events of ezetimibe were minimal and did not outweigh the benefits.

PCSK9i (alirocumab or evolocumab) versus placebo or usual care

The committee noted that LDL cholesterol was more commonly reported than non-HDL cholesterol, and that there was some inconsistency between studies in the lipid outcomes. However, adding alirocumab or evolocumab to statin, with or without ezetimibe, resulted in additional lipid lowering compared with placebo or usual care and the size of the effects, showing a large benefit of PCSK9i compared with control, were as the committee would expect based on their clinical experience.

As for ezetimibe, there was limited evidence to demonstrate whether this benefit translated into a reduction in MACE. The committee noted that despite there being a greater lowering of LDL cholesterol with PCSK9i than with ezetimibe, the MACE benefit in terms of the absolute effect was similar. They discussed that this could be due to the PCSK9i trials being shorter due to insufficient funding for longer durations, which could mean that the maximal benefit for this outcome was not observed during the trials.

There were no clinically important differences in terms of adverse events including myopathy/rhabdomyolysis, new onset diabetes, increased liver transaminases, injection-site reactions or nausea. The committee noted that although the effect was not clinically important compared to control, a small proportion of people receiving PCSK9i experienced injection-site reactions. They agreed that this reflected a low number of events and that injection-site reactions are not likely to be significant or long-lasting.

PCSK9i versus ezetimibe

Amongst participants receiving stable maximally tolerated statin therapy PCSK9i achieved greater reductions in LDL cholesterol and non-HDL cholesterol compared to ezetimibe. There were no clinically important differences in terms of MACE, new onset of diabetes or increased liver transaminases. The committee agreed evidence for this comparison was limited considering the number of participants included and the relatively short duration of follow-up. They agreed evidence contributed to the NMA results but was of limited usefulness in its own right.

PCSK9i plus ezetimibe versus ezetimibe alone

The committee noted that evidence for this comparison was very limited as it was only available from one study with a total of 129 participants and the short duration of follow-up limiting the extent to which conclusions could be drawn.

Inclisiran versus placebo

Participants were receiving stable maximally tolerated statin therapy, with 6-10% also receiving ezetimibe, which continued alongside the randomised interventions. Evidence showed a large clinical benefit of inclisiran compared to placebo in terms of LDL cholesterol reduction, which the committee agreed reflected their experience. There was no clinically important difference between inclisiran and placebo in terms of MACE (definition including non-adjudicated events: CV death, cardiac arrest, non-fatal myocardial infarction and non-fatal stroke), but the committee agreed that the size of the absolute benefit of inclisiran was encouraging considering that the MACE outcome was exploratory and so the trials were not powered to detect a difference. They agreed that this exploratory endpoint gives indicative evidence that supports the likely translation of decreased cholesterol levels to reduced cardiovascular events, and they had confidence in the findings as being sufficient to inform the economic model.

The committee noted that inclisiran did result in more injection site reactions compared to placebo. However, they noted that the trials reported most of these to be mild (discomfort noticed, but no disruption to daily activity) and some moderate (discomfort sufficient to reduce or affect normal daily activity), but none were severe or persistent. The committee agreed that the effect was not clinically important particularly as injection frequency of inclisiran is low (every 6 months).

Sensitivity analyses (all comparisons)

It was noted that some studies conducted sensitivity analyses exploring the effect of different baseline LDL cholesterol and non-HDL cholesterol levels and of different statin intensities used by study participants upon lipid and MACE outcomes. Forest plots of those analyses were presented to the committee and it was agreed that while there was often insufficient outcome data to test robustly, there was no consistent signal of any difference in LDL cholesterol, non-HDL cholesterol or MACE reductions achieved by any of the interventions according to baseline LDL cholesterol or non-HDL cholesterol or by statin intensity. Thus, decision making was based on the primary analysis using the total population.

Summary

The pairwise evidence showed a benefit of all reviewed lipid lowering therapies for additional reduction of LDL cholesterol beyond that achieved by statins alone, without any clinically important increase in adverse events. Although there was some imprecision and heterogeneity, the findings for efficacy and adverse events were consistent with the committee's clinical experience and expectations. Therefore, they agreed that the evidence was reliable to help inform the network meta-analysis and economic model.

Network meta-analyses

The committee discussed the effect estimates that draw on all available clinical evidence to provide consistent effect sizes compared to a control group (labelled placebo, but which included statin treatment) across all treatments in the network. They agreed that the findings for LDL cholesterol and non-HDL cholesterol broadly aligned with their expectations and experience, showing a large benefit of PCSK9i compared to control, with a similar but slightly lower benefit for inclisiran and a benefit for ezetimibe that was considerably less than that for PCSK9 or inclisiran.

The committee noted that they would expect to see a greater relative benefit for LDL cholesterol than for non-HDL cholesterol, but that this was not the case for the ezetimibe effect estimates from the NMA. The committee discussed that the greater benefit for non-HDL cholesterol in the ezetimibe data could be due to the fact that only 1 small study reported non-HDL cholesterol percentage change for ezetimibe versus statin alone, and showed a larger benefit for serum cholesterol than some other studies. The committee also discussed the possibility that ezetimibe can lead to 2-5% increase in HDL cholesterol and therefore this may also contribute to the NMA findings. Therefore, the NMA estimate for ezetimibe versus control was informed more by the indirect effect of alirocumab compared to ezetimibe, which may have caused the discrepancy from expectations.

The NMA effect estimates for inclisiran and PCSK9i were broadly consistent with those from the pairwise meta-analysis for all 4 outcomes assessed. However, for ezetimibe the NMA estimate for percentage change in LDL cholesterol and non-HDL cholesterol were higher than the results from the pairwise analyses. For non-HDL cholesterol this was likely to be due to the limited evidence available for percentage change in the direct comparison of ezetimibe versus control, meaning the NMA estimates were more influenced by the indirect comparisons.

Meta-regression models were conducted to explore the impact of mean baseline lipid levels on the treatment effect. However, there was very limited evidence with which to estimate the meta-regression models, and the, although effects were very uncertain, did not indicate any effect modification by baseline mean lipid levels in the studies. Therefore, the committee agreed that the meta-regression models were not useful to inform any further analyses.

Cost effectiveness and resource use

No published economic evaluations were found that compared different lipid targets. Therefore, original economic modelling was undertaken.

Cost effectiveness modelling of treatment escalation

As noted above, the treatments available for escalation for people with CVD who are on a statin were found to be both effective and safe. Although the injectable therapies (inclisiran and the PCSK9 inhibitors) were more effective than ezetimibe, they are considerably more costly due to the acquisition cost (even at confidential price levels that are discounted for the NHS) and the need for health care professionals to administer injections. Inclisiran has a lower cost than the PCSK9 inhibitors, even though patients taking PCSK9 inhibitors can self-inject.

The committee agreed that the cost of escalation treatment will be at least partially offset by reduced admissions and procedures for cardiovascular disease; therefore, it is important to weigh up the cost savings and health gain against the cost of treatment.

For the population, ezetimibe was the most cost-effective escalation treatment, with a cost per QALY under £1000. However, further routine escalation to any injectable treatment would cost over £30,000 per QALY. It is clearly not cost-effective to offer the full range of treatments to everyone with CVD, so it is important to assess at which baseline lipid levels, escalation could be cost effective.

Cost effectiveness of escalation by baseline lipid level

The economic models was developed using two alternative approaches. For each approach, separate analyses were conducted using treatment effects based on LDL cholesterol reduction and non-HDL cholesterol reduction. In both approaches, the sequence of escalation from a statin was first ezetimibe and then inclisiran. They differed as follows:

- In the first approach the lipid levels at which it is cost effective to escalate therapy were estimated separately for adding ezetimibe to a statin and then for adding inclisiran to ezetimibe and a statin.
- The second approach looked at a single lipid level at which it was cost effective to escalate treatment.

In patients maintained on statin therapy, the first approach demonstrated the cost effectiveness (at £20,000 per QALY gained) of adding ezetimibe irrespective of the actual LDL cholesterol or non-HDL cholesterol level and therefore a threshold value for the introduction of ezetimibe was not defined. With all patients maintained on both statin and ezetimibe, the addition of inclisiran was only cost-effective for those individuals with LDL cholesterol levels above 3.1 mmol/litre (or 4.1 mmol/litre for non-HDL cholesterol).

The second economic model approach demonstrated that escalation was cost effective for people with LDL cholesterol levels above 2.2 mmol/litre (or 2.9 mmol/litre for non-HDL cholesterol) after treatment with a statin i.e. only patients with LDL cholesterol > 2.0 mmol/litre (or non-HDL cholesterol > 2.9 mmol/litre) despite receiving statin therapy would then be prescribed ezetimibe, and only if the target of LDL cholesterol 2.2 mmol/litre (or non-HDL cholesterol 2.9 mmol/litre) was still not achieved would inclisiran be added. However, there was uncertainty in the region between 2.0 and 2.2 as, in the probabilistic analysis, 2.0 was the most cost-effective target in around 40% of the simulation. It was noted that amongst the CVD population (all receiving statin therapy) used for these models, the mean LDL cholesterol was 1.9 mmol/litre prior to any therapy escalation.

The base case scenario of the second approach defined a specific escalation pathway involving statins, followed by ezetimibe plus statin and finally inclisiran plus ezetimibe plus statin. In practice, the pathway does not always follow this sequence. As specified in TA733,

people may be escalated to inclisiran without first receiving ezetimibe based on current cholesterol level and clinical judgement. Scenario analyses were conducted for 3 alternative pathways allowing some people to start an injectable therapy without first receiving ezetimibe. The most cost-effective target increased to 2.4 mmol/litre in the pathway where people could receive ezetimibe alone, inclisiran alone or ezetimibe together with an injectable therapy. When combination therapies or PCSK9i were excluded, the cost-effective target remained at 2.2 mmol/litre LDL-C.

Within each approach, the model identified a strategy that was most cost effective (below £20,000 per QALY):

- Treatment-specific cholesterol thresholds - Ezetimibe for all at outset and then add inclisiran above 3.1 mmol/litre LDL cholesterol (4.1 mmol/litre non-HDL cholesterol).
- Singe cholesterol target - Statin therapy only, UNLESS a target value of LDL cholesterol 2.2 mmol/litre (non-HDL cholesterol 2.9 mmol/litre) has not been achieved.

The reason that the second approach had a lower optimal cholesterol threshold was because the cost effectiveness of escalation is based on the cost effectiveness of both ezetimibe and inclisiran combined, rather than just inclisiran alone. Comparing the two strategies with each other, the single target strategy saw fewer people on ezetimibe, more people on inclisiran. It had a higher cost and more QALYs but the cost per additional QALY was greater than £30,000 per QALY. Both strategies are likely to cost less than £20,000 per QALY compared to current practice, where escalation is uncommon and they would be cost saving compared with an LDL cholesterol target of 1.8 (non-HDL cholesterol 2.5 mmol/litre), as currently recommended in the NHS Quality Outcomes Framework.

The results were robust to sensitivity analysis, except that:

- The inclisiran treatment threshold was lower when alternative utility scores were used.
- Both targets were lower if a £30,000 per QALY threshold was used.
- The single target was higher when people were less adherent to ezetimibe and lower when people were less adherent to inclisiran.
- Both targets were higher if PCSK9 inhibitors were used instead of inclisiran.
- Both targets were higher if a treatment effect was applied only to cardiovascular mortality (not to all-cause mortality) but this approach is likely to under-estimate the benefits of escalation.
- The single target was slightly higher when a different treatment pathway allowing people to use inclisiran with or without ezetimibe was used.

However, the committee were satisfied that the base case analyses were based on the most plausible assumptions.

For each approach, models were run twice with treatment effects based first on LDL cholesterol and then separately based on non-HDL cholesterol. Although, the base case results of each model were consistent, the LDL-c targets were generally considered more robust for the following reasons:

- There was more trial evidence for the estimates of the percentage reduction in LDL cholesterol than there were for the estimates of non-HDL cholesterol.
- There was more statin trial evidence for the effect of LDL cholesterol on cardiovascular events than there was for the effect of non-HDL cholesterol on cardiovascular events. For some of the cardiovascular events the results had to be approximated as there was only empirical evidence for MI and stroke.

However, the committee agreed that a non-HDL cholesterol target should also be given when LDL cholesterol is not requested or calculated.

Committee interpretation and recommendations

The committee acknowledged that giving ezetimibe to everyone who has CVD and is on a statin and then inclisiran or other injectable for those above an LDL cholesterol of 3.1 mmol/litre would be a relatively low cost and efficient strategy. However, they chose to recommend treating people to a LDL cholesterol target of 2.0 mmol/litre for the following reasons:

- A target that is similar to that recommended by other organizations would be more likely to lead to increased use of cost-effective treatments, including statins.
- Although it would mean people at low levels of cholesterol do not get ezetimibe, it would mean people with LDL levels between 2.0 and 3.1 mmol/litre after eztemibe would get other lipid lowering treatment, and so it favours people in more need of treatment.
- The target of 2.0 was found to be cost-effective in a significant proportion of the simulations of the probabilistic analysis and would enable the treatment of a larger population with elevated LDL-c levels, mitigating their high risk of future CVD events.

Using the distributions from the CPRD dataset, a 2.0 LDL cholesterol equivalent target that would lead to the same proportion (42%) of people escalating would be 2.6 non-HDL cholesterol. As an alternative approach, non-HDL cholesterol was calculated using the Friedewald equation and the mean triglyceride level of 1.4 mmol/litre. This method also resulted in a non-HDL cholesterol of 2.6 mmol/litre.

Given that the evidence showed that ezetimibe was cost effective regardless of the person's lipid levels, the committee also decided that it could be considered for people with lipid levels below the agreed targets of 2.0 mmol/litre for LDL cholesterol and 2.6 mmol/litre for non-HDL cholesterol, taking into account the trade-off between increasing medication (the committee noted that a combination pill of Atorvastatin and ezetimibe is available in the USA), minimising risk and the burden of implementation which is most likely to fall within primary care.

It is expected that this update to the guideline will substantially increase prescribing of ezetimibe and inclisiran and that this will represent a substantial resource impact for the NHS. However, it will also be associated with reduced admissions for stroke, MI and cardiovascular procedures and longer survival for patients. Overall, the committee concluded that this target would increase NHS costs but would be cost effective.

People who are statin intolerant

Pre-consultation feedback on the draft guideline from external stakeholders highlighted the absence of recommendations on the treatment pathway for people who are statin intolerant and specifically the role of bempedoic acid. They also questioned if the draft treatment target applied to people who are statin-intolerant. The committee therefore made recommendations based on the technology appraisal TA694 Bempedoic acid with ezetimibe for treating primary hypercholesterolaemia or mixed dyslipidaemia and on economic modelling of people who are statin intolerant.

The committee discussed that statin intolerance is very difficult to define. The current guideline refers to trying three different statins whereas other definitions are less prescriptive, for example the presence of clinically significant adverse effects that represent an unacceptable risk to the patient or that may reduce compliance with therapy (NICE TA385 Ezetimibe for treating primary heterozygous familial and non-familial hypercholesterolaemia).

The committee discussed that the proportion of people who are unable to take statins due to side effects or adverse events is very small and therefore true statin intolerance is rare. The proportion of people reporting side effects in trials is often at a similar rate in the statin and

placebo arms and evidence used to calculate the prevalence of statin intolerance does not take this into account.

The committee emphasised that statin therapy is the most effective method of reducing the risk of CVD events and that this should be the mainstay of treatment. They highlighted the importance of following recommendation 1.4.30 on strategies to use if someone reports adverse effects when taking a statin.

The committee discussed, but did not review, the evidence from the NICE technology appraisal on bempedoic acid (TA694), as well as from the CLEAR Outcomes trial that was published after TA694. They noted that people in the control arms of the trials were not on the optimal lipid lowering therapies, which could result in an over-estimation of the effectiveness of bempedoic acid. They also noted the high incidence of renal adverse events in CLEAR Outcomes. It is not clear if the observed changes to renal outcomes would have resulted in serious complications had the treatment not been stopped, or what form of monitoring would be helpful. In addition, the mean age of the people in this trial was 7 years lower than the mean age of the people with CVD in whom the drug would be offered in clinical practice. Therefore, the incidence of adverse events may be higher and a proportion are likely to be unable to tolerate bempedoic acid.

The committee discussed whether the target should be different in the statin intolerant population because of the different treatment options and associated costs. However, it was noted that this may introduce inequality regarding access to lipid-lowering treatment, and that the target at which escalation is cost effective did not change when the statin intolerant population was included in the model, largely because the prevalence of statin intolerance is relatively low. Therefore, the committee agreed that the target for people who are statin intolerant should be the same as for those who are on statin therapy, supported by the health economic sensitivity analysis. They made recommendations consistent with those in the NICE TA694 to offer ezetimibe and if this does not result in the person achieving the target or less, then other lipid lowering therapies should be offered in addition. Which therapy to offer should be discussed as part of shared decision making and depends on several different factors, for example bempedoic acid is an oral preparation whereas inclisiran, evolocumab and alirocumab are injectable formulations. The committee also highlighted that the recommendation would no longer be a cost-effective use of NHS resources if the number of people being labelled as statin intolerant and following the associated treatment pathway increased too far beyond the 9.1% estimate included in the model sensitivity analysis. Therefore, they emphasised the importance of trialling of statin therapy in line with the recommendations in this guideline before considering someone to be statin intolerant because the proportion who are truly statin intolerant is likely to be less than 9.1% and the best way to help people to achieve the target will be following the statin pathway in the majority of people. The committee noted that there is guidance from the Accelerated Access Collaborative for people who are statin intolerant.

A sensitivity analysis including people who are statin intolerant was added to the economic models which included a different escalation pathway with bempedoic acid. The sensitivity analysis found that the inclusion of this population would not affect the optimal LDL-c single target which remained 2.2 mmol/litre.

People at very high risk

The committee looked for a single LDL cholesterol target for all people with CVD and on a statin. Some people will be at higher cardiovascular risk due to risk factors other than their cholesterol levels, for example if they smoke or if they have had multiple CVD events. Potentially these people have even more to gain from lipid lowering therapy escalation. However, we do not know if a lower target would be cost-effective for these patients. We cannot be sure that the relationship between cholesterol reduction and cardiovascular outcomes, as measured by the CTTC, is the same as for the population as a whole and the

gain in life expectancy could be less given their additional risk factors. These people are included in the trial and observational data inputting in to the model but were not analysed as a separate subgroup.

Other factors the committee took into account

The committee heard evidence from an expert witness; Andrew Black, vice Chair of the NICE indicator advisory committee (IAC). A written account of the testimony is provided in Appendix L. The testimony provided additional contextual information to the committee regarding what is considered when deciding on an indicator. The committee were informed of the request to develop indicators for cholesterol targets due to the existing recommendation in CG181 to aim for a 40% reduction in non-HDL cholesterol levels not being measurable in electronic clinical systems as the systems are unable to extract the two measurements to calculate the percentage, and in some cases due to baseline data being lacking even if percentages were calculated and entered manually. The lack of baseline cholesterol levels was a particular problem in secondary prevention when people may be initiated on treatment following occurrence of an acute event and the lipid level at that time not being recorded. The committee were also made aware of a draft lipid target that was put out to consultation by the IAC, with a non-HDL cholesterol value of 3.3 mmol/litre, but this was not accepted due to negative stakeholder feedback on both sides.

The committee discussed whether indicators could be based on treatment received rather than target levels, as targets could discourage treatment of people if their lipid levels are just below the target. A measure that incentivised increasing the number of people on recommended treatment may be of better value. It was noted, however, that in the case of lipid management this was problematic as the number of people on statins could be measured from electronic systems, but not those on high-intensity statins or a particular dose of statin. It was also not possible to capture whether a prescription had been filled by the person, or whether the medicines were taken and so adherence could not be captured.

The committee were also aware that NHS England had introduced an indicator for the 2023/24 Quality Outcomes Framework (QOF) in the absence of a NICE indicator. The QOF indicator included target lipid levels of lower than 2.5 mmol/litre non-HDL cholesterol and lower than 1.8 mmol/litre LDL cholesterol. The committee noted that the evidence-based treatment target demonstrated in the single target model approach developed as part of this update was broadly in line with this. Although slightly higher, the committee agreed it was the correct level to recommend in the guideline as it was based on a robust review and analysis of data. A target of 1.8 mmol/litre LDL had a cost per QALY gained that was substantially above £20,000 when compared to 2.0 mmol/litre. It would require many more people to use an injectable therapy and the opportunity cost to other NHS patients would be considerable.

The committee discussed that CG181 to date included recommendations for initial measurements for people starting on lipid lowering therapy, which stated that total cholesterol, HDL cholesterol and triglycerides should be measured, along with non-HDL cholesterol which is calculated from these. The recommendations specifically state that a fasting sample is not required, which would be needed for a robust calculation of LDL cholesterol. Although non-HDL cholesterol is more commonly used in primary care, for these reasons, the committee noted that guidance for other lipid lowering therapies includes eligibility based in part on LDL cholesterol levels. Other guidelines that have included lipid targets and the QOF include both non-HDL and LDL cholesterol. Therefore, the committee agreed that recommendations for targets needed to include both measures. They agreed the recommendation for what should be measured when starting on statin should clarify that total cholesterol, HDL cholesterol and triglyceride levels should be measured in order to calculate non-HDL cholesterol and LDL cholesterol, so as not to imply that LDL cholesterol needed to be measured directly.

Committee consensus opinion, informed by national audits, was that uptake of statins was suboptimal (there are a reasonably small number of CVD patients who are not on any statin but many who are most likely not on the highest dose/intensity that they could tolerate) even

in those who had CVD. They agreed it was important to ensure that people with CVD were offered atorvastatin 80 mg, as recommended in this guideline, and if already on a statin, to ensure people were receiving the maximum tolerated high intensity statin dose. Evidence considered within this update demonstrated that the addition of ezetimibe to maximally tolerated statin would have a favourable impact on an individual's lipid profile and would be cost-effective. Again, the committee were aware that ezetimibe prescribing at present was relatively low. The committee agreed that an increase in prescribing and uptake of ezetimibe in people with CVD could have a substantial impact on achieving lower LDL-c / non-HDL-c levels. The committee did however consider the pragmatic implications of recommending both high intensity statin therapy and ezetimibe to all patients with CVD, particularly given the limited experience and use of ezetimibe in both primary and secondary care. The implementation process would place a significant additional burden on primary care both in terms of a systematic review of all patients with CVD in order to offer ezetimibe therapy as well as the assessment of adherence, side-effects and impact of polypharmacy. In addition, many patients who are maintained on statin therapy believe their cholesterol levels to be "well controlled" and therefore the rationale for introducing another lipid lowering drug without a specific target to base this upon may lead to both confusion and reticence amongst patients. Furthermore, for those statin naive individuals with a new diagnosis of CVD, it is unclear as to whether or not introducing both high intensity statin and ezetimibe immediately would be deemed acceptable and appropriate given the potential impact on perceived adherence/tolerance of these therapies (particularly given that the majority of CVD event reduction is achieved by the high intensity statin alone). The committee therefore agreed that whilst there was persuasive cost-evidence to justify the routine use of ezetimibe (in addition to statin therapy) to all patients with established CVD, the various logistic/pragmatic factors described resulted in a consensus position that ezetimibe could be "considered" (as opposed to "offered") to all patients with CVD, irrespective of their measured/calculated cholesterol values.

The committee also discussed that to achieve lower treatment targets, people starting from a high baseline LDL-c / non-HDL-c level, may require a number of medicines to reduce their lipid levels substantially. The committee highlighted the importance of shared decision making when discussing the risks and benefits of taking additional medicines. As noted, lipid lowering treatment options other than statins and ezetimibe are only available as subcutaneous injections. The committee noted that self-injection may pose a barrier for some people, such as people with certain cognitive or physical disabilities. However, there are support schemes available and these treatments are most commonly delivered in clinics at present, typically by practice or community nurses.

The committee agreed that the recommendations should not differ for older people or those who are frail, however, they noted that appropriateness of escalating treatment to all older/frail people should be determined by clinical judgement. Consideration of risk and benefits and factors such as polypharmacy, multimorbidity, frailty and life expectancy are particularly important in older age groups.

The RCGP and BMA position statement on use of inclisiran was also raised, which was more cautious about its use than the NICE technology appraisal recommendation. Particular concerns relating to the lack of outcome data or long-term data. Some of the committee considered that alongside the increased cost and resource implications, these were good reasons to be cautious about recommending low treatment targets that may necessitate more people to be prescribed inclisiran to achieve it, especially when the outcome data are still pending.

The committee highlighted that some groups of people are under prescribed statins for example people with peripheral artery disease and it is important that the recommendations are applied to all people with established cardiovascular disease.

1.1.10 Recommendations supported by this evidence review

This evidence review supports recommendations 1.7.1, 1.7.8 to 1.7.11 and 1.10.1 to 1.10.2.

1.1.11 References

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54. Zhan S, Tang M, Liu F, Xia P, Shu M, Wu X. Ezetimibe for the prevention of cardiovascular disease and all-cause mortality events. The Cochrane database of systematic reviews. 2018; 11:cd012502

Appendices

Appendix A Review protocols

A.1 Review protocol for escalation of lipid modification therapy for secondary prevention of CVD

ID	Field	Content
1.	Review title	Escalation of lipid modification therapy for secondary prevention of CVD
2.	Review question	In adults with CVD requiring escalation of therapy beyond statins, what is the effectiveness of lipid-lowering therapy?
3.	Objective	To provide evidence on lipid lowering, CVD event risk reduction achieved, and adverse events experienced during escalation of lipid modification therapy to support the identification of a target for secondary prevention of CVD. This review will not be considering sequencing of treatment options listed in the interventions.
4.	Searches	Key papers: • IMPROVE-IT • FOURIER • ODYSSEY OUTCOMES • ORION-10 and -11 • Cochrane review on Ezetimibe • Cochrane review on PCSK9 monoclonals The following databases will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE

		• Epistemonikos Searches will be restricted by: • English language studies • Human studies Other searches: • Reference searching • Citation searching • Inclusion lists of systematic reviews The full search strategies will be published in the final review. Medline search strategy to be quality assured using the PRESS evidence-based checklist (see methods chapter for full details).
5.	Condition or domain being studied	Cardiovascular disease

6.	Population	**Inclusion:**
		• Adults (aged 18 years and older) with CVD.
		  ○ Studies that include ≥80% participants with CVD (or presenting subgroup data for those with CVD) will be preferentially included.
		  ○ If insufficient data are available from CVD populations, studies including mixed populations with and without CVD (50-79% CVD) will be considered for inclusion. This will be decided separately for each comparison.
		CVD is defined as including people with/requiring the following:
		• Ischaemic stroke
		• Transient ischaemic attack
		• Myocardial infarction
		• Coronary heart disease (for example unstable and stable angina)
		• Peripheral artery disease
		• Coronary or non-coronary arterial revascularisation procedures

		Exclusion: • Children aged under 18 years of age. • People who are intolerant of or have contraindications to statins. • People with familial hypercholesterolaemia. • People receiving renal replacement therapy. • People with familial clotting disorders that increase cardiovascular risk. • People with other monogenic disorders that increase cardiovascular risk. • People at high risk of CVD or abnormalities of lipid metabolism because of endocrine or other secondary disease processes other than diabetes. **Indirect populations:** Studies with indirect populations must have ≥80% participants matching the protocol to be included, for example: • Studies including those with and without familial hypercholesterolaemia (FH) must have ≥80% without FH (or report subgroup data for the group without FH). • Studies including those with and without renal replacement therapy must have ≥80% without or report subgroup data for this group.
7.	Interventions	• Ezetimibe (+ high or medium intensity statin*) • Inclisiran (+ high or medium intensity statin*) • Alirocumab or evolocumab (+ high or medium intensity statin*) - assuming a class effect for PCSK9 monoclonal antibodies • Combinations of the above interventions (for example, inclisiran + ezetimibe + high or medium intensity statin; or alirocumab/evolocumab + ezetimibe + high or medium intensity statin*) Mode of delivery: • Statin – oral • Ezetimibe – oral

		• Inclisiran – sub-cutaneous injection • Alirocumab or evolocumab – sub-cutaneous injection Pooling of interventions: • Trials investigating ezetimibe, inclisiran or PCSK9 monoclonal antibodies will be pooled into these intervention groups regardless of what other lipid-lowering agents these are combined with as background treatment, if the additional agents are balanced between the intervention and control groups. ***Statin treatment** Studies will be included if ≥50% of participants are receiving high or medium intensity statin therapy as background or randomised treatment (or report subgroup data for the group taking high or medium intensity statins). • Studies with only 50-79% of participants receiving high- or medium-intensity statin therapy will be downgraded for intervention indirectness. Note: high intensity statins are atorvastatin 20–80 mg or rosuvastatin 10–40 mg and medium intensity statins are atorvastatin 10 mg, fluvastatin 80 mg, rosuvastatin 5 mg or simvastatin 20–40 mg.
8.	Comparators	• Interventions compared with each other • Placebo / no treatment • High or medium intensity statin
9.	Types of study to be included	<u>Inclusion</u>: • RCTs • Published systematic reviews, network meta-analyses (NMAs) and individual participant data (IPD) meta-analyses of RCT data. <u>Exclusion:</u> • Cross-over RCTs • Non-randomised studies • Conference abstracts
10.	Other exclusion criteria	• Trials with aims other than CVD prevention or lipid lowering (e.g., for preventing chemotherapy toxicity).

		• Non-English language studies. • Follow-up < 3 months. • Trials comparing adding an intervention to statin therapy with doubling the statin dose. • Trials using statin agents or intervention doses not licenced or used in the UK (e.g., pitavastatin, lovastatin, simvastatin 80 mg).
11.	Context	This will inform an update of the recommendation to aim for >40% reduction in non-HDL-C.
12.	Primary outcomes (critical outcomes)	All outcomes are considered equally important for decision making and therefore have all been rated as critical: • LDL-C (change from baseline: absolute change and % change) • Non-HDL-C (change from baseline: absolute change and % change) • Combined major adverse cardiovascular events (CVD death, nonfatal MI, nonfatal ischaemic stroke) (time-to-event) ○ Other definitions will be included, and indirectness will be discussed on a case-by-case basis • Quality of life, any validated measure (continuous) Treatment-related adverse effects (dichotomous): • Myopathy/rhabdomyolysis • New-onset diabetes • Increased liver transaminases (>3-times upper-limit of normal) • Cancer • Gall-bladder related disease • Injection site reactions • Nausea • Influenza **Time points for data extraction:** • Lipid level outcomes: 3-12 months (use the latest reported in this range). • CVD events and quality of life: 1 year and ≥2 years (use the latest reported). For studies that do not report at these time points, events reported at ≥6 but <12 months will be extracted but downgraded for indirectness.

		• Adverse event outcomes: use the latest reported.
13.	Data extraction (selection and coding)	EndNote will be used for reference management, citations and bibliographies. All references identified by the searches and from other sources will be uploaded into EPPI reviewer and de-duplicated for sifting. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. A standardised form will be used to extract data from studies (see Developing NICE guidelines: the manual section 6.4). 10% of all evidence reviews are quality assured by a senior reviewer. This includes checking: • papers were included/excluded appropriately • a sample of the data extractions • correct methods are used to synthesise data • a sample of the risk of bias assessments Disagreements between the review authors over the risk of bias in particular studies will be resolved by discussion, with involvement of a third review author where necessary.
14.	Risk of bias (quality) assessment	Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual. • Systematic reviews: Risk of Bias in Systematic Reviews (ROBIS) • Randomised controlled trials: Cochrane RoB (2.0)
15.	Strategy for data synthesis	Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5). Fixed-effects (Mantel-Haenszel) techniques will be used to calculate risk ratios for the binary outcomes where possible. Continuous outcomes will be analysed using an inverse variance method for pooling weighted mean differences. For time-to-event outcomes, if sufficient information is provided, hazard ratios will be reported in addition to risk ratios. Only one measure will be considered for decision making. This will be agreed with the

		committee taking into account the proportion of studies that report sufficient data to calculate the risk ratio and the hazard ratio, in order to maximise the available pooled data. If there are differences in effect estimates between the two measures, potential reasons for this will be considered in the interpretation of the evidence. For continuous outcomes, if the same outcome is reported on different numerical scales these will be pooled where possible. If the studies use the same outcome measured in different units, this will be converted one to another using a simple multiplier. Otherwise, the standardised mean difference will be calculated if different scales are used for the same outcome across studies. Heterogeneity between the studies in effect measures will be assessed using the I^2 statistic and visually inspected. An I^2 value greater than 50% will be considered indicative of substantial heterogeneity. Sensitivity analyses will be conducted based on pre-specified subgroups using stratified meta-analysis to explore the heterogeneity in effect estimates. If this does not explain the heterogeneity, the results will be presented pooled using random-effects. GRADEpro will be used to assess the quality of evidence for each outcome, taking into account individual study quality and the meta-analysis results. The 4 main quality elements (risk of bias, indirectness, inconsistency and imprecision) will be appraised for each outcome. Publication bias will be considered with the guideline committee, and if suspected will be tested for when there are more than 5 studies for that outcome. The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/ Where meta-analysis is not possible, data will be presented and quality assessed individually per outcome. WinBUGS will be used for network meta-analysis, which will be considered for the outcome of percentage change in LDL-C if possible, given the data identified. This will be discussed with the committee to determine whether it is appropriate and of added benefit to conduct a network meta-analysis given the available data once the pairwise analysis has been completed.
16.	Analysis of sub-groups	Sensitivity analyses will be carried out for the following subgroups if data are available (regardless of heterogeneity): • baseline LDL-C: as reported by trials • baseline non-HDL-C: as reported by trials • statin intensity during trial period (medium; high; or mixed)

		Subgroups that will be investigated if heterogeneity is present: • Use of concomitant lipid-lowering therapies versus no background lipid-lowering therapies.	
17.	Type and method of review	☒	Intervention
		☐	Diagnostic
		☐	Prognostic
		☐	Qualitative
		☐	Epidemiologic
		☐	Service Delivery
		☐	Other (please specify)
18.	Language	English	
19.	Country	England	
20.	Anticipated or actual start date	December 2022	
21.	Anticipated completion date	September 2023	
22.	Stage of review at time of this submission	Review stage	Started / Completed
		Preliminary searches	☑ / ☑
		Piloting of the study selection process	☑ / ☑
		Formal screening of search results against eligibility criteria	☑ / ☑
		Data extraction	☑ / ☑

		Risk of bias (quality) assessment	☑	☑
		Data analysis	☑	☑
23.	Named contact	Guideline Development Team NGC E-mail: cvdescalationtherapy@nice.org.uk Organisational affiliation of the review: National Institute for Health and Care Excellence (NICE)		
24.	Review team members	From NICE: Serena Carville Eleanor Samarasekera Melina Vasileiou Kate Lovibond Alfredo Mariani David Wonderling Lina Gulhane		
25.	Funding sources/sponsor	Development of this systematic review is being funded by NICE.		
26.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.		
27.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: https://www.nice.org.uk/guidance/indevelopment/gid-ng10368		

28.	Other registration details	NA	
29.	Reference/URL for published protocol	https://www.nice.org.uk/guidance/indevelopment/gid-ng10368/documents	
30.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.	
31.	Keywords	CVD; cardiovascular disease; secondary prevention; statin; ezetimibe; PCSK9; alirocumab; evolocumab; inclisiran; LDL-C; non HDL-C; target.	
32.	Details of existing review of same topic by same authors	NA	
33.	Current review status	☒	Ongoing
		☐	Completed but not published
		☐	Completed and published
		☐	Completed, published and being updated
		☐	Discontinued
34.	Additional information	NA	
35.	Details of final publication	www.nice.org.uk	

A.2 Health economic review protocol

Not applicable.

Appendix B Literature search strategies

The following literature search strategies were used for the following review:

- In adults with CVD requiring escalation of therapy beyond statins, what is the effectiveness of lipid-lowering therapy?

The literature searches for this review are detailed below and complied with the methodology outlined in Developing NICE guidelines: the manual. [28]

For more information, please see the Methodology review published as part of the accompanying documents for this guideline.

B.1 Clinical search literature search strategy

Searches were constructed using a PICO framework where population (P) terms were combined with Intervention (I) and in some cases Comparison (C) terms. Outcomes (O) are rarely used in search strategies as these concepts may not be indexed or described in the title or abstract and are therefore difficult to retrieve. Search filters were applied to the search where appropriate.

Table 8: Database parameters, filters and limits applied

Database	Dates searched	Search filter used
Medline (OVID)	1946 – 12 January 2023	Randomised controlled trials Systematic review studies Exclusions (animal studies, letters, comments, editorials, case studies/reports) English language
Embase (OVID)	1974 – 12 January 2023	Randomised controlled trials Systematic review studies Exclusions (animal studies, letters, comments, editorials, case studies/reports, conference abstracts) English language
The Cochrane Library (Wiley)	Cochrane Database of Systematic Reviews to Issue 1 of 12, January 2023 Cochrane Central Register of Controlled Trials to Issue 12 of 12, December 2022	Exclusions (clinical trials, conference abstracts)
Epistemonikos (The Epistemonikos Foundation)	Inception to 12 January 2023	Systematic review Intervention Exclusions (Cochrane reviews)

Medline (Ovid) search terms

1.	*Cardiovascular Diseases/
2.	*Heart diseases/
3.	*Myocardial Ischemia/
4.	exp *Angina Pectoris/
5.	*Coronary Disease/
6.	*Coronary Artery Disease/
7.	exp *Coronary Stenosis/
8.	*Myocardial Infarction/
9.	exp *Heart Failure/
10.	*Arrhythmias, cardiac/ or *Atrial fibrillation/
11.	*Vascular Diseases/
12.	*Hypertension/
13.	*Atherosclerosis/
14.	*Peripheral Arterial Disease/
15.	*Peripheral Vascular Diseases/
16.	*Arteriosclerosis/
17.	*Cerebrovascular Disorders/
18.	exp *Stroke/
19.	exp *brain ischemia/
20.	exp *heart arrest/
21.	((cardiovascular or cardio vascular) adj3 (event* or disease* or disorder*)).ti,ab.
22.	((coronary or peripheral vascular or heart or peripheral arter*) adj3 (disease* or event* or disorder*)).ti,ab.
23.	(MI or myocardial infarct*).ti,ab.
24.	((heart or cardiopulmonary or cardiac) adj3 (death* or arrest* or attack*)).ti,ab.
25.	(CVD or CHD or CAD or PAD or CVA).ti,ab.
26.	(hypertension or hypertensive*).ti,ab.
27.	((high or raised or elevated) adj2 (blood pressure or bp)).ti,ab.
28.	(atheroscleros* or arterioscleros*).ti,ab.
29.	(cerebrovascular accident* or cerebrovascular disorder* or strokes or stroke).ti,ab.
30.	(ACS or angina or acute coronary syndrome*).ti,ab.
31.	(AF or atrial fibrillation).ti,ab.
32.	((chronic or congestive) adj2 heart failure).ti,ab.
33.	or/1-32
34.	letter/
35.	editorial/
36.	news/
37.	exp historical article/
38.	Anecdotes as Topic/
39.	comment/
40.	Case reports/
41.	(letter or comment*).ti.
42.	or/34-41

43.	randomized controlled trial/ or random*.ti,ab.
44.	42 not 43
45.	animals/ not humans/
46.	exp Animals, Laboratory/
47.	exp Animal Experimentation/
48.	exp Models, Animal/
49.	exp Rodentia/
50.	(rat or rats or mouse or mice or rodent*).ti.
51.	or/44-50
52.	33 not 51
53.	limit 52 to English language
54.	exp Ezetimibe/
55.	(ezetimibe* or ezetimib or ezetrol or zetia or vytorin or inegy or "SCH 58235" or SCH58235).ti,ab,kf.
56.	PCSK9 Inhibitors/
57.	PCSK9*.ti,ab,kf.
58.	Proprotein Convertase 9/
59.	("proprotein convertase 9" or "pro protein convertase 9" or "proprotein convertase subtilisin kexin type 9" or "pro protein convertase subtilisin kexin type 9" or "proprotein convertase subtilisin/kexin type 9" or "pro protein convertase subtilisin/kexin type 9").ti,ab,kf.
60.	(inclisiran or "ALN-PCSsc" or "ALN-60212" or ALM60212 or leqvio).ti,ab,kf.
61.	(alirocumab or praluent or "regn 727" or regn727 or "sar 236553" or sar236553).ti,ab,kf.
62.	(evolocumab or repatha or amg145 or "amg 145").ti,ab,kf.
63.	or/54-62
64.	53 and 63
65.	Meta-Analysis/
66.	Meta-Analysis as Topic/
67.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
68.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
69.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
70.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
71.	(search* adj4 literature).ab.
72.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
73.	cochrane.jw.
74.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
75.	
76.	ontrolled trial.pt.
77.	ical trial.pt.
78.	b.
79.	
80.	
81.	s topic.sh.

82.	
83.	
84.	83)

Embase (Ovid) search terms

1.	*cardiovascular disease/
2.	*coronary artery disease/
3.	*vascular disease/
4.	*coronary artery atherosclerosis/
5.	*peripheral vascular disease/
6.	*peripheral occlusive artery disease/
7.	*arteriosclerosis/
8.	*ischemic heart disease/
9.	exp *Stroke/ or *stroke patient/
10.	*coronary artery obstruction/
11.	*hypertension/
12.	*heart disease/
13.	*heart arrhythmia/
14.	*heart fibrillation/ or *heart atrium fibrillation/
15.	*heart failure/ or exp *congestive heart failure/
16.	*acute coronary syndrome/ or exp *angina pectoris/ or *heart infarction/
17.	*cerebrovascular disease/
18.	*cerebrovascular accident/
19.	exp *brain ischemia/
20.	exp *heart arrest/ or *heart death/
21.	*brain infarction/
22.	*atherosclerosis/
23.	((cardiovascular or cardio vascular) adj3 (event* or disease* or disorder*)).ti,ab.
24.	((coronary or peripheral vascular or heart or peripheral arter*) adj3 (disease* or event* or disorder*)).ti,ab.
25.	(MI or myocardial infarct*).ti,ab.
26.	((heart or cardiopulmonary or cardiac) adj3 (death* or arrest* or attack*)).ti,ab.
27.	(CVD or CHD or CAD or PAD or CVA).ti,ab.
28.	(hypertension or hypertensive*).ti,ab.
29.	((high or raised or elevated) adj2 (blood pressure or bp)).ti,ab.
30.	(atheroscleros* or arterioscleros*).ti,ab.
31.	(cerebrovascular accident* or cerebrovascular disorder* or strokes or stroke).ti,ab.
32.	(ACS or angina or acute coronary syndrome*).ti,ab.
33.	(AF or atrial fibrillation).ti,ab.
34.	((chronic or congestive) adj2 heart failure).ti,ab.
35.	or/1-34
36.	letter.pt. or letter/
37.	note.pt.
38.	editorial.pt.
39.	Case reports/ or case study/
40.	(letter or comment*).ti.

41.	(conference abstract* or conference review or conference paper or conference proceeding).db,pt,su.
42.	or/36-41
43.	randomized controlled trial/ or random*.ti,ab.
44.	42 not 43
45.	animal/ not human/
46.	nonhuman/
47.	exp Animal Experiment/
48.	exp Experimental Animal/
49.	animal model/
50.	exp Rodent/
51.	(rat or rats or mouse or mice or rodent*).ti.
52.	or/44-51
53.	35 not 52
54.	limit 53 to English language
55.	Atorvastatin plus ezetimibe/ or Ezetimibe plus simvastatin/ or Ezetimibe/ or Ezetimibe plus rosuvastatin/
56.	(ezetimibe* or ezetimib or ezetrol or zetia or vytorin or inegy or "SCH 58235" or SCH58235).ti,ab,kf.
57.	exp PCSK9 Inhibitor/
58.	PCSK9*.ti,ab,kf.
59.	Proprotein Convertase 9/
60.	("proprotein convertase 9" or "pro protein convertase 9" or "proprotein convertase subtilisin kexin type 9" or "pro protein convertase subtilisin kexin type 9" or "proprotein convertase subtilisin/kexin type 9" or "pro protein convertase subtilisin/kexin type 9").ti,ab,kf.
61.	(inclisiran or "ALN-PCSsc" or "ALN-60212" or ALM60212 or leqvio).ti,ab,kf.
62.	(alirocumab or praluent or "regn 727" or regn727 or "sar 236553" or sar236553).ti,ab,kf.
63.	(evolocumab or repatha or amg145 or "amg 145").ti,ab,kf.
64.	or/55-63
65.	54 and 64
66.	systematic review/
67.	Meta-Analysis/
68.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
69.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
70.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
71.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
72.	(search* adj4 literature).ab.
73.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
74.	cochrane.jw.
75.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
76.	or/66-75
77.	random*.ti,ab.

78.	factorial*.ti,ab.
79.	(crossover* or cross over*).ti,ab.
80.	((doubl* or singl*) adj blind*).ti,ab.
81.	(assign* or allocat* or volunteer* or placebo*).ti,ab.
82.	crossover procedure/
83.	single blind procedure/
84.	ontrolled trial/
85.	rocedure/
86.	
87.	86)

Cochrane Library (Wiley) search terms

#1.	MeSH descriptor: [Cardiovascular Diseases] this term only
#2.	MeSH descriptor: [Heart Diseases] this term only
#3.	MeSH descriptor: [Myocardial Ischemia] this term only
#4.	MeSH descriptor: [Angina Pectoris] explode all trees
#5.	MeSH descriptor: [Coronary Disease] this term only
#6.	MeSH descriptor: [Coronary Artery Disease] this term only
#7.	MeSH descriptor: [Coronary Stenosis] explode all trees
#8.	MeSH descriptor: [Myocardial Infarction] this term only
#9.	MeSH descriptor: [Heart Failure] explode all trees
#10.	MeSH descriptor: [Arrhythmias, Cardiac] this term only
#11.	MeSH descriptor: [Vascular Diseases] this term only
#12.	MeSH descriptor: [Atrial Fibrillation] this term only
#13.	MeSH descriptor: [Hypertension] this term only
#14.	MeSH descriptor: [Atherosclerosis] this term only
#15.	MeSH descriptor: [Peripheral Vascular Diseases] this term only
#16.	MeSH descriptor: [Peripheral Arterial Disease] this term only
#17.	MeSH descriptor: [Arteriosclerosis] this term only
#18.	MeSH descriptor: [Cerebrovascular Disorders] this term only
#19.	MeSH descriptor: [Stroke] explode all trees
#20.	MeSH descriptor: [Brain Ischemia] explode all trees
#21.	MeSH descriptor: [Heart Arrest] explode all trees
#22.	((cardiovascular or cardio vascular) near/3 (event* or disease* or disorder*)):ti,ab,kw
#23.	((coronary or "peripheral vascular" or heart or "peripheral NEXT arter*") near/3 (disease* or event* or disorder*)):ti,ab,kw
#24.	(MI or myocardial infarct*):ti,ab,kw
#25.	((heart or cardiopulmonary or cardiac) near/3 (death* or arrest* or attack*)):ti,ab,kw
#26.	(CVD or CHD or CAD or PAD or CVA):ti,ab,kw
#27.	(hypertension or hypertensive*):ti,ab,kw
#28.	((high or raised or elevated) near/2 (blood pressure or bp)):ti,ab,kw
#29.	(atheroscleros* or arterioscleros*):ti,ab,kw
#30.	("cerebrovascular NEXT accident*" or "cerebrovascular NEXT disorder*" or strokes or stroke):ti,ab,kw
#31.	(ACS or angina or acute coronary syndrome*):ti,ab,kw
#32.	(AF or atrial fibrillation):ti,ab,kw

#33.	((chronic or congestive) near/2 heart failure):ti,ab,kw
#34.	(or #1-#33)
#35.	conference:pt or (clinicaltrials or trialsearch):so
#36.	#34 not #35
#37.	MeSH descriptor: [Ezetimibe] explode all trees
#38.	(ezetimibe* or ezetimib or ezetrol or zetia or vytorin or inegy or "SCH NEXT 58235" or SCH58235):ti,ab
#39.	MeSH descriptor: [PCSK9 Inhibitors] explode all trees
#40.	PCSK9*:ti,ab
#41.	MeSH descriptor: [Proprotein Convertase 9] explode all trees
#42.	("proprotein convertase 9" or "pro protein convertase 9" or "proprotein convertase subtilisin kexin type 9" or "pro protein convertase subtilisin kexin type 9" or "proprotein convertase subtilisin/kexin type 9" or "pro protein convertase subtilisin/kexin type 9"):ti,ab
#43.	(inclisiran or "ALN-PCSsc" or "ALN-60212" or ALM60212 or leqvio):ti,ab
#44.	(alirocumab or praluent or "regn NEXT 727" or regn727 or "sar NEXT 236553" or sar236553):ti,ab
#45.	(evolocumab or repatha or amg145 or "amg NEXT 145"):ti,ab
#46.	(or #37-#45)
#47.	#36 and #46

Epistemonikos search terms

1.	(title:((ezetimibe* OR ezetimib OR ezetrol OR zetia OR vytorin OR inegy OR inclisiran OR leqvio OR alirocumab OR praluent OR evolocumab OR repatha)) OR abstract:((ezetimibe* OR ezetimib OR ezetrol OR zetia OR vytorin OR inegy OR inclisiran OR leqvio OR alirocumab OR praluent OR evolocumab OR repatha)))

Table 9: Database parameters, filters and limits applied

Database	Dates searched	Search filter used
Medline (OVID)	2013 – 17 November 2022	Systematic review studies Exclusions (animal studies, letters, comments, editorials, case studies/reports) English language
Embase (OVID)	2013 – 17 November 2022	Systematic review studies Exclusions (animal studies, letters, comments, editorials, case studies/reports, conference abstracts) English language
The Cochrane Library (Wiley)	Cochrane Database of Systematic Reviews to Issue 11 of 12, November 2022	Exclusions (clinical trials, conference abstracts)

Database	Dates searched	Search filter used
Epistemonikos (The Epistemonikos Foundation)	Jan 2013- 17 November 2022	Systematic review Exclusions (Cochrane reviews)

Medline (Ovid) search terms

1.	*Cardiovascular Diseases/
2.	*Heart diseases/
3.	*Myocardial Ischemia/
4.	exp *Angina Pectoris/
5.	*Coronary Disease/
6.	*Coronary Artery Disease/
7.	exp *Coronary Stenosis/
8.	*Myocardial Infarction/
9.	exp *Heart Failure/
10.	*Arrhythmias, cardiac/ or *Atrial fibrillation/
11.	*Vascular Diseases/
12.	*Hypertension/
13.	*Atherosclerosis/
14.	*Peripheral Arterial Disease/
15.	*Peripheral Vascular Diseases/
16.	*Arteriosclerosis/
17.	*Cerebrovascular Disorders/
18.	exp *Stroke/
19.	exp *brain ischemia/
20.	exp *heart arrest/
21.	((cardiovascular or cardio vascular) adj3 (event* or disease* or disorder*)).ti,ab.
22.	((coronary or peripheral vascular or heart or peripheral arter*) adj3 (disease* or event* or disorder*)).ti,ab.
23.	(MI or myocardial infarct*).ti,ab.
24.	((heart or cardiopulmonary or cardiac) adj3 (death* or arrest* or attack*)).ti,ab.
25.	(CVD or CHD or CAD or PAD or CVA).ti,ab.
26.	(hypertension or hypertensive*).ti,ab.
27.	((high or raised or elevated) adj2 (blood pressure or bp)).ti,ab.
28.	(atheroscleros* or arterioscleros*).ti,ab.
29.	(cerebrovascular accident* or cerebrovascular disorder* or strokes or stroke).ti,ab.
30.	(ACS or angina or acute coronary syndrome*).ti,ab.
31.	(AF or atrial fibrillation).ti,ab.
32.	((chronic or congestive) adj2 heart failure).ti,ab.
33.	or/1-32
34.	letter/
35.	editorial/
36.	news/
37.	exp historical article/
38.	Anecdotes as Topic/

39.	comment/
40.	Case reports/
41.	(letter or comment*).ti.
42.	or/34-41
43.	randomized controlled trial/ or random*.ti,ab.
44.	42 not 43
45.	animals/ not humans/
46.	exp Animals, Laboratory/
47.	exp Animal Experimentation/
48.	exp Models, Animal/
49.	exp Rodentia/
50.	(rat or rats or mouse or mice or rodent*).ti.
51.	or/44-50
52.	33 not 51
53.	limit 52 to English language
54.	*Hydroxymethylglutaryl-CoA Reductase Inhibitors/
55.	((Hydroxymethylglutaryl or HMG) adj (Coenzyme A or CoA)).ti,ab,kf.
56.	*Atorvastatin/
57.	*Rosuvastatin Calcium/
58.	exp *Pravastatin/
59.	*Fluvastatin/
60.	exp *Lovastatin/
61.	(statin* or atorvastatin* or rosuvastatin* or pravastatin* or fluvastatin* or lovastatin* or pitavastatin* or simvastatin*).ti,ab,kf.
62.	or/54-61
63.	53 and 62
64.	randomized controlled trial.pt.
65.	controlled clinical trial.pt.
66.	randomi#ed.ab.
67.	placebo.ab.
68.	randomly.ab.
69.	clinical trials as topic.sh.
70.	trial.ti.
71.	or/64-70
72.	Meta-Analysis/
73.	Meta-Analysis as Topic/
74.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
75.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
76.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
77.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
78.	(search* adj4 literature).ab.
79.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
80.	cochrane.jw.

81.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
82.	or/72-81
83.	63 and (71 or 82)

Embase (Ovid) search terms

1.	*cardiovascular disease/
2.	*coronary artery disease/
3.	*vascular disease/
4.	*coronary artery atherosclerosis/
5.	*peripheral vascular disease/
6.	*peripheral occlusive artery disease/
7.	*arteriosclerosis/
8.	*ischemic heart disease/
9.	exp *Stroke/ or *stroke patient/
10.	*coronary artery obstruction/
11.	*hypertension/
12.	*heart disease/
13.	*heart arrhythmia/
14.	*heart fibrillation/ or *heart atrium fibrillation/
15.	*heart failure/ or exp *congestive heart failure/
16.	*acute coronary syndrome/ or exp *angina pectoris/ or *heart infarction/
17.	*cerebrovascular disease/
18.	*cerebrovascular accident/
19.	exp *brain ischemia/
20.	exp *heart arrest/ or *heart death/
21.	*brain infarction/
22.	*atherosclerosis/
23.	((cardiovascular or cardio vascular) adj3 (event* or disease* or disorder*)).ti,ab.
24.	((coronary or peripheral vascular or heart or peripheral arter*) adj3 (disease* or event* or disorder*)).ti,ab.
25.	(MI or myocardial infarct*).ti,ab.
26.	((heart or cardiopulmonary or cardiac) adj3 (death* or arrest* or attack*)).ti,ab.
27.	(CVD or CHD or CAD or PAD or CVA).ti,ab.
28.	(hypertension or hypertensive*).ti,ab.
29.	((high or raised or elevated) adj2 (blood pressure or bp)).ti,ab.
30.	(atheroscleros* or arterioscleros*).ti,ab.
31.	(cerebrovascular accident* or cerebrovascular disorder* or strokes or stroke).ti,ab.
32.	(ACS or angina or acute coronary syndrome*).ti,ab.
33.	(AF or atrial fibrillation).ti,ab.
34.	((chronic or congestive) adj2 heart failure).ti,ab.
35.	or/1-34
36.	letter.pt. or letter/
37.	note.pt.
38.	editorial.pt.
39.	Case reports/ or case study/
40.	(letter or comment*).ti.

41.	(conference abstract or conference paper).pt.
42.	or/36-41
43.	randomized controlled trial/ or random*.ti,ab.
44.	42 not 43
45.	animal/ not human/
46.	nonhuman/
47.	exp Animal Experiment/
48.	exp Experimental Animal/
49.	animal model/
50.	exp Rodent/
51.	(rat or rats or mouse or mice or rodent*).ti.
52.	or/44-51
53.	35 not 52
54.	limit 53 to English language
55.	*Hydroxymethylglutaryl-CoA Reductase Inhibitors/
56.	((Hydroxymethylglutaryl or HMG) adj (Coenzyme A or CoA)).ti,ab,kf.
57.	exp *Simvastatin/
58.	*Atorvastatin/
59.	*Rosuvastatin/
60.	exp *Pravastatin/
61.	*Fluvastatin/
62.	*pitavastatin/
63.	(statin* or atorvastatin* or rosuvastatin* or pravastatin* or fluvastatin* or lovastatin* or pitavastatin* or simvastatin*).ti,ab,kf.
64.	or/55-63
65.	54 and 64
66.	random*.ti,ab.
67.	factorial*.ti,ab.
68.	(crossover* or cross over*).ti,ab.
69.	((doubl* or singl*) adj blind*).ti,ab.
70.	(assign* or allocat* or volunteer* or placebo*).ti,ab.
71.	crossover procedure/
72.	single blind procedure/
73.	randomized controlled trial/
74.	double blind procedure/
75.	or/66-74
76.	systematic review/
77.	Meta-Analysis/
78.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
79.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
80.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
81.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
82.	(search* adj4 literature).ab.

83.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
84.	
85.	tment* or indirect or mixed) adj2 comparison*).ti,ab.
86.	
87.	86)

Cochrane Library (Wiley) search terms

#1.	MeSH descriptor: [Cardiovascular Diseases] this term only
#2.	MeSH descriptor: [Heart Diseases] this term only
#3.	MeSH descriptor: [Myocardial Ischemia] this term only
#4.	MeSH descriptor: [Angina Pectoris] explode all trees
#5.	MeSH descriptor: [Coronary Disease] this term only
#6.	MeSH descriptor: [Coronary Artery Disease] this term only
#7.	MeSH descriptor: [Coronary Stenosis] explode all trees
#8.	MeSH descriptor: [Myocardial Infarction] this term only
#9.	MeSH descriptor: [Heart Failure] explode all trees
#10.	MeSH descriptor: [Arrhythmias, Cardiac] this term only
#11.	MeSH descriptor: [Vascular Diseases] this term only
#12.	MeSH descriptor: [Atrial Fibrillation] this term only
#13.	MeSH descriptor: [Hypertension] this term only
#14.	MeSH descriptor: [Atherosclerosis] this term only
#15.	MeSH descriptor: [Peripheral Vascular Diseases] this term only
#16.	MeSH descriptor: [Peripheral Arterial Disease] this term only
#17.	MeSH descriptor: [Arteriosclerosis] this term only
#18.	MeSH descriptor: [Cerebrovascular Disorders] this term only
#19.	MeSH descriptor: [Stroke] explode all trees
#20.	MeSH descriptor: [Brain Ischemia] explode all trees
#21.	MeSH descriptor: [Heart Arrest] explode all trees
#22.	((cardiovascular or cardio vascular) near/3 (event* or disease* or disorder*)):ti,ab,kw
#23.	((coronary or "peripheral vascular" or heart or "peripheral NEXT arter*") near/3 (disease* or event* or disorder*)):ti,ab,kw
#24.	(MI or myocardial infarct*):ti,ab,kw
#25.	((heart or cardiopulmonary or cardiac) near/3 (death* or arrest* or attack*)):ti,ab,kw
#26.	(CVD or CHD or CAD or PAD or CVA):ti,ab,kw
#27.	(hypertension or hypertensive*):ti,ab,kw
#28.	((high or raised or elevated) near/2 (blood pressure or bp)):ti,ab,kw
#29.	(atheroscleros* or arterioscleros*):ti,ab,kw
#30.	("cerebrovascular NEXT accident*" or "cerebrovascular NEXT disorder*" or strokes or stroke):ti,ab,kw
#31.	(ACS or angina or acute coronary syndrome*):ti,ab,kw
#32.	(AF or atrial fibrillation):ti,ab,kw
#33.	((chronic or congestive) near/2 heart failure):ti,ab,kw
#34.	(or #1-#33)
#35.	conference:pt or (clinicaltrials or trialsearch):so
#36.	#34 not #35

#37.	MeSH descriptor: [Ezetimibe] explode all trees
#38.	(ezetimibe* or ezetimib or ezetrol or zetia or vytorin or inegy or "SCH NEXT 58235" or SCH58235):ti,ab
#39.	MeSH descriptor: [PCSK9 Inhibitors] explode all trees
#40.	PCSK9*:ti,ab
#41.	MeSH descriptor: [Proprotein Convertase 9] explode all trees
#42.	("proprotein convertase 9" or "pro protein convertase 9" or "proprotein convertase subtilisin kexin type 9" or "pro protein convertase subtilisin kexin type 9" or "proprotein convertase subtilisin/kexin type 9" or "pro protein convertase subtilisin/kexin type 9"):ti,ab
#43.	(inclisiran or "ALN-PCSsc" or "ALN-60212" or ALM60212 or leqvio):ti,ab
#44.	(alirocumab or praluent or "regn NEXT 727" or regn727 or "sar NEXT 236553" or sar236553):ti,ab
#45.	(evolocumab or repatha or amg145 or "amg NEXT 145"):ti,ab
#46.	(or #37-#45)
#47.	#36 and #46

Epistemonikos search terms

1.	(title:((title:(Cardiovascular Disease* OR "Heart disease*" OR "Myocardial Ischemia" OR "Angina Pectoris" OR "Coronary Disease*" OR "Coronary Artery Disease*" OR "Coronary Stenosis" OR "Myocardial Infarction*" OR "Heart Failure" OR Arrhythmia* OR "Atrial fibrillation" OR "Vascular Disease*" OR Hypertension OR Atherosclerosis OR "Peripheral Arterial Disease*" OR "Peripheral Vascular Disease*" OR Arteriosclerosis OR "Cerebrovascular Disorder*" OR Stroke OR strokes OR "brain ischemia" OR "heart arrest*" OR "heart attack*" OR "cardiac arrest*" OR "cardiac attack*" OR "heart failure*" OR "high blood pressure" OR angina OR "acute coronary syndrome*") OR abstract:(Cardiovascular Disease* OR "Heart disease*" OR "Myocardial Ischemia" OR "Angina Pectoris" OR "Coronary Disease*" OR "Coronary Artery Disease*" OR "Coronary Stenosis" OR "Myocardial Infarction*" OR "Heart Failure" OR Arrhythmia* OR "Atrial fibrillation" OR "Vascular Disease*" OR Hypertension OR Atherosclerosis OR "Peripheral Arterial Disease*" OR "Peripheral Vascular Disease*" OR Arteriosclerosis OR "Cerebrovascular Disorder*" OR Stroke OR strokes OR "brain ischemia" OR "heart arrest*" OR "heart attack*" OR "cardiac arrest*" OR "cardiac attack*" OR "heart failure*" OR "high blood pressure" OR angina OR "acute coronary syndrome*")) AND (title:(Hydroxymethylglutaryl-CoA OR "HMG-CoA" OR "Hydroxymethylglutaryl-Coenzyme" OR statin* OR atorvastatin* OR pravastatin* OR rosuvastatin* OR simvastatin* OR fluvastatin* OR lovastatin*) OR abstract:(Hydroxymethylglutaryl-CoA OR "HMG-CoA" OR "Hydroxymethylglutaryl-Coenzyme" OR statin* OR atorvastatin* OR pravastatin* OR rosuvastatin* OR simvastatin* OR fluvastatin* OR lovastatin*))) OR abstract:((title:(Cardiovascular Disease* OR "Heart disease*" OR "Myocardial Ischemia" OR "Angina Pectoris" OR "Coronary Disease*" OR "Coronary Artery Disease*" OR "Coronary Stenosis" OR "Myocardial Infarction*" OR "Heart Failure" OR Arrhythmia* OR "Atrial fibrillation" OR "Vascular Disease*" OR Hypertension OR Atherosclerosis OR "Peripheral Arterial Disease*" OR "Peripheral Vascular Disease*" OR Arteriosclerosis OR "Cerebrovascular Disorder*" OR Stroke OR strokes OR "brain ischemia" OR "heart arrest*" OR "heart attack*" OR "cardiac arrest*" OR "cardiac attack*" OR "heart failure*" OR "high blood pressure" OR angina OR "acute coronary syndrome*") OR abstract:(Cardiovascular Disease* OR "Heart disease*" OR "Myocardial Ischemia" OR "Angina Pectoris" OR "Coronary Disease*" OR "Coronary Artery Disease*" OR "Coronary Stenosis" OR "Myocardial Infarction*" OR "Heart Failure" OR Arrhythmia* OR "Atrial fibrillation" OR "Vascular Disease*" OR Hypertension OR Atherosclerosis OR "Peripheral Arterial Disease*" OR "Peripheral Vascular Disease*" OR Arteriosclerosis OR "Cerebrovascular Disorder*" OR Stroke OR strokes OR "brain ischemia" OR "heart arrest*" OR "heart attack*" OR "cardiac arrest*" OR "cardiac attack*" OR "heart failure*" OR "high blood pressure" OR angina OR "acute coronary

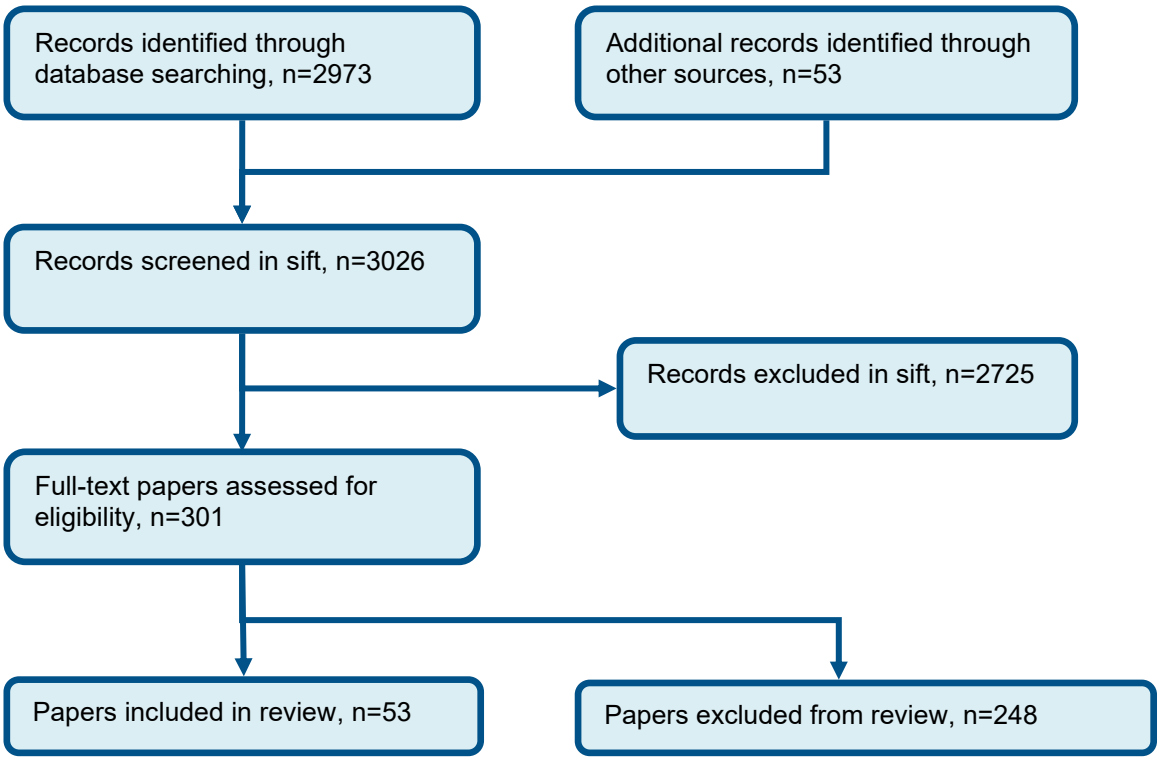
	syndrome*")) AND (title:(Hydroxymethylglutaryl-CoA OR "HMG-CoA" OR "Hydroxymethylglutaryl-Coenzyme" OR statin* OR atorvastatin* OR pravastatin* OR rosuvastatin* OR simvastatin* OR fluvastatin* OR lovastatin*) OR abstract:(Hydroxymethylglutaryl-CoA OR "HMG-CoA" OR "Hydroxymethylglutaryl-Coenzyme" OR statin* OR atorvastatin* OR pravastatin* OR rosuvastatin* OR simvastatin* OR fluvastatin* OR lovastatin*))))

B.2 Economic evaluation search strategy

Not applicable.

Appendix C Effectiveness evidence study selection

Figure 1: Flow chart of clinical study selection for the review of secondary prevention treatment escalation


Records identified through database searching, n=2973
Additional records identified through other sources, n=53
Records screened in sift, n=3026
Records excluded in sift, n=2725
Full-text papers assessed for eligibility, n=301
Papers included in review, n=53
Papers excluded from review, n=248

Appendix D Effectiveness evidence

D.1 Key trial characteristics

Author, year (trial name)	Intervention	Control	N for analysis	% CVD	Statin treatment during trial (statin intensity)	Statin pre-treatment	Follow up
Ezetimibe							
Arimoura 2012[3]	Ezetimibe and atorvastatin (10 mg)	Atorvastatin (10 mg)	50	100% (stable angina + coronary stent)	Medium	57%	6 months
Cannon 2015a[5] Blazing 2014[4] Cannon 2008[7], Oyama 2021[32] IMPROVE-IT	Simvastatin 40 mg/day + ezetimibe10mg/d	Simvastatin 40 mg/day + placebo	18144	100% (ACS)	Medium	34.4%	6 years (median)
Hougaard 2017[16] OCTIVUS trial	Atorvastatin 80 mg/day + ezetimibe10 mg/day	Atorvastatin 80 mg/day + placebo	87	100% (MI)	High	0%	1 year
Joshi 2017[17]	Ezetimibe 10 mg/day + rosuvastatin 10 mg/day	Rosuvastatin 10 mg/day	80	100% (CAD)	High	NR	24 weeks
Kouvelos 2013[21]	Ezetimibe 10 mg/day + rosuvastatin 10 mg/day	Rosuvastatin 10 mg/day	262	100% (vascular surgery)	High	0% (washout period)	1 year
Luo 2014[23]	Atorvastatin 20 mg/day + ezetimibe10 mg/day	Atorvastatin 20 mg/day	84	83.3% (CHD)	High	Unclear	1 year
Luo 2016[24]	Atorvastatin 20 mg/day + ezetimibe10 mg/day	Atorvastatin 20 mg/day	148	100% (CHD)	High	Unclear	1 year

Author, year (trial name)	Intervention	Control	N for analysis	% CVD	Statin treatment during trial (statin intensity)	Statin pre-treatment	Follow up
Masuda 2015[25]	Ezetimibe 10mg/d + rosuvastatin 5mg/d	Rosuvastatin 5mg/d	40	100% (CAD + PCI)	Medium	40%	6 months
Ran 2017[35]	Ezetimibe 10mg/d + rosuvastatin 10mg	Rosuvastatin 10mg/d	125	100% (MI + PCI)	High	0%	12 weeks
Ren 2017[39]	Rosuvastatin 10 mg/day + ezetimibe 10 mg/day	Rosuvastatin 10 mg/day	113	100% (acute MI)	High	9.7%	1 year
Tsujita 2015[46, 47] PRECISE-IVUS	Atorvastatin + ezetimibe 10 mg/day	Atorvastatin	246	100% (CAD)	Unclear	47%	10 months
Ueda 2017[48] Hiro 2014[15] (protocol) ZIPANGU	Ezetimibe 10mg/d plus atorvastatin 10mg/d increased to 20mg if LDL-C >70mg/dl after 3 months	Atorvastatin 10mg/d increased to 20mg if LDL-C >100mg/dl at 3 months	131	100% (CAD + PCI)	Medium/high (proportion with dose titration not stated)	7%	9 months
Wang 2016[50]	Ezetimibe 10 mg/day + rosuvastatin 10 mg/day	Rosuvastatin 10 mg/day	106	100% (CAD)	High	Not stated	1 year
Wang 2017[49]	Atorvastatin 20 mg/day + ezetimibe10 mg/day	Atorvastatin 20 mg/day	100	100% (CAD)	High	100%	1 year
West 2011/2011a[51, 52]	Simvastatin 40 mg/day + ezetimibe 10 mg/day	Simvastatin 40 mg	44	100% (PAD)	Medium	23.5%	1 year
PCSK9i							
Ako 2019[2] Ako 2018[1] (protocol) ODYSSEY J-IVUS	Alirocumab 75/150 mg every 2 weeks	Usual care	206	100%	100% (majority medium intensity)	Yes	36 weeks
Gao 2021[11]	Alirocumab 75mg every 2 weeks + high-intensity statin	High-intensity statin	61	100%	100% (all high intensity)	Yes	36 weeks

Author, year (trial name)	Intervention	Control	N for analysis	% CVD	Statin treatment during trial (statin intensity)	Statin pre-treatment	Follow up
Giugliano 2012[12] Kohli 2012[20] (protocol) LAPLACE-TIMI-57	Evolocumab (140 mg every 2 weeks or 420 mg monthly)	Matched placebo	159	81%	100% (unclear intensity)	Yes	12 weeks
Kereiakes 2015[18] Colhoun 2014[8] (rationale) ODYSSEY COMBO I	Alirocumab 75/150 mg every 2 weeks	Placebo	316	82%	99.5% (63% 'high intensity')	Yes	1 year
Koh 2017[19] ODYSSEY KT	Alirocumab 75/150 mg every 2 weeks	Placebo	199	96%	100% (72.4% 'high intensity')	Yes	24 weeks
McCullough 2018[26] ODYSSEY Long Term	Alirocumab 150 mg every 2 weeks	Placebo	2341	77% - use IPD analysis of ASVCD subgroup	Max tolerated (46% 'high intensity')	Yes	24 and 78 weeks
Nicholls 2016[31] Puri 2016[33] (protocol) GLAGOV	Evolocumab (420 mg monthly)	Placebo	968	100%	98% (59% 'high intensity')	Yes	18 months
Nicholls 2022[29] 2021[30] (protocol) HUYGENS- trial	Evolocumab (420 mg monthly)	Placebo	161	100%	95% (80.7% 'high intensity')	Yes	50 weeks

Author, year (trial name)	Intervention	Control	N for analysis	% CVD	Statin treatment during trial (statin intensity)	Statin pre-treatment	Follow up
Raber 2022[34] Zachin 2021[53] (rationale and design) PACMAN-AMI	Alirocumab 150mg + rosuvastatin 20mg/d	Placebo + rosuvastatin 20mg/d	300	100%	100% (all high intensity)	Majority statin naïve (only 12% had prior statin)	52 weeks
Ray 2019[36] Muller-Wieland 2017[27] ODYSSEY DM-DYSLEPIDIMIA	Alirocumab 75/150 mg every 2 weeks	Usual care	142	34% - use IPD analysis of ASVCD subgroup	86 % (Max tolerated; majority high intensity)	Yes	24 weeks
Ray 2019[36] Muller-Wieland 2017[27] ODYSSEY DM-INSULIN	Alirocumab 75/150 mg every 2 weeks	Placebo	177	37% - use IPD analysis of ASVCD subgroup	74% (Max tolerated; majority medium intensity)	Yes	24 weeks
Rehberger 2022[38]	Alirocumab: 150mg every 2 weeks Evolocumab: 140mg every 2 weeks	Usual care	100	100%	Max tolerated	Yes	6 months
Sabatine 2017[42] Sabatine 2016[41] (protocol) FOURIER trial	Evolocumab (140 mg every 2 weeks or 420 mg monthly)	Placebo	27563	100%	100% (69.3% 'high intensity')	Yes	2 years
Schwartz 2018[45] Diaz 2022[9] (subgroup),	Alirocumab 75/150 mg every 2 weeks	Placebo	18924	100%	96% (88% 'high intensity')	Yes	2.8 years

Author, year (trial name)	Intervention	Control	N for analysis	% CVD	Statin treatment during trial (statin intensity)	Statin pre-treatment	Follow up
Schwartz 2014[44] (protocol) ODYSSEY OUTCOMES trial							
PCSK9i vs ezetimibe							
Cannon 2015[6] Colhoun 2014[8] (rationale); El Shahawy 2017[10] (104 week data); Leiter 2017[22] (influenza outcome) ODYSSEY COMBO II	Alirocumab 75/150 mg every 2 weeks	Ezetimibe	615	98%	Max tolerated (68% 'high intensity')	Yes	24 weeks
Han 2020[13] ODYSSEY EAST	Alirocumab 75/150 mg every 2 weeks	Ezetimibe	720	90%	100% (majority high intensity)	Yes	104 weeks
PCSK9i + ezetimibe vs ezetimibe							
Hao 2022[14]	Evolocumab: 140mg every 2 weeks plus atorvastatin 40mg/d and ezetimibe 10mg/d N=68	Atorvastatin 40mg/d and ezetimibe 10mg/d N=61	129	100%	100% (high intensity)	Yes	3 months
Inclisiran							
Ray 2020[37] ORION 10	Inclisiran: 284mg (day 1, 90, 270 and 450)	Placebo	1561	100%	89%	89% (68% 'high-intensity')	540 days

Author, year (trial name)	Intervention	Control	N for analysis	% CVD	Statin treatment during trial (statin intensity)	Statin pre-treatment	Follow up
Ray 2020[37] ORION 11	Inclisiran: 284mg (day 1, 90, 270 and 450)	Placebo	1617	88%	95%	95% (78% 'high-intensity')	540 days

D.2 Evidence tables

Ako, 2018

Bibliographic Reference	Ako, Junya; Hibi, Kiyoshi; Kozuma, Ken; Miyauchi, Katsumi; Morino, Yoshihiro; Shinke, Toshiro; Tsujita, Kenichi; Uno, Kiyoko; Kawabata, Yumiko; Hiro, Takafumi; Effect of alirocumab on coronary atheroma volume in Japanese patients with acute coronary syndromes and hypercholesterolemia not adequately controlled with statins: ODYSSEY J-IVUS rationale and design.; Journal of cardiology; 2018; vol. 71 (no. 6); 583-589

Study details

Secondary publication of another included study- see primary study for details	Rationale and study design for ODYSSEY J-IVUS trial (NCT02984982); Full details in main trial entry (Ako, 2019)

Ako, 2019

Bibliographic Reference	Ako, Junya; Hibi, Kiyoshi; Tsujita, Kenichi; Hiro, Takafumi; Morino, Yoshihiro; Kozuma, Ken; Shinke, Toshiro; Otake, Hiromasa; Uno, Kiyoko; Louie, Michael J; Takagi, Yoshiharu; Miyauchi, Katsumi; Effect of Alirocumab on Coronary Atheroma Volume in Japanese Patients With Acute Coronary Syndrome - The ODYSSEY J-IVUS Trial.; Circulation journal : official journal of the Japanese Circulation Society; 2019; vol. 83 (no. 10); 2025-2033

Study details

Other publications associated with this	Ako 2018 (rationale and design of trial)

study included in review	
Trial name / registration number	ODYSSEY J-IVUS/ NCT02984982
Study type	Randomised controlled trial (RCT)
Study location	Multicentre: 40 Japanese sites
Study setting	Secondary care
Study dates	Enrolment dates: November 2016 to November 2017; 36-week follow-up
Sources of funding	This study was funded by Sanofi and Regeneron Pharmaceuticals, Inc.
Inclusion criteria	Patients who at index acute coronary syndrome (ACS) diagnosis either had low-density lipoprotein cholesterol (LDL-C) ≥2.59mmol/l (≥100mg/dl) despite stable statin therapy, or were not on statins with LDL-C levels above target after statin initiation; had undergone IVUS imaging as part of usual clinical practice in Japan, and had an analyzable IVUS image of the culprit or non-culprit vessel with ≥50% angiographic stenosis of the culprit vessel within 1 week after ACS onset. ACS was defined as ST elevation myocardial infarction (STEMI), non-STEMI, and unstable angina. Eligible patients with LDL-C ≥2.59mmol/l (≥100mg/dl) who had been on any statin therapy at ACS onset received atorvastatin ≥10mg/day or rosuvastatin ≥5mg/day (if not already on these), based on the investigator's judgement. Eligible patients with LDL-C ≥2.59mmol/l (≥100mg/dl) not taking a statin at ACS diagnosis were started on atorvastatin 10mg/day or rosuvastatin 5mg/day immediately after diagnosis, and could enter the study if their LDL-C level was ≥2.59mmol/l (≥100mg/dl; or ≥1.81mmol/l [≥70mg/dl], if the investigator deemed it appropriate) after 2–4 weeks.
Exclusion criteria	Patients who have been treated previously with at least one dose of any anti-PCSK9 monoclonal antibody; Uncontrolled hypertension (multiple reading with systolic blood pressure >180mmHg or diastolic blood pressure >110 mmHg) between the acute coronary syndrome diagnosis and randomization visit; Known history of haemorrhagic stroke; Currently under treatment for cancer; Patients on lipoprotein apheresis; any clinically significant abnormality identified that in the judgment of the investigator or any sub-investigator would preclude safe completion of the study or constrain endpoint assessment such as major systemic diseases, patients with short life expectancy; those deemed unable to meet specific protocol requirements, such as scheduled visits; Presence of any other condition (e.g. geographic, social, etc.) actual or anticipated, that the investigator feels would restrict or limit the patient's participation for the duration of the study; laboratory findings measured within 2 weeks after the acute coronary syndrome diagnosis (positive serum or urine pregnancy test in women of childbearing potential); All contraindications to statin or other lipid-modifying therapies or warning/precaution of use (when appropriate) as displayed in the respective national product labelling for these treatments; All contraindications to alirocumab as displayed in the respective national product labelling for these treatments; Known hypersensitivity to monoclonal antibody

	including alirocumab or any component of the drug product used in the current study; pregnant or breast-feeding women. Women of childbearing potential not protected by highly effective method (s) of birth control (as defined for contraception in the informed consent form and/or in a local protocol addendum) and/or who are unwilling or unable to be tested for pregnancy; Patients who has withdrawn consent before enrolment/randomization (starting from signed informed consent form).
Recruitment / selection of participants	Patients meeting inclusion criteria; recruitment method not specified.
Intervention(s)	Alirocumab: 75mg every 2 weeks every 2 weeks in addition to stable dose background statin therapy with/without other LLTs; At Week 14 the study allowed alirocumab dose increase to 150mg every 2 weeks if Week 12 LDL-C was ≥2.59mmol/l (≥100mg/dl).
Comparator	Standard of care (SoC): atorvastatin ≥10mg/day or rosuvastatin ≥5mg/day; i.e. stable dose statin therapy, with optional dose adjustment (within the range approved by health authority). In patients receiving statin monotherapy in the SoC arm, non-statin, non-PCSK9 inhibitor LLTs could be added by investigators if LDL-C goal <2.59mmol/l (<100mg/dl) could not be achieved; adjustments could be made after randomization during the treatment phase.
Background treatment	Concomitant statin therapy as specified above with/without other lipid lowering therapy added as seen fit by the investigator to meet LDL targets.
Number of participants	206
Duration of follow-up	36 ±2 weeks
Indirectness	none
Additional comments	All lipids were measured by a central laboratory. LDL-C was calculated using the Friedewald formula. If triglyceride values exceeded 4.5mmol/l (400mg/dl), the central laboratory automatically measured LDL-C directly, using the β-quantification method. Analyses were performed in the modified intent-to-treat (mITT) population: including randomized patients who took ≥1 dose or part of a dose of study drug and had an available value of normalized TAV before randomization and after 24 weeks of treatment. Statistical significance of the primary efficacy endpoint at the 0.05 alpha level was required before sequentially testing key secondary efficacy endpoints at the 0.05 level.

Study arms

Alirocumab (N = 93)

75mg every 2 weeks/up to 150mg every 2 weeks, in addition to stable dose background statin therapy with/without other LLTs

Standard care (N = 89)
atorvastatin ≥10mg/day or rosuvastatin ≥5mg/day with optional dose adjustment (within the range approved by health authority).

Characteristics

Arm-level characteristics

Characteristic	Alirocumab (N = 93)	Standard care (N = 89)
% Female Sample size	n = 74 ; % = 79.6	n = 72 ; % = 80.9
Mean age (SD) Mean (SD)	61.8 (10.2)	60.5 (11.6)
Existing CVD diagnoses		
Coronary artery disease (prior to ACS diagnosis) Sample size	n = 12 ; % = 12.9	n = 10 ; % = 11.2
Ischemic Stroke Sample size	n = 5 ; % = 5.4	n = 3 ; % = 3.4
Peripheral arterial disease Sample size	n = 1 ; % = 1.1	n = 0 ; % = 0
Index ACS event: STEMI Sample size	n = 49 ; % = 55.1	n = 53 ; % = 57
Index ACS event: NSTEMI Sample size	n = 13 ; % = 14	n = 15 ; % = 16.9
Index ACS event: Unstable angina	n = 27 ; % = 29	n = 25 ; % = 28.1

Characteristic	Alirocumab (N = 93)	Standard care (N = 89)
Sample size		
Type 2 diabetes Sample size	n = 27 ; % = 29	n = 30 ; % = 33.7
Chronic kidney disease Sample size	n = 9 ; % = 9.7	n = 10 ; % = 11.2
LDL cholesterol (mmol/l) Calculated Mean (SD)	2.54 (0.6)	2.48 (0.57)
Non-HDL cholesterol (mmol/l) Mean (SD)	3.21 (0.65)	3.22 (0.7)
Statins used Statin therapy at ACS onset Sample size	n = 34 ; % = 36.6	n = 31 ; % = 34.8
Other lipid-lowering medication used Sample size	n = 11 ; % = 11.8	n = 13 ; % = 14.6
Ezetimibe Sample size	n = 7 ; % = 7.5	n = 7 ; % = 7.9
Fibrate Sample size	n = 0 ; % = 0	n = 0 ; % = 0
Other Sample size	n = 4 ; % = 4.3	n = 6 ; % = 6.7
Statins used Statin therapy during trial Sample size		
Atorvastatin 10mg	n = 51 ; % = 54.8	n = 46 ; % = 51.7

Characteristic	Alirocumab (N = 93)	Standard care (N = 89)
Sample size		
Atorvastatin 20mg Sample size	n = 5 ; % = 5.4	n = 3 ; % = 3.7
Rosuvastatin 5mg Sample size	n = 35 ; % = 37.6	n = 39 ; % = 43.8
Rosuvastatin 10mg Sample size	n = 2 ; % = 2.2	n = 0 ; % = 0
Rosuvastatin 20mg Sample size	n = 0 ; % = 0	n = 1 ; % = 1.1
Aspirin or oral ADP receptor antagonist Sample size	n = 93 ; % = 100	n = 89 ; % = 100

Outcomes

Study timepoints

- 36 week

LDL-C

Outcome	Alirocumab, 36 week, N = 93	Standard care, 36 week, N = 89
LDL-C (calculated) absolute change from baseline (mmol/l) Least squares mean (SE); LS mean difference= −1.24 (0.07) mmol/l [−47.8 (2.5) mg/dl] Mean (SE)	-1.64 (0.05)	-0.4 (0.05)
mg/dl	-63.2 (1.8)	-15.5 (1.8)

Outcome	Alirocumab, 36 week, N = 93	Standard care, 36 week, N = 89
Mean (SE)		
LDL-C (calculated) % change from baseline LS mean (SE); LS mean difference= −50.5 (2.8) Mean (SE)	-63.9 (1.9)	-13.4 (2)

LDL-C (calculated) absolute change from baseline - Polarity - Lower values are better
LDL-C (calculated) % change from baseline - Polarity - Higher values are better (greater reduction is better)
All lipids were measured by a central laboratory. LDL-C was calculated using the Friedewald formula.13 If triglyceride values exceeded 4.5mmol/l (400mg/dl), the central laboratory automatically measured LDL-C directly, using the β-quantification method.

non-HDL-C

Outcome	Alirocumab, 36 week, N = 93	Standard care, 36 week, N = 89
non-HDL-C absolute change from baseline (mmol/l) LS mean (SE); LS mean difference= −1.26 (0.07) mmol/l [−48.9 (2.8) mg/dl] Mean (SE)	-1.79 (0.05)	-0.53 (0.05)
non-HDL-C absolute change from baseline (**mg/dl**) Mean (SE)	-69.2 (2)	-20.3 (2)
non-HDL percentage change from baseline, %, LS mean (SE); LS mean difference= −40.5 (2.4) Mean (SE)	-54.5 (1.7)	-14.1 (1.7)

non-HDL-C absolute change from baseline - Polarity - Lower values are better
non-HDL percentage change from baseline, %, - Polarity - Higher values are better (greater reduction is better)

Safety parameters

Outcome	Alirocumab, 36 week, N = 103	Standard care, 36 week, N = 102
Treatment-emergent CVD events confirmed by adjudication number of people	n = 8 ; % = 7.8	n = 4 ; % = 3.9

Outcome	Alirocumab, 36 week, N = 103	Standard care, 36 week, N = 102
No of events		
Injection-site reactions No of events	n = 7 ; % = 6.8	n = 0 ; % = 0
Type 2 diabetes No of events	n = 0 ; % = 0	n = 3 ; % = 2.9

Treatment-emergent CVD events confirmed by adjudication - Polarity - Lower values are better
Assessed throughout the 36-week follow-up; measured in the safety population, defined as the randomized population who received ≥1 dose or part of a dose of the study drug and analysed according to the treatment received. Randomized patients for whom it was unclear whether they took the study drug were included in the safety population.

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

LDL-C-absolute change (mmol/l)

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(due to potential deviations from intended interventions: LLTs could be added by the investigators if LDL-C goal could not be achieved and optional adjustments could be made to statin dose during the treatment phase with no data available for statin dose changes)*
Overall bias and Directness	Overall Directness	Directly applicable

LDL-C-absolute change (mg/dl)

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(due to potential deviations from intended interventions: LLTs could be added by the investigators if LDL-C goal could not*

Section	Question	Answer
		be achieved and optional adjustments could be made to statin dose during the treatment phase with no data available for statin dose changes)
Overall bias and Directness	Overall Directness	Directly applicable

LDL-C % change

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(due to potential deviations from intended interventions: LLTs could be added by the investigators if LDL-C goal could not be achieved and optional adjustments could be made to statin dose during the treatment phase with no data available for statin dose changes)*
Overall bias and Directness	Overall Directness	Directly applicable

non-HDL-C-absolute change (mmol/l)

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(due to potential deviations from intended interventions: LLTs could be added by the investigators if LDL-C goal could not be achieved and optional adjustments could be made to statin dose during the treatment phase with no data available for statin dose changes)*
Overall bias and Directness	Overall Directness	Directly applicable

non-HDL-C-absolute change mg/dl

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(due to potential deviations from intended interventions: LLTs could be added by the investigators if LDL-C goal could not be achieved and optional adjustments could be made to statin dose during the treatment phase with no data available for statin dose changes)*
Overall bias and Directness	Overall Directness	Directly applicable

non-HDL-C-% change

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(due to potential deviations from intended interventions: LLTs could be added by the investigators if LDL-C goal could not be achieved and optional adjustments could be made to statin dose during the treatment phase with no data available for statin dose changes)*
Overall bias and Directness	Overall Directness	Directly applicable

Treatment-emergent CVD events confirmed by adjudication

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(due to potential deviations from intended interventions: LLTs could be added by the investigators if LDL-C goal could not be achieved and optional adjustments could be made to statin dose during the treatment phase with no data available for statin dose changes; also randomised patients for whom it was unclear whether they took the study drug were included in the safety population)*
Overall bias and Directness	Overall Directness	Directly applicable

Injection-site reaction

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(due to potential deviations from intended interventions: LLTs could be added by the investigators if LDL-C goal could not be achieved and optional adjustments could be made to statin dose during the treatment phase with no data available for statin dose changes; also randomised patients for whom it was unclear whether they took the study drug were included in the safety population)*
Overall bias and Directness	Overall Directness	Directly applicable

Type 2 diabetes

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(due to potential deviations from intended interventions: LLTs could be added by the investigators if LDL-C goal could not be achieved and optional adjustments could be made to statin dose during the treatment phase with no data available for statin dose changes; also randomised patients for whom it was unclear whether they took the study drug were included in the safety population)*
Overall bias and Directness	Overall Directness	Directly applicable

Arimura, 2012

Bibliographic Reference	Arimura, Tadaaki; Miura, Shin-ichiro; Ike, Amane; Sugihara, Makoto; Iwata, Atsushi; Nishikawa, Hiroaki; Kawamura, Akira; Saku, Keijiro; Comparison of the efficacy and safety of statin and statin/ezetimibe therapy after coronary stent implantation in patients with stable angina.; Journal of cardiology; 2012; vol. 60 (no. 2); 111-8

Study details

Study type	Randomised controlled trial (RCT)

Study location	Japan.
Study setting	Fukuoka University Hospital
Study dates	June 2009 to December 2010.
Sources of funding	Not reported.
Inclusion criteria	Consecutive patients with stable angina and DL who were successfully implanted with a drug-eluting stent (DES) or a bare-metal stent (BMS) at Fukuoka University Hospital.
Exclusion criteria	Familial hypercholesterolemia, liver dysfunction, renal dysfunction, inadequate control of diabetes, or a history of hypersensitivity toward the constituents of the study drug. Women with a possibility of pregnancy and patient's contraindicated for the study drugs were excluded.
Recruitment / selection of participants	Consecutive patients
Intervention(s)	Ezetimibe 10 mg/day and atorvastatin 10 mg/day (medium intensity statin). Medications were started the day after stent implantation. Follow-up coronary angiography performed after stenting (6-8 months).
Comparator	Atorvastatin 10 mg/day (medium intensity statin).
Background treatment	All participants received aspirin and ticlopidine or clopidogrel throughout the study period. **Other treatments at baseline** **Ezetimibe and atorvastatin group** Calcium channel blocker: 64% B-blocker:32% Diuretic:14% Nitroglycerin:9% Nicorandil: 18% ACE-I/ARB: 77% Sulfonylurea: 18% Pioglitazone: 0% **Atorvastatin group**

	Calcium channel blocker: 41% B-blocker: 18% Diuretic: 18% Nitroglycerin: 14% Nicorandil: 36% ACE-I/ARB: 73% Sulfonylurea:14% Pioglitazone:9%
Number of participants	50
Duration of follow-up	6-8 months (mean 253 ± 77 days).
Indirectness	No indirectness.
Additional comments	Available case analysis.

Study arms

Ezetimibe and atorvastatin (N = 25)

Ezetimibe 10 mg/day and atorvastatin 10 mg/day (medium intensity statin).

Atorvastatin (N = 25)

Atorvastatin 10 mg/day (medium intensity statin).

Characteristics

Arm-level characteristics

Characteristic	Ezetimibe and atorvastatin (N = 25)	Atorvastatin (N = 25)
% Female Baseline characteristics reported for number analysed rather than randomised (22 in each arm) Sample size	n = 6 ; % = 27	n = 7 ; % = 32
Mean age (SD) Mean (SD)	69 (9)	69 (8)
Ethnicity Nominal	NR	NR
Existing CVD diagnosis		
Prior myocardial infarction Sample size	n = NR ; % = 23	n = NR ; % = 18
Type 2 diabetes Diabetes (type not specified) Sample size	n = 7 ; % = 32	n = 6 ; % = 27
Chronic kidney disease Sample size	n = NR ; % = NR	n = NR ; % = NR
LDL-cholesterol Nominal	NR	NR
Non-HDL cholesterol Nominal	NR	NR
Statin used Sample size	n = 13 ; % = 59	n = 12 ; % = 55
Other lipid lowering medication used	NR	NR

Characteristic	Ezetimibe and atorvastatin (N = 25)	Atorvastatin (N = 25)
Nominal		

Outcomes

Study timepoints

- Baseline
- 6 month (6-8 months)

Continuous outcomes - lipids 6 months

Outcome	Ezetimibe and atorvastatin, Baseline, N = 25	Ezetimibe and atorvastatin, 6 month, N = 22	Atorvastatin , Baseline, N = 25	Atorvastatin , 6 month, N = 22
LDL cholesterol (mg/dl) Baseline figures on a bar chart so unable to report Mean (SD)	NR (NR)	60 (17)	NR (NR)	73 (16)

LDL cholesterol - Polarity - Lower values are better

Dichotomous – 6-8 months

Outcome	Ezetimibe and atorvastatin, Baseline,	Ezetimibe and atorvastatin, 6 month, N = 22	Atorvastatin , Baseline,	Atorvastatin , 6 month, N = 22
MACE (cardiac death, Q wave AMI and target lesion revascularization)	*NA*	n = 3 ; % = 22	*NA*	n = 2 ; % = 22

Outcome	Ezetimibe and atorvastatin, Baseline,	Ezetimibe and atorvastatin, 6 month, N = 22	Atorvastatin , Baseline,	Atorvastatin , 6 month, N = 22
No of events				

MACE (cardiac death, Q wave AMI and target lesion revascularization) - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

LDL cholesterol absolute

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Unclear allocation concealment)*
Overall bias and Directness	Overall Directness	Directly applicable

Dichotomous-MACE

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Unclear allocation concealment)*
Overall bias and Directness	Overall Directness	Indirectly applicable *(Reported at 6-8 months (<12 months))*

Blazing, 2014

Bibliographic Reference	Blazing, Michael A; Giugliano, Robert P; Cannon, Christopher P; Musliner, Thomas A; Tershakovec, Andrew M; White, Jennifer A; Reist, Craig; McCagg, Amy; Braunwald, Eugene; Califf, Robert M; Evaluating cardiovascular event reduction with ezetimibe as an adjunct to simvastatin in 18,144 patients after acute coronary syndromes: final baseline characteristics of the IMPROVE-IT study population.; American heart journal; 2014; vol. 168 (no. 2); 205-12e1

Study details

Secondary publication of another included study- see primary study for details	Baseline ethnicity details for IMPROVE-IT[5]
Other publications associated with this study included in review	Cannon 2008 (study rational and design) and Cannon 2015a (main paper); Oyama 2021 (contains data on subgroup analysis)

Cannon, 2015a

Bibliographic Reference	Cannon, Christopher P; Blazing, Michael A; Giugliano, Robert P; McCagg, Amy; White, Jennifer A; Theroux, Pierre; Darius, Harald; Lewis, Basil S; Ophuis, Ton Oude; Jukema, J Wouter; De Ferrari, Gaetano M; Ruzyllo, Witold; De Lucca, Paul; Im, KyungAh; Bohula, Erin A; Reist, Craig; Wiviott, Stephen D; Tershakovec, Andrew M; Musliner, Thomas A; Braunwald, Eugene; Califf, Robert M; IMPROVE-IT, Investigators; Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes.; The New England journal of medicine; 2015; vol. 372 (no. 25); 2387-97

Study details

Other publications associated with this study included in review	Cannon 2008 - IMPROVE-IT trial rationale and design; Blazing 2014 (used ethnicity data for population characteristics), Oyama 2021 (contains data on subgroup analysis)
Trial name / registration number	Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) ClinicalTrials.gov: NCT00202878
Study type	Randomised controlled trial (RCT)
Study location	39 countries Argentina (332 patients, 24 centres) Australia (116 patients, 10 centres) Austria (249 patients, 16 centres) Belgium (249 patients, 19 centres) Brazil (423 patients, 34 centres) Canada (1107 patients, 65 centres) Chile (152 patients, 9 centres) Colombia (568 patients, 20 centres) Czech Republic (371 patients, 22 centres) Denmark (576 patients, 19 centres) Ecuador (45 patients, 5 centres)

	Estonia (10 patients, 2 centres) Finland (342 patients, 17 centres) France (286 patients, 28 centres) Germany (935 patients, 55 centres) Hong Kong (58 patients, 2 centres) Hungary (116 patients, 15 centres) India (260 patients, 23 centres) Israel (655 patients, 26 centres) Italy (593 patients, 69 centres) Malaysia (59 patients, 4 centres) Netherlands (1191 patients, 40 centres) New zealand (164 patients, 8 centres) Norway (295 patients, 20 centres) Peru (65 patients, 13 centres) Poland (589 patients, 30 centres) Portugal (102 patients, 13 centres) Singapore (75 patients, 2 centres) Slovakia (121 patients, 13 centres) South africa (186 patients, 17 centres)

	South korea (118 patients, 12 centres) Spain (551 patient, 38 centres) Sweden (480 patients, 24 centres) Switzerland (265 patients, 12 centres) Taiwan (46 patients, 6 centres) Turkey (50 patients, 7 centres) Ukraine (159 patients, 16 centres) United Kingdom (319 patients, 16 centres) **United States (5866 patients, 367 centres)**
Study setting	1158 enrolling centres: inpatient and outpatient follow-up
Study dates	Recruitment: 26 October 2005 to 8 July 2010
Sources of funding	Supported by Merck
Inclusion criteria	**Key Inclusion criteria:** At least 50 years of age Hospitalized within the previous 10 days for an acute coronary syndrome (ACS; an acute myocardial infarction, with or without ST-segment elevation on electrocardiography, or high-risk unstable angina) LDL cholesterol level (in first 24 h after ACS onset) of 50 mg per deciliter (1.3 mmol per liter) or higher, and if not receiving long-term lipid-lowering therapy, LDL cholesterol ≤125 mg/dl (3.2 mmol/l);

	if receiving lipid-lowering therapy, LDL cholesterol ≤100 mg/dl (2.6 mmol/l).
Exclusion criteria	**Key exclusion criteria** Planned coronary-artery bypass grafting for the ACS event, Creatinine clearance <30 ml/min, Active liver disease or persistent serum transaminase elevations (≥2 x ULN), Use of lipid-lowering therapy with intensity greater than 40 mg of simvastatin before hospitalisation (simvastatin >40 mg; atorvastatin ≥40 mg; all doses of rosuvastatin; ezetimibe coadministered with any dose of any statin)
Recruitment / selection of participants	Recruited from enrolling centres if hospitalised for ACS; Randomization was stratified according to prior use of lipid-lowering therapy, type of acute coronary syndrome, and status with respect to enrolment in the concurrent Early Glycoprotein IIb/IIIa Inhibition in Non–ST-Segment Elevation Acute Coronary Syndrome (EARLY ACS) trial.
Population subgroups	None of relevance to this review protocol
Intervention(s)	Once daily simvastatin (40 mg; medium intensity) plus ezetimibe (10 mg) as a fixed dose combination tablet For patients in either study group who had LDL cholesterol levels higher than 79 mg per deciliter (2.0 mmol per liter) on two consecutive measurements, the simvastatin dose was increased to 80 mg in a double-blind manner. As a result, the simvastatin dose was increased to 80 mg for LDL cholesterol levels >79 mg/dl in 6% of the patients. If an LDL cholesterol measurement on the new regimen was confirmed to be higher than 100 mg per deciliter, the study drug could be discontinued and more potent therapy initiated.
Comparator	Once daily simvastatin (40 mg; medium intensity) alone. The simvastatin dose was increased to 80 mg for LDL cholesterol levels >79 mg/dl in 27% of the patients.

Background treatment	Patients received standard medical and interventional treatment for acute coronary syndrome Matched between groups: Aspirin: 97% Thienopyridine: 86% Beta-blocker: 87% ACE inhibitor or ARB: 76%
Number of participants	18,1444
Duration of follow-up	Median duration: 6 years Follow-up visits at 30 days, at 4 months, and then every 4 months. Blood samples were taken at randomization, at 1, 4, 8, and 12 months, and then annually for those attending clinic visits.
Indirectness	Serious comparator indirectness: 27% in control group had the simvastatin dose increased to 80 mg
Additional comments	ITT

Study arms

Ezetimibe + simvastatin (N = 9067)

Once daily simvastatin (40 mg; medium intensity) plus ezetimibe (10 mg)

Simvastatin + placebo (N = 9077)

Simvastatin (40 mg; medium intensity)

Characteristics

Study-level characteristics

Characteristic	**Study (N = 18141)**
Ethnicity	
American Indian or Alaskan Native Sample size	n = 52 ; % = 0.3
Asian Sample size	n = 773 ; % = 4
Black Sample size	n = 498 ; % = 3
Spanish descent Sample size	n = 808 ; % = 5
Native Hawaiian or Pacific Islander Sample size	n = 19
Caucasian Sample size	n = 15203 ; % = 84

Characteristic	Study (N = 18141)
Other Sample size	n = 771
Collection prohibited Sample size	n = 17 ; % = 0.1

Arm-level characteristics

Characteristic	Ezetimibe + simvastatin (N = 9067)	Simvastatin + placebo (N = 9077)
% Female Sample size	n = 2225 ; % = 24.5	n = 2191 ; % = 24.1
Mean age (SD) Mean (SD)	63.6 (9.7)	63.6 (9.8)
Qualifying ACS event: MI with ST-segment elevation No of events	n = 2584 ; % = 28.5	n = 2606 ; % = 28.7
Qualifying ACS event: MI without ST-segment elevation No of events	n = 4302 ; % = 47.5	n = 4253 ; % = 46.9
Qualifying ACS event: Unstable angina No of events	n = 2175 ; % = 24	n = 2211 ; % = 24.4
Existing CVD diagnoses		
Previous MI No of events	n = 1925 ; % = 21.3	n = 1881 ; % = 20.7
Peripheral arterial disease No of events	n = 487 ; % = 5.4	n = 518 ; % = 5.7

Congestive heart failure No of events	n = 419 ; % = 4.6	n = 371 ; % = 4.1
Type 2 diabetes 'Diabetes' No of events	n = 2459 ; % = 27.1	n = 2473 ; % = 27.3
Chronic kidney disease Nominal	NR	NR
LDL cholesterol (mg/dl) N=8990 and 9009; at time of hospitalisation Mean (SD)	93.8 (NR)	93.8 (NR)
LDL cholesterol (mg/dl) N=8990 and 9009; at time of hospitalisation Median (IQR)	95 (79 to 110)	95 (79 to 110.2)
Non-HDL cholesterol (mg/dl) N=8894 and 8899; at time of hospitalisation Mean (SD)	120.5 (NR)	120.5 (NR)
Non-HDL cholesterol (mg/dl) N=8894 and 8899; at time of hospitalisation Median (IQR)	120 (103 to 138)	120 (102 to 138)

Statins used before index event No of events	n = 3135 ; % = 34.6	n = 3111 ; % = 34.3

Outcomes

Study timepoints

- Baseline
- 1 year
- 6 year (End of follow-up; median 6 years)
- 7 year (7-year Kaplan-Meier estimates)

Continuous outcomes - difference between groups in final score

Outcome	Ezetimibe + simvastatin vs Simvastatin + placebo, 1 year vs Baseline, N2 = 6864, N1 = 6939
LDL-C (mg/dl) % reduction Custom value	-24%
LDL-C (mg/dl) Least squares mean and confidence limits based on SE Mean (95% CI)	-16.75 (-17.49 to -16.02)

Outcome	Ezetimibe + simvastatin vs Simvastatin + placebo, 1 year vs Baseline, N2 = 6864, N1 = 6939
non-HDL-C (mg/dl) Least squares mean and confidence limits based on SE Mean (95% CI)	-19.95 (-20.86 to -19.03)

LDL-C - Polarity - Lower values are better

non-HDL-C - Polarity - Lower values are better

Continuous - LDL-C final scores (least squares mean)

Outcome	Ezetimibe + simvastatin, Baseline, N = 8990	Ezetimibe + simvastatin, 1 year, N = 6864	Ezetimibe + simvastatin, 6 year, N = 9067	Simvastatin + placebo, Baseline, N = 9009	Simvastatin + placebo, 1 year, N = 6939	Simvastatin + placebo, 6 year, N = 9077
LDL-C absolute value (mg/dl) Mean (95% CI)	93.8	55.04 (53.23 to 56.85)	-	93.8	71.8 (70 to 73.6)	-
Time-weighted average Mean (95% CI)	-	-	53.7	-	-	69.5

LDL-C absolute value - Polarity - Lower values are better

Continuous - non-HDL-C final scores (least squares mean)

Outcome	Ezetimibe + simvastatin, Baseline, N = 8894	Ezetimibe + simvastatin, 1 year, N = 6368	Simvastatin + placebo, Baseline, N = 8899	Simvastatin + placebo, 1 year, N = 6427
non-HDL-C absolute value (mg/dl) Mean (95% CI)	120.5	80.45 (78.15 to 82.75)	120.5	100.4 (98.12 to 102.69)

non-HDL-C absolute value - Polarity - Lower values are better

Dichotomous outcomes

Outcome	Ezetimibe + simvastatin, 6 year, N = 9067	Ezetimibe + simvastatin, 7 year, N = 9067	Simvastatin + placebo, 6 year, N = 9077	Simvastatin + placebo, 7 year, N = 9077
MACE (major vascular events) Death from cardiovascular causes, major coronary event or, I , nonfatal stroke). No of events	-	n = 2572 ; % = 32.7	-	n = 2742 ; % = 34.7
Myopathy Otherwise unexplained muscle pain, weakness, or tenderness with either CK ≥10 x ULN; or with two consecutive observations of CPK ≥5 x ULN and <10 x ULN No of events	n = 15 ; % = 0.2	-	n = 10 ; % = 0.1	-
Rhabdomyolysis	n = 13 ; % = 0.1	-	n = 18 ; % = 0.2	-

Outcome	Ezetimibe + simvastatin, 6 year, N = 9067	Ezetimibe + simvastatin, 7 year, N = 9067	Simvastatin + placebo, 6 year, N = 9077	Simvastatin + placebo, 7 year, N = 9077
No of events				
ALT, AST or both ≥3XULN No of events	n = 224 ; % = 2.5	-	n = 208 ; % = 2.3	-
Cancer new, relapsing, or worsening No of events	n = 748 ; % = 10.2	-	n = 732 ; % = 10.2	-
Gall-bladder-related adverse events No of events	n = 281 ; % = 3.1	-	n = 321 ; % = 3.5	-

Major vascular events - Polarity - Lower values are better

Myopathy - Polarity - Lower values are better

Rhabdomyolysis - Polarity - Lower values are better

ALT, AST or both ≥3XULN - Polarity - Lower values are better

Gall-bladder-related adverse events - Polarity - Lower values are better

Hazard ratio

Outcome	Ezetimibe + simvastatin vs Simvastatin + placebo, 7 year, N2 = 9067, N1 = 9077
Major adverse CVD events Death from cardiovascular causes, major coronary event or non-fatal stroke Hazard ratio/95% CI	0.94 (0.89 to 0.99)

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

LDL-C final scores - 1 year

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Not a pre-specified endpoint, but planned to assess as part of trial review procedure)*
Overall bias and Directness	Overall Directness	Indirectly applicable *(Serious comparator indirectness: 27% in control group had the simvastatin dose increased to 80 mg compared to only 6% in ezetimibe group)*

non-HDL-C - 1 year

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Not a pre-specified endpoint, but planned to assess as part of trial review procedure)*

Section	Question	Answer
Overall bias and Directness	Overall Directness	Indirectly applicable *(Serious comparator indirectness: 27% in control group had the simvastatin dose increased to 80 mg compared to only 6% in ezetimibe group)*

Between group difference in LDL-C

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Not a pre-specified endpoint, but planned to assess as part of trial review procedure)*
Overall bias and Directness	Overall Directness	Indirectly applicable *(Serious comparator indirectness: 27% in control group had the simvastatin dose increased to 80 mg compared to only 6% in ezetimibe group)*

LDL-C % between group difference - 1 year

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Not a pre-specified endpoint, but planned to assess as part of trial review procedure)*
Overall bias and Directness	Overall Directness	Indirectly applicable *(Serious comparator indirectness: 27% in control group had the simvastatin dose increased to 80 mg compared to only 6% in ezetimibe group)*

non-HDL-C- between group difference - 1 year

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Not a pre-specified endpoint, but planned to assess as part of trial review procedure)*
Overall bias and Directness	Overall Directness	Indirectly applicable *(Serious comparator indirectness: 27% in control group had the simvastatin dose increased to 80 mg compared to only 6% in ezetimibe group)*

MACE - 7 years

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Indirectly applicable *(Serious comparator indirectness: 27% in control group had the simvastatin dose increased to 80 mg compared to only 6% in ezetimibe group)*

Myopathy - 6 years

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low

Section	Question	Answer
Overall bias and Directness	Overall Directness	Indirectly applicable *(>20% in control arm received simvastatin 80 mg)*

Rhabdomyolysis - 6 years

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Indirectly applicable *(>20% in control arm received simvastatin 80 mg)*

ALT, AST or both ≥3XULN - 6 years

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Cancer - 6 years

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Gall-bladder-related adverse events - 6 years

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

MACE - Hazard ratio

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Cannon, 2015

Bibliographic Reference	Cannon, Christopher P; Cariou, Bertrand; Blom, Dirk; McKenney, James M; Lorenzato, Christelle; Pordy, Robert; Chaudhari, Umesh; Colhoun, Helen M; ODYSSEY COMBO II, Investigators; Efficacy and safety of alirocumab in high cardiovascular risk

patients with inadequately controlled hypercholesterolaemia on maximally tolerated doses of statins: the ODYSSEY COMBO II randomized controlled trial.; European heart journal; 2015; vol. 36 (no. 19); 1186-94

Study details

Other publications associated with this study included in review	Colhoun 2014 - Study design and rationale El Shahawy 2017 - 104 week data Leiter 2017 - influenza outcome
Trial name / registration number	ODYSSEY COMBO II NCT01644188.
Study type	Randomised controlled trial (RCT)
Study location	126 sites (Europe, Israel, North America, South Africa, South Korea)
Study setting	Out patient care
Study dates	August 2012 and July 2015
Sources of funding	Sanofi and Regeneron
Inclusion criteria	Patients with hypercholesterolaemia and established CHD or CHD risk equivalents with LDL-C poorly controlled with a maximally tolerated daily dose of statin at stable dose for ≥4 weeks before screening LDL-C ≥ 1.8 mmol/l (≥ 70 mg/dl) with history CHD LDL-C ≥ 2.6 mmol/l (≥ 100 mg/dl) without history CHD

	Document history of CHD included 1 or more of the following: Acute MI Silent MI Unstable angina Coronary revascularisation procedure (percutaneous coronary intervention or coronary artery bypass graft surgery) Clinically significant CHD diagnosed by invasive or non-invasive testing (such as coronary angiography, stress test using treadmill, stress echocardiography, or nuclear imaging) CHD risk equivalents: Documented peripheral artery disease Documented previous ischaemic stroke with a focal ischaemic neurological deficit that persisted >24 hours, considered as being of atherothrombotic origin. Documented chronic kidney disease defined as eGFR 30–< 60 mL/min/1.73 m2 for ≥3 months Known history of diabetes mellitus and ≥2 additional risk factors: History of hypertension Documented history of ankle-brachial index ≤ 0.90 Documented history of microalbuminuria or macroalbuminuria OR dipstick urinalysis at screening visit with > 2+ protein Documented history of preproliferative or proliferative retinopathy or laser treatment for retinopathy Known family history of premature CHD (CHD in father or brother < 55 years of age; CHD in mother or sister < 65 years of age)
Exclusion criteria	Age <18 years of age

	Fasting serum triglycerides > 4.5 mmol/l during the screening period Currently on a statin that is not simvastatin, atorvastatin, or rosuvastatin taken daily at a registered dose Use of concomitant medications: Ezetimibe, omega-3 fatty acid (at doses ≥ 1000 mg daily), nicotinic acid, bile acid-binding sequestrant, or red yeast rice products in the past 4 weeks prior to screening visit (week –3); fibrates in the past 6 weeks prior to screening visit
Recruitment / selection of participants	Screening period of up to 21 days to check laboratory values and provide training for self-administration of study drugs.
Population subgroups	Statin intensity Baseline LDL-C
Intervention(s)	Subcutaneous alirocumab 75 mg (in 1 mL volume) every 2 weeks (plus oral placebo for ezetimibe daily). The dose was automatically increased at Week 12 to 150 mg every 2 weeks (1 mL volume) if the week-8 LDL-C value was ≥1.8 mmol/l. This occurred in 18.4% (82 patients).
Comparator	10 mg oral ezetimibe daily (plus subcutaneous placebo every 2 weeks for alirocumab)
Background treatment	Statins continued
Number of participants	720
Duration of follow-up	Mean up to this analysis: 58 weeks Randomised phase: 104 weeks Post-treatment observational phase: 8 weeks

Indirectness	Not serious
Additional comments	ITT

Study arms

Alirocumab (+ oral placebo) (N = 479)

75 mg every 2 weeks with increase to 150 mg (with background statin)

Ezetimibe (+ subcutaneous placebo) (N = 241)

10 mg/day (with background statin)

Characteristics

Arm-level characteristics

Characteristic	Alirocumab (+ oral placebo) (N = 479)	Ezetimibe (+ subcutaneous placebo) (N = 241)
% Female Sample size	% = 24.8	% = 29.5
Mean age (SD) Mean (SD)	61.7 (9.4)	61.3 (9.2)
Ethnicity		

Characteristic	Alirocumab (+ oral placebo) (N = 479)	Ezetimibe (+ subcutaneous placebo) (N = 241)
White Sample size	n = 404 ; % = 84.3	n = 206 ; % = 85.5
Black or African American Sample size	n = 21 ; % = 4.4	n = 7 ; % = 2.9
Other **Asian, American Indian, Alaska Native, Other**. Sample size	n = 54 ; % = 11.3	n = 28 ; % = 11.6
Existing CVD diagnoses		
Coronary heart disease **MI, unstable angina, revascularisation** Sample size	n = 437 ; % = 91.2	n = 212 ; % = 88
Ischaemic stroke Sample size	n = 40 ; % = 8.4	n = 20 ; % = 8.3
PAD Sample size	n = 24 ; % = 5	n = 11 ; % = 4.6
Type 2 diabetes Sample size	n = 145 ; % = 30.3	n = 76 ; % = 31.5

Characteristic	Alirocumab (+ oral placebo) (N = 479)	Ezetimibe (+ subcutaneous placebo) (N = 241)
Chronic kidney disease **Moderate CKD** Sample size	n = 61 ; % = 12.7	n = 23 ; % = 9.5
LDL cholesterol (mmol/l) **Friedewald formula** Mean (SD)	2.8 (0.9)	2.7 (0.9)
Non-HDL cholesterol (mmol/l) Mean (SD)	3.6 (1)	3.5 (1)
Statin use		
Any statin Sample size	n = 478 ; % = 99.8	n = 241 ; % = 100
High-intensity statin **40–80 mg/day atorvastatin or 20–40 mg/day rosuvastatin** Sample size	n = 320 ; % = 66.8	n = 160 ; % = 66.4
Atorvastatin Sample size	n = 237 ; % = 49.5	n = 160 ; % = 66.4
Rosuvastatin Sample size	n = 137 ; % = 28.6	n = 75 ; % = 31.1

Characteristic	Alirocumab (+ oral placebo) (N = 479)	Ezetimibe (+ subcutaneous placebo) (N = 241)
Simvastatin Sample size	n = 105 ; % = 21.9	n = 49 ; % = 20.3

Outcomes

Study timepoints

- Baseline
- 24 week
- 52 week

Continuous

Outcome	Alirocumab (+ oral placebo), Baseline, N = 479	Alirocumab (+ oral placebo), 24 week, N = 467	Alirocumab (+ oral placebo), 52 week, N = 467	Ezetimibe (+ subcutaneous placebo), Baseline, N = 241	Ezetimibe (+ subcutaneous placebo), 24 week, N = 240	Ezetimibe (+ subcutaneous placebo), 52 week, N = 240
% change LDL-C from baseline least squares mean Mean (SE)	-	-50.6 (1.4)	-49.5 (1.5)	-	-20.7 (1.9)	-18.3 (2.1)

Outcome	Alirocumab (+ oral placebo), Baseline, N = 479	Alirocumab (+ oral placebo), 24 week, N = 467	Alirocumab (+ oral placebo), 52 week, N = 467	Ezetimibe (+ subcutaneous placebo), Baseline, N = 241	Ezetimibe (+ subcutaneous placebo), 24 week, N = 240	Ezetimibe (+ subcutaneous placebo), 52 week, N = 240
LDL-C absolute values (mmol/l) Mean (SD)	2.8 (0.9)	1.3 (0.86)	1.4 (-)	2.7 (0.9)	2.1 (0.9)	2.2 (-)
LDL-C absolute values (mmol/l) Mean (SE)	-	1.3 (0.04)	-	-	2.1 (0.05)	-
% change non-HDL-C from baseline least squares mean Mean (SE)	-	-42.1 (1.2)	-	-	-19.2 (1.7)	-

% change LDL-C from baseline - Polarity - Higher values are better (greater reduction is better)

LDL-C absolute values - Polarity - Lower values are better

% change non-HDL-C from baseline - Polarity - Higher values are better (greater reduction in better)

Dichotomous

Outcome	Alirocumab (+ oral placebo), 52 week, N = 479	Ezetimibe (+ subcutaneous placebo), 52 week, N = 479
Cardiovascular events (adjudicated) CHD death; non-fatal MI; fatal/non-fatal ischaemic stroke; unstable angina hospitalisation; HF hospitalisation; ischaemia-driven coronary revascularisation No of events	n = 23 ; % = 4.8	n = 9 ; % = 3.7

Cardiovascular events (adjudicated) - Polarity - Lower values are better

Sensitivity analyses: difference between means

Outcome: % change in LDL-C	Alirocumab (+ oral placebo) vs Ezetimibe (+ subcutaneous placebo), 24 week, N2 = 467, N1 = 240	
High intensity statins n=302 vs 152 Mean (95% CI)	-28.2 (-33.9 to -22.5)	
No high intensity statins n=165 vs 88 Mean (95% CI)	-32.8 (-40.4 to -25.1)	
Baseline LDL-C <100 mg/dl n=231 vs 126 Mean (95% CI)	-32.8 (-39.2 to -26.5)	

Outcome: % change in LDL-C	Alirocumab (+ oral placebo) vs Ezetimibe (+ subcutaneous placebo), 24 week, N2 = 467, N1 = 240	
Baseline LDL-C ≥100 to <130 mg/dl n=136 vs 64 Mean (95% CI)	-27.3 (-36 to -18.5)	
Baseline LDL-C ≥130 to <160 mg/dl n=59 vs 33 Mean (95% CI)	-29.6 (-42 to -17.1)	
Baseline LDL-C ≥160 mg/dl n=41 vs 17 Mean (95% CI)	-24.1 (-40.8 to -7.3)	

% change in LDL-C: statin intensity subgroup - Polarity - Higher values are better (greater reduction is better)

% change in LDL-C: baseline LDL-C subgroup - Polarity - Higher values are better (greater reduction is better)

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

% change LDL-24 weeks

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

% change LDL-C-52 weeks

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

% change non-HDL-C-24 weeks

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

MACE - 52 weeks

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Indirectly applicable *(Approximately 50% of events were revascularistion (not in protocol definition of outcome))*

Sensitivity analysis: LDL-C 24 weeks (statin intensity subgroups)

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

Sensitivity analysis: LDL-C 24 weeks (baseline LDL-C subgroups)

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Subgroup analysis not prespecified and no information about how the categories were selected)*
Overall bias and Directness	Overall Directness	Directly applicable

Cannon, 2008

Bibliographic Reference	Cannon, Christopher P; Giugliano, Robert P; Blazing, Michael A; Harrington, Robert A; Peterson, John L; Sisk, Christine McCrary; Strony, John; Musliner, Thomas A; McCabe, Carolyn H; Veltri, Enrico; Braunwald, Eugene; Califf, Robert M; IMPROVE-IT, Investigators; Rationale and design of IMPROVE-IT (IMProved Reduction of Outcomes: Vytorin Efficacy International Trial): comparison of ezetimbe/simvastatin versus simvastatin monotherapy on cardiovascular outcomes in patients with acute coronary syndromes.; American heart journal; 2008; vol. 156 (no. 5); 826-32

Study details

Secondary publication of another included study- see primary study for details	Rationale and design of IMPROVE-IT: see Cannon 2015 for full details

Colhoun, 2014

Bibliographic Reference	Colhoun, Helen M; Robinson, Jennifer G; Farnier, Michel; Cariou, Bertrand; Blom, Dirk; Kereiakes, Dean J; Lorenzato, Christelle; Pordy, Robert; Chaudhari, Umesh; Efficacy and safety of alirocumab, a fully human PCSK9 monoclonal antibody, in high cardiovascular risk patients with poorly controlled hypercholesterolemia on maximally tolerated doses of statins: rationale and design of the ODYSSEY COMBO I and II trials.; BMC cardiovascular disorders; 2014; vol. 14; 121

Study details

Secondary publication of another included study- see primary study for details	Rationale and design of ODYSSEY COMBO I and II trials; see Kereiakes 2015 for study details

Diaz, 2021

Bibliographic Reference	Diaz, Rafael; Li, Qian H; Bhatt, Deepak L; Bittner, Vera A; Baccara-Dinet, Marie T; Goodman, Shaun G; Jukema, J Wouter; Kimura, Takeshi; Parkhomenko, Alexander; Pordy, Robert; Reiner, Zeljko; Roe, Matthew T; Szarek, Michael; Tse, Hung-Fat; White, Harvey D; Zahger, Doron; Zeiher, Andreas M; Schwartz, Gregory G; Steg, Ph Gabriel; ODYSSEY OUTCOMES Committees and, Investigators; Intensity of statin treatment after acute coronary syndrome, residual risk, and its modification by alirocumab: insights from the ODYSSEY OUTCOMES trial.; European journal of preventive cardiology; 2021; vol. 28 (no. 1); 33-43

Study details

Secondary publication of	Subgroup analysis of ODYSSEY OUTCOMES trial - see Schwartz 2018

another included study- see primary study for details	

Study arms

Alirocumab (N = 9462)

Placebo (N = 9462)

Characteristics

Arm-level characteristics

Characteristic	Alirocumab (N = 9462)	Placebo (N = 9462)
LDL cholesterol (mg/dl)		
High-intensity statin Median (IQR)	85 (72 to 102)	86 (73 to 102)
Low/moderate intensity statin Median (IQR)	89 (76 to 107)	89 (74 to 106)
No statin Median (IQR)	141 (116 to 172)	136 (114 to 168)
Non-HDL cholesterol (mg/dl)		
High intensity statin	114 (99 to 134)	114 (99 to 135)

Characteristic	Alirocumab (N = 9462)	Placebo (N = 9462)
Median (IQR)		
Low/moderate intensity statin Median (IQR)	117 (102 to 138)	116 (101 to 138)
No statin Median (IQR)	177 (148 to 211)	178 (149 to 214)

Outcomes

Study timepoints

- Baseline
- 4 month
- 2.8 year (median follow-up)

Continuous

	Alirocumab, 4 month, N = 9462	Placebo, 4 month, N = 9462
Outcome: % change LDL-C from baseline		
High intensity statin N = 8380 vs 8431 Mean (SD)	-57.2 (-)	4.6 (-)

	Alirocumab, 4 month, N = 9462	Placebo, 4 month, N = 9462
Outcome: % change LDL-C from baseline		
Low/moderate intensity statin N = 849 vs 804 Mean (SD)	-59.4 (-)	3.9 (-)
No statin N = 233 vs 227 Mean (SD)	-58.7 (-)	2 (-)
Outcome: LDL-C absolute change (mg/dl)		
High intensity statin N = 8380 vs 8431 Mean (SD)	-52.9 (-)	1.1 (-)
Low/moderate intensity statin N = 849 vs 804 Mean (SD)	-56.7 (-)	0.3 (-)
No statin N = 233 vs 227 Mean (SD)	-86.1 (-)	-0.2 (-)

% change LDL-C - Polarity - Higher values are better (greater reduction is better)

LDL-C absolute change - Polarity - Lower values are better

Dichotomous

Outcome: Injection-site reactions	Alirocumab, 2.8 year, N = 9462	Placebo, 2.8 year, N = 9462
High intensity statin N = 8380 vs 8431 No of events	n = 307	n = 181
Low/moderate intensity statin N = 849 vs 804 No of events	n = 33	n = 13
No statin N = 233 vs 227 No of events	n = 20	n = 9

Injection site reactions - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

% change LDL-C-4 month

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

LDL-C absolute change - 4 month

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Injection site reactions

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

El Shahawy, 2017

Bibliographic Reference	El Shahawy, Mahfouz; Cannon, Christopher P; Blom, Dirk J; McKenney, James M; Cariou, Bertrand; Lecorps, Guillaume; Pordy, Robert; Chaudhari, Umesh; Colhoun, Helen M; Efficacy and Safety of Alirocumab Versus Ezetimibe Over 2 Years (from ODYSSEY COMBO II).; The American journal of cardiology; 2017; vol. 120 (no. 6); 931-939

Study details

Secondary publication of another included study- see primary study for details	MACE, elevated liver outcomes and injection-site reactions outcome data for ODYSSEY COMBO II trial. Full study details reported in main trial entry (Cannon 2015: EPPI ID: 12982607)
Other publications associated with this study included in review	Colhoun 2014 - Study design and rationale

Study arms

Alirocumab (+ oral placebo) (N = 479)

75 mg every 2 weeks with increase to 150 mg (with background statin)

Ezetimibe (+ subcutaneous placebo) (N = 241)

10 mg/day (with background statin)

Outcomes

Study timepoints

- 104 week

Dichotomous

Outcome	Alirocumab (+ oral placebo), 104 week, N = 479	Ezetimibe (+ subcutaneous placebo), 104 week, N = 241
MACE (Number of patients with at least 1 MACE) **CHD death, nonfatal MI, ischemic stroke, or unstable angina requiring hospitalization (differs from definition at 52 weeks).** No of events	n = 23 ; % = 4.8	n = 8 ; % = 3.3
Increased liver transaminases: Alanine aminotransferase >3 x ULN No of events	n = 10	n = 2
Increased liver transaminases: Aspartate aminotransferase >3 x ULN No of events	n = 11	n = 1
Local injection-site reactions No of events	n = 13; %= 2.7%	n = 3 ; % = 1.2

MACE - Polarity - Lower values are better

Increased liver transaminases - Polarity - Lower values are better

Local injection-site reactions - Polarity - Lower values are better

Dichotomous (without diabetes at baseline)

Outcome: Diabetes onset	Alirocumab (+ oral placebo), 104 week, N = 331	Ezetimibe (+ subcutaneous placebo), 104 week, N = 164
Diabetes mellitus No of events	n = 5 ; % = 3.4	n = 3 ; % = 1.8

Outcome: Diabetes onset	Alirocumab (+ oral placebo), 104 week, N = 331	Ezetimibe (+ subcutaneous placebo), 104 week, N = 164
Type 2 diabetes mellitus No of events	n = 9 ; % = 2.7	n = 3 ; % = 1.8

'Diabetes mellitus' or 'Type 2 diabetes mellitus' codes - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

MACE - 104 weeks

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Unclear how definition of MACE chosen and differs from 52 week assessment definition)*
Overall bias and Directness	Overall Directness	Directly applicable

Increased liver transaminases -104 weeks

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Local injection site reactions - 104 weeks

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Diabetes onset - 104 weeks

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Indirectly applicable *(Unclear if relates to 'new onset diabetes' (based on Medical Dictionary of Regulatory Activities queries))*

Gao, 2021

Bibliographic Reference	Gao, Fei; Wang, Zhi Jian; Ma, Xiao Teng; Shen, Hua; Yang, Li Xia; Zhou, Yu Jie; Effect of alirocumab on coronary plaque in patients with coronary artery disease assessed by optical coherence tomography.; Lipids in health and disease; 2021; vol. 20 (no. 1); 106

Study details

Trial name / registration number	NCT04851769

Study type	Randomised controlled trial (RCT)
Study location	Beijing, China
Study setting	An Zhen Hospital, Beijing China
Study dates	March 2019 to Jan 2020,
Sources of funding	Capital's Funds for Health Improvement and Research.
Inclusion criteria	People who were: 18–80 years of age, diagnosed as stable coronary artery disease or acute coronary syndrome, received OCT imaging measurement, LDL cholesterol values ≥1.81 mmol/l for patients with ACS or ≥ 2.59 mmol/l for non-ACS patients despite statin therapy, At least one intermediate lesion (50–70% diameter stenosis) in de novo coronary arteries, provided written informed consent
Exclusion criteria	Known hypersensitivity or contraindications to alirocumab and/or statin therapy; Received balloon angioplasty or stent implantation for target lesion; Unable to conduct OCT imaging analysis; Prior usage of PCSK9 inhibitors; Severe renal dysfunction (creatinine clearance < 30 mL/min); Severe hepatic dysfunction Baseline triglyceride > 400 mg/dl; History of haemorrhagic stroke; Pregnant or breast-feeding women Life expectancy < 1 year Inappropriate for the study for any reason based on the investigators' judgement
Recruitment / selection of participants	All consecutive patients who received coronary angiogram and OCT imaging in An Zhen Hospital, meeting inclusion criteria.
Intervention(s)	Alirocumab 75 mg once every two weeks every 2 weeks on top of standard statin therapy (atorvastatin 20 mg/day or rosuvastatin 10 mg/day). The last dose of alirocumab was given at week 34.
Comparator	Standard care: atorvastatin 20 mg/day or rosuvastatin 10 mg/day; Nearly half of the patients (15/31) in the standard care arm received ezetimibe and statin combination therapy.

Background treatment	Statin dose escalation or the addition of other concomitant non-statin lipid-lowering therapies could be considered by the physicians responsible for achieving the target LDL cholesterol levels. Antithrombotic therapy and other concomitant medications were exclusively decided by their responsible physicians; All the participants were prescribed antiplatelet therapy, and approximately 90% of them were treated with beta blockers.
Number of participants	61
Duration of follow-up	36 ± 2 weeks (treatment initiating within 4 weeks of baseline coronary angiogram)
Additional comments	Continuous variables are reported as the means ± standard deviations or median (interquartile ranges). Categorical variables are presented as counts and percentages. Continuous variables between the two groups were compared by the Mann–Whitney U test. Comparisons of continuous variables between baseline and follow-up were performed by the Wilcoxon signed rank test. Comparisons of categorical variables were performed by the Fisher's exact test. A two-tailed test P value < 0.05 was considered as statistically significant. The SPSS Statistics 25.0 package was used

Study arms

Alirocumab + Statin (N = 30)

Alirocumab 75 mg every 2 weeks on top of standard statin therapy (atorvastatin 20 mg/day or rosuvastatin 10 mg/day) i.e. high intensity statins

Standard care (N = 31)

Atorvastatin 20mg/day or rosuvastatin 10 mg/day

Characteristics

Arm-level characteristics

Characteristic	Alirocumab + Statin (N = 30)	Standard care (N = 31)
% Female Sample size	n = 10 ; % = 33.3	n = 8 ; % = 25.8
Mean age (SD) Mean (SD)	61.3 (8.9)	61.3 (9.9)
Prior CVD diagnosis		
Prior MI Sample size	n = 4 ; % = 13.3	n = 3 ; % = 9.7
Prior stroke Sample size	n = 1 ; % = 3.2	n = 3 ; % = 10
Acute Coronary Syndrome Sample size	n = 11 ; % = 36.7	n = 13 ; % = 41.9
Type 2 diabetes Sample size	n = 7 ; % = 23.3	n = 8 ; % = 25.8
LDL cholesterol (mmol/l) Mean (SD)	3.04 (0.78)	3.18 (0.97)
Statins used Chronic statin use before enrollment Sample size	n = 8 ; % = 26.7	n = 10 ; % = 32.3

Characteristic	Alirocumab + Statin (N = 30)	Standard care (N = 31)
Anti-platelet Sample size	n = 30 ; % = 100	n = 31 ; % = 100
Beta blocker Sample size	n = 28 ; % = 93.3	n = 28 ; % = 90.3
Angiotensin converting enzyme inhibitors/angiotensin receptor blockers Sample size	n = 18 ; % = 60	n = 20 ; % = 64.5

Outcomes

Study timepoints

- 36 week (Cardiovascular events and treatment-related adverse reactions occurring within the 36-week follow-up were reported)

LDL-C

Outcome	Alirocumab + Statin, 36 week, N = 30	Standard care, 36 week, N = 31
Absolute change in LDL-C (mmol/l) Mean (SD)	-1.72 (0.51)	-0.96 (0.59)

Absolute change in LDL-C - Polarity - Lower values are better

Clinical events

Outcome	Alirocumab + Statin, 36 week, N = 30	Standard care, 36 week, N = 31
Adverse cardiac events No of events	n = 0 ; % = 0	n = 0 ; % = 0
Injection site reactions No of events	n = 1 ; % = 3.3	n = 0 ; % = 0

Adverse cardiac events - Polarity - Lower values are better

Injection site reactions - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

LDL-C-Absolute change

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(due to lack of blinding and potential deviation from protocol: Statin dose escalation or other concomitant lipid-lowering therapies could be considered by the responsible physicians to achieve target LDL-C levels and no information about such dose escalations)*
Overall bias and Directness	Overall Directness	Directly applicable

Adverse cardiac events

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(due to lack of blinding and potential deviation from protocol: Statin dose escalation or other concomitant lipid-lowering therapies could be considered by the responsible physicians to achieve target LDL-C levels and no information about such dose escalations)*
Overall bias and Directness	Overall Directness	Directly applicable

Injection-site reactions

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Giugliano, 2012

Bibliographic Reference	Giugliano, Robert P; Desai, Nihar R; Kohli, Payal; Rogers, William J; Somaratne, Ransi; Huang, Fannie; Liu, Thomas; Mohanavelu, Satishkumar; Hoffman, Elaine B; McDonald, Shannon T; Abrahamsen, Timothy E; Wasserman, Scott M; Scott, Robert; Sabatine, Marc S; LAPLACE-TIMI 57, Investigators; Efficacy, safety, and tolerability of a monoclonal antibody to proprotein convertase subtilisin/kexin type 9 in combination with a statin in patients with hypercholesterolaemia (LAPLACE-TIMI

57): a randomised, placebo-controlled, dose-ranging, phase 2 study.; Lancet (London, England); 2012; vol. 380 (no. 9858); 2007-17

Study details

Other publications associated with this study included in review	Kholi 2012 (study design and protocol)
Trial name / registration number	LAPLACE-TIMI 57/ NCT01380730
Study type	Randomised controlled trial (RCT)
Study location	Multinational trial done in 78 centres in five countries (USA, Canada, Denmark, Hungary, and Czech Republic)
Study setting	Primary care
Study dates	Subject recruitment began on July 6, 2011, and was completed on December 22, 2011; randomisation occurred between July 18 and Dec 22, 2011; Results taken February 2, 2012
Sources of funding	Amgen.
Inclusion criteria	Eligible patients (aged 18–80 years) had a history of hypercholesterolaemia and fasting LDL-C concentration greater than 2.2 mmol/l while on a stable dose of statin (with or without ezetimibe) for at least 4 weeks. If a subject was on a non-statin lipid-modifying agent (other than ezetimibe) prior to enrolment, the investigator could withdraw this therapy and allow for a 4-week ‘‘wash-out’’ period prior to screening the subject again for enrolment.

Exclusion criteria	Subjects with a recent acute coronary syndrome, severe heart failure, or a recent serious arrhythmia were excluded, as were subjects with severe chronic kidney disease or other major medical comorbidities and those taking lipid-lowering drugs other than ezetimibe.
Recruitment / selection of participants	Not specified; people meeting inclusion criteria
Population subgroups	Subgroup analysis available based on different baseline LDL-C levels, stating intensity (intensive vs non intensive) and use of concomitant ezetimibe (vs no use)
Intervention(s)	AMG 124 140 mg every 2 weeks or 420mg every 4 weeks; The total volume of the every 2 week subcutaneous injections was 2 mL and that of the every 4 week subcutaneous injections was 6 mL, with a recommended volume of 2 mL per injection. The last dose was administered on week 10 for the groups treated every 2 weeks and week 8 for the groups treated every 4 weeks, with an end of study visit 4 weeks after the last dose in each group.
Comparator	matching placebo every 2 weeks or every 4 weeks
Background treatment	Statin therapy: Simvastatin, atorvastatin, rosuvastatin, other statin specified in baseline characteristics table; Ezetimibe
Number of participants	The study included 631 participants. Of these, part were randomised to dose regimens not licenced in the UK. Data from these participants has not been extracted. 315 people were randomised in study arms relevant to the present review and have been included in the present data extraction table.
Duration of follow-up	12 weeks
Indirectness	29% were on high intensity statins but that included Simvastatin 80mg. Statin intensity for 71% of participants randomised to arms extracted in the present review was not specified. Approximately 10% in each of the four comparison groups were on statins not relevant to the review protocol (Lovastatin, Pitavastatin, Pravastatin)

Additional comments	Analyses of the primary and secondary efficacy endpoints were done with an ANCOVA model with covariates for treatment group and the stratification factors—screening LDL concentration (<3.4 mmol/l vs ≥ 3.4 mmol/l) and baseline use of ezetimibe (yes vs no). All efficacy endpoints were analysed with last observation carried forward (LOCF) imputation. A sensitivity analysis was done for patients who completed treatment and had an ultracentrifugation LDL-C concentration measured at week 12. Completion of treatment was defined as completing all the per-protocol scheduled visits up until the last visit injection. Primary, secondary, and exploratory endpoints were evaluated independently for the groups treated every 2 weeks and every 4 weeks and compared with their respective placebo groups at a significance level of 0.05.

Study arms

Evolocumab 140mg (N = 78)

AMG 145 (human monoclonal IgG2 antibody against PCSK9): 140mg every 2 weeks

Placebo every 2 weeks (N = 78)

Evolocumab 420mg (N = 80)

AMG 145 420mg every 4 weeks

Placebo every 4 weeks (N = 79)

Characteristics

Arm-level characteristics

Characteristic	Evolocumab 140mg (N = 78)	Placebo every 2 weeks (N = 78)	Evolocumab 420mg (N = 80)	Placebo every 4 weeks (N = 79)
% Female Sample size	n = 45 ; % = 58	n = 42 ; % = 54	n = 44 ; % = 55	n = 42 ; % = 53
Mean age (SD) Median (IQR)	63.5 (56 to 69)	61 (55 to 67)	63 (57 to 68)	63 (56 to 67)
Ethncity: White Sample size	n = 67 ; % = 86	n = 72 ; % = 92	n = 70 ; % = 88	n = 76 ; % = 96
Existing CVD diagnoses				
Coronary artery disease Sample size	n = 31 ; % = 40	n = 22 ; % = 28	n = 28 ; % = 35	n = 20 ; % = 25
Myocardial Infarction Sample size	n = 19 ; % = 24	n = 11 ; % = 14	n = 16 ; % = 20	n = 9 ; % = 11
Coronary artery bypass graft Sample size	n = 7 ; % = 9	n = 8 ; % = 10	n = 8 ; % = 10	n = 5 ; % = 6
Percutaneous coronary intervention Sample size	n = 19 ; % = 24	n = 12 ; % = 15	n = 13 ; % = 16	n = 9 ; % = 11.4
Cerebrovascular or peripheral arterial disease	n = 9 ; % = 12	n = 8 ; % = 10	n = 9 ; % = 11	n = 6 ; % = 8

Characteristic	Evolocumab 140mg (N = 78)	Placebo every 2 weeks (N = 78)	Evolocumab 420mg (N = 80)	Placebo every 4 weeks (N = 79)
Sample size				
Type 2 diabetes Sample size	n = 15 ; % = 19	n = 9 ; % = 12	n = 19 ; % = 24	n = 9 ; % = 11
LDL cholesterol (mmol/l) Ultracentrifuge Mean (SD)	3.1 (0.6)	3.2 (0.7)	3.1 (0.7)	3.2 (0.8)
Non-HDL cholesterol (mmol**/l)** Mean (SD)	3.8 (0.7)	3.8 (0.8)	3.7 (0.8)	3.9 (0.9)
Statins used Sample size	n = 78 ; % = 100	n = 78 ; % = 100	n = 80 ; % = 100	n = 77 ; % = 97
Atorvastatin Sample size	n = 22 ; % = 28	n = 15 ; % = 19	n = 24 ; % = 30	n = 28 ; % = 35
Fluvastatin Sample size	n = 0 ; % = 0	n = 0 ; % = 0	n = 2 ; % = 3	n = 0 ; % = 0
Lovastatin Sample size	n = 2 ; % = 3	n = 1 ; % = 1	n = 3 ; % = 4	n = 3 ; % = 4
Pitavastatin Sample size	n = 0 ; % = 0	n = 0 ; % = 0	n = 0 ; % = 0	n = 0 ; % = 0

Characteristic	Evolocumab 140mg (N = 78)	Placebo every 2 weeks (N = 78)	Evolocumab 420mg (N = 80)	Placebo every 4 weeks (N = 79)
Pravastatin Sample size	n = 6 ; % = 8	n = 7 ; % = 9	n = 3 ; % = 4	n = 7 ; % = 9
Rosuvastatin Sample size	n = 13 ; % = 17	n = 16 ; % = 21	n = 13 ; % = 16	n = 13
Simvastatin Sample size	n = 35 ; % = 45	n = 39 ; % = 50	n = 36 ; % = 45	n = 26 ; % = 33
High-intensity statins Sample size	n = 25 ; % = 32	n = 19 ; % = 24	n = 29 ; % = 36	n = 19 ; % = 25
Ezetimibe Sample size	n = 7 ; % = 9	n = 7 ; % = 9	n = 7 ; % = 9	n = 8 ; % = 10
Screening LDL-C <3.4 mmol/l (mmol/l) Sample size	n = 52 ; % = 67	n = 51 ; % = 65	n = 53 ; % = 66	n = 52 ; % = 66

Outcomes

Study timepoints

- 12 week

LDL-C

Outcome	Evolocumab 140mg vs Placebo every 2 weeks, 12 week, N2 = 78, N1 = 78	Evolocumab 420mg vs Placebo every 4 weeks, 12 week, N2 = 80, N1 = 79
Mean change in ultracentrifugation LDL-C vs placebo Mean % change (95% CI); SE for each group respectively was :2.7/ 2.9; The treatment difference compared with placebo was calculated with least squares mean, in the same dose frequency from the ANCOVA model, which includes treatment group and stratification factors (screening LDL, baseline use of ezetimibe) as covariates Mean (95% CI)	-66.1 (-71.6 to -60.7)	-50.3 (-56 to -44.6)

Mean change in ultracentrifugation LDL-C vs placebo - Polarity - Higher values are better (greater reduction is better)

Absolute change in LDL-C versus placebo

Outcome	Evolocumab 140mg vs Placebo every 2 weeks, 12 week, N2 = 78, N1 = 78	Evolocumab 420mg vs Placebo every 4 weeks, 12 week, N2 = 80, N1 = 79
Absolute change in LDL-C vs placebo (95% CI) (mmol/l) Custom value	-2.04 (-2.24 to -1.76)	-1.58 (-1.77 to -1.39)
Absolute change in LDL-C vs placebo (95% CI) (mmol/l) Mean (SE)	-2.04 (0.1)	-1.58 (0.1)

Absolute change in LDL-C vs placebo (95% CI) - Polarity - Lower values are better

Mean change in non-HDL concentration versus placebo

Outcome	Evolocumab 140mg vs Placebo every 2 weeks, 12 week, N2 = 78, N1 = 78	Evolocumab 420mg vs Placebo every 4 weeks, 12 week, N2 = 80, N1 = 79
Mean change in (%) non-HDL-C SE given for each group was: 2.5/2.6 respectively; The treatment difference compared with placebo was calculated with least squares mean, in the same dose frequency from the ANCOVA model, which includes treatment group and stratification factors (screening LDL, baseline use of ezetimibe) as covariates. Mean (95% CI)	-61.4 (-66.4 to -56.4)	-47.6 (-52.7 to -42.4)

Mean change in (%) non-HDL-C – Polarity – Higher values are better (greater reduction is better)

Percentage change in ultracentrifugation LDL-C subgroup analyses: baseline LDL-C <2.6

Outcome	Evolocumab 140mg, 12 week, N = 12	Placebo every 2 weeks, 12 week, N = 15	Evolocumab 420mg, 12 week, N = 17	Placebo every 4 weeks, 12 week, N = 12
% change in LDL-C at week 12 in people with baseline LDL-C <2.6 (mmol/l) Custom value	-56.1	-12.7	-54.7	-4.6

% change in LDL-C at week 12 in people with baseline LDL-C <2.6 – Polarity – Higher values are better (greater reduction is better)

Treatment differences (95% CI) compared with placebo were calculated by use of least squares mean and treatment group and stratification factors as covariates.

% change in LDL-C in subgroup of people with baseline LDL-C 2.6 to <3.4

Outcome	Evolocumab 140mg, 12 week, N = 40	Placebo every 2 weeks, 12 week, N = 40	Evolocumab 420mg, 12 week, N = 40	Placebo every 4 weeks, 12 week, N = 42
% change in LDL-C in people with baseline LDL-C 2.6 to <3.4 Custom value	-61.8	3.1	-53.7	-0.8

% change in LDL-C in people with baseline LDL-C 2.6 to <3.4 - Polarity - Higher values are better (greater reduction is better)

% change in LDL-C in subgroup of people with baseline LDL-C > or equal to 3.4

Outcome	Evolocumab 140mg, 12 week, N = 25	Placebo every 2 weeks, 12 week, N = 23	Evolocumab 420mg, 12 week, N = 21	Placebo every 4 weeks, 12 week, N = 23
% change in LDL-C in people with baseline LDL-C higher or equal to 3.4 (mmol/l) Custom value	-70.5	-9.1	-50.6	-3

% change in LDL-C in people with baseline LDL-C higher or equal to 3.4 - Polarity - Higher values are better (greater reduction is better)

Percentage change in ultracentrifugation LDL-C in subgroup with intensive statin regimen

Outcome	Evolocumab 140mg, 12 week, N = 25	Placebo every 2 weeks, 12 week, N = 52	Evolocumab 420mg, 12 week, N = 19	Placebo every 4 weeks, 12 week, N = 59
% change in LDL-C Custom value	-61.5	4.2	-50.7	2.5

% change in LDL-C - Polarity - Higher values are better (greater reduction is better)

Percentage change in ultracentrifugation LDL-C in subgroup with non-intensive statin regimen

Outcome	Evolocumab 140mg, 12 week, N = 52	Placebo every 2 weeks, 12 week, N = 59	Evolocumab 420mg, 12 week, N = 50	Placebo every 4 weeks, 12 week, N = 58
% change in LDL-C Custom value	-65.3	1.2	-55.7	5.7

% change in LDL-C - Polarity - Higher values are better (greater reduction is better)

Adverse events

Outcome	Evolocumab 140mg, 12 week, N = 78	Placebo every 2 weeks, 12 week, N = 78	Evolocumab 420mg, 12 week, N = 80	Placebo every 4 weeks, 12 week, N = 77
Injection site reactions No of events	n = 0 ; % = 0	n = 2 ; % = 3	n = 1 ; % = 1	n = 1 ; % = 1
Positively adjudicated clinical cardiovascular events Acute coronary syndrome, coronary revascularisation, transient ischaemic attack, congestive heart failure requiring hospital admission, or death. No of events	n = 4 ; % = 5	n = 1 ; % = 1	n = 0 ; % = 0	n = 0 ; % = 0

Injection site reactions - Polarity - Lower values are better

Positively adjudicated clinical cardiovascular events - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

LDL-C-Mean change

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Partially applicable *(Some participants (unclear how many) were taking Simvastatin 80mg and about 10% in each treatment groups were on statins not relevant to the review protocol)*

Absolute change LDL-C

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Partially applicable *(Some participants (unclear how many) were taking Simvastatin 80mg and about 10% in each treatment groups were on statins not relevant to the review protocol)*

Mean change in non-HDL-C

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low

Section	Question	Answer
Overall bias and Directness	Overall Directness	Partially applicable *(Some participants (unclear how many) were taking Simvastatin 80mg and about 10% in each treatment groups were on statins not relevant to the review protocol)*

% change LDL-C: subgroup with non-intensive statin regimen

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Partially applicable *(Some participants (unclear how many) were taking Simvastatin 80mg and about 10% in each treatment groups were on statins not relevant to the review protocol)*

% change LDL-C: subgroup with intensive statin regimen

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Partially applicable *(Some participants (unclear how many) were taking Simvastatin 80mg and about 10% in each treatment groups were on statins not relevant to the review protocol)*

% change LDL-C baseline LDL-C at least 3.4

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Partially applicable *(Some participants (unclear how many) were taking Simvastatin 80mg and about 10% in each treatment groups were on statins not relevant to the review protocol)*

% change LDL-C baseline LDL-C 2.6 to <3.4

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Partially applicable *(Some participants (unclear how many) were taking Simvastatin 80mg and about 10% in each treatment groups were on statins not relevant to the review protocol)*

% change LDL-C

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low

Section	Question	Answer
Overall bias and Directness	Overall Directness	Partially applicable *(Some participants (unclear how many) were taking Simvastatin 80mg and about 10% in each treatment groups were on statins not relevant to the review protocol)*

Positively adjudicated clinical cardiovascular events

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Partially applicable *(Some participants (unclear how many) were taking Simvastatin 80mg and about 10% in each treatment groups were on statins not relevant to the review protocol)*

Injection-site reactions

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Han, 2020

Bibliographic Reference	Han, Y; Chen, J; Chopra, VK; Zhang, S; Su, G; Ma, C; Huang, Z; Ma, Y; Yao, Z; Yuan, Z; et, al.; ODYSSEY EAST: alirocumab efficacy and safety vs ezetimibe in high cardiovascular risk patients with hypercholesterolemia and on maximally tolerated statin in China, India, and Thailand; Journal of clinical lipidology; 2020; vol. 14 (no. 1); 98-108.e8

Study details

Trial name / registration number	ODYSSEY EAST/ NCT02715726
Study type	Randomised controlled trial (RCT)
Study location	Multicentre trial conducted in 3 countries with a total of 61 active sites (40 in China, 17 in India, and 4 in Thailand);
Study setting	Primary care
Study dates	Patient enrolment began on July 27, 2016, and the study completed on August 6, 2018: screening period of up to 3 weeks, followed by 24 weeks of double-blind treatment and 8 weeks of follow-up (off treatment)
Sources of funding	Sanofi and Regeneron Pharmaceuticals, Inc.
Inclusion criteria	Patients with hypercholesterolemia and established CHD or CHD risk equivalents who were inadequately controlled with stable maximally tolerated statin therapy for at least 4 weeks before the screening visit (week 23). Patients with a history of CV disease (defined as CHD or CHD risk equivalents) were included if their LDL-C levels were ≥1.81 mmol/l (70 mg/dl) despite their current LLT. Those without a history of CV disease (but with other risk factors) were required to have a baseline LDL-C ≥2.59 mmol/l (100 mg/dl). All patients were on stable maximally tolerated statin therapy for at least 4 weeks before the screening visit. Maximally tolerated statin was defined as atorvastatin 40 to 80 mg daily, rosuvastatin 20 to 40 mg daily, simvastatin 40 mg daily, or lower doses of these if there was a documented reason such as adverse events (AEs) on higher doses, advanced age, low body mass index, local prescribing information, concomitant medications, and comorbid conditions such as impaired glucose tolerance/impaired fasting glucose. CHD was defined as acute or silent

	myocardial infarction (MI), unstable angina, coronary revascularization procedure, or clinically significant CHD diagnosed by invasive or noninvasive testing. CHD risk equivalents included documented peripheral arterial disease, documented previous ischemic stroke with focal ischemic neurological deficit of atherothrombotic origin that persisted for more than 24 hours, documented chronic kidney disease, known diabetes mellitus, or 2 or more additional risk factors
Exclusion criteria	Patients with a known history of familial hypercholesterolemia Patients without established CHD or CHD risk equivalents; LDL-C <70 mg/dl (<1.81 mmol/l) at the screening visit (week 23) in patients with a history of documented cardiovascular disease (defined as CHD, ischemic stroke, or peripheral arterial disease as described previously); LDL-C <100 mg/dl (<2.59 mmol/l) at the screening visit (week 23) in patients without history of documented cardiovascular disease; Change in statin dose or dose regimen from screening to randomization; Taking a statin that was not atorvastatin, rosuvastatin, or simvastatin; Atorvastatin, rosuvastatin, or simvastatin not taken daily or not taken at a registered dose; Daily dose above atorvastatin 80 mg, rosuvastatin 40 mg, or simvastatin 40 mg. 8) Use of cholesterol absorption inhibitor (ie. ezetimibe), omega-3 fatty acid (at doses ≥1000 mg daily), nicotinic acid, fibrates, bile acid–binding sequestrant, or red yeast rice products within the past 4 wk before screening visit (week 23) or between screening and randomization visits; Use of nutraceutical products or over-the-counter therapies that may affect lipids which had not been at a stable dose/amount for at least 4 wk before the screening visit (week 23) or between screening and randomization visits; Patients who had received plasmapheresis treatment within 2 mo before the screening visit (week 23) or were planning to receive this during the study; History of an MI, unstable angina leading to hospitalization, CABG, PCI, uncontrolled cardiac arrhythmia, carotid surgery or stenting, stroke, transient ischemic attack, carotid revascularization, endovascular procedure, or surgical intervention for peripheral vascular disease within 3 mo before the screening visit (week -3, V1); Planning to undergo scheduled PCI, CABG, or carotid or peripheral revascularization during the study; Systolic blood pressure >160 mmHg or diastolic blood pressure >100 mmHg at screening visit or randomization visit; History of New York Heart Association Class III or IV heart failure within the past 12 mo; Known history of haemorrhagic stroke; Age <18 y or legal age of majority at the screening visit (week 23), whichever was greater; Patients not previously instructed to follow a cholesterol-lowering diet before the screening visit (week 23); Newly diagnosed (within 3 mo before randomization visit [week 0]) or poorly controlled diabetes (HbA1c .9% at the screening visit [week 23]); Presence of any clinically significant uncontrolled endocrine disease known to influence serum lipids or lipoproteins. Patients on thyroid replacement therapy were included if the dosage had been stable for at least 12 wk before screening and between screening and randomization visits, and TSH level was within the normal range at the screening visit; History of bariatric surgery within 12 mo before the screening visit (week 23); Unstable weight defined by a variation >5 kg within 2 mo before the screening visit (week 23)

Recruitment / selection of participants	Randomization was stratified according to prior history of MI or ischemic stroke, high-intensity statin treatment, and country.
Intervention(s)	1) Alirocumab 75 mg every 2 weeks (Q2W) via subcutaneous injection with a prefilled pen; Alirocumab-treated patients not achieving LDL-C levels of <1.81 mmol/L (70 mg/dL) at week 8 had their dosing regimen changed to 150 mg Q2W from week 12 in a blinded fashion.
Comparator	Ezetimibe (10 mg oral daily)
Background treatment	Maximally tolerated statins: atorvastatin 40 to 80 mg daily, rosuvastatin 20 to 40 mg daily, simvastatin 40 mg daily, or lower doses of these if there was a documented reason such as adverse events (AEs) on higher doses, advanced age, low body mass index, local prescribing information, concomitant medications, and comorbid conditions such as impaired glucose tolerance/impaired fasting glucose.
Number of participants	615
Duration of follow-up	24 weeks
Additional comments	ITT population included all randomized patients with an LDL-C measurement available at baseline and at least one of the post randomisation time points between weeks 4 and 24, regardless of treatment adherence. This was used for the primary outcome (% change in LDL-C at week 24 from baseline). The primary efficacy endpoint was analysed in the ITT population using a mixed-effect model with repeated measures approach to handle missing data. All postbaseline data available within the week 4 to week 24 analysis window were used (on-treatment and off-treatment through week 24). The model included the fixed categorical effects of treatment group (alirocumab vs ezetimibe), time point (weeks 4, 8, 12, 16, and 24), randomization strata, treatment-by-time point interaction, and strata-by time point interaction, as well as the continuous fixed covariates of baseline LDL-C value and baseline value-by-time point interaction. Alirocumab was compared to ezetimibe using appropriate contrasts, and the 95% confidence interval of the difference was provided. The key secondary efficacy endpoints were analysed using a hierarchical procedure to control type I error and handle multiple endpoints. If the primary endpoint analysis was significant at the 5% alpha level, key secondary endpoints were tested sequentially. Continuous secondary endpoints anticipated to

	have a normal distribution (ie, lipids other than Lp(a) and TGs) were analysed using the same mixed-effect model with repeated-measures model as for the primary endpoint with the continuous fixed covariates of corresponding baseline value and baseline value-by-time point interaction. Continuous secondary endpoints anticipated to have a non-normal distribution (ie, Lp(a) and TGs) were analysed using multiple imputation approach for handling of missing values followed by robust regression. Binary secondary endpoints (eg, proportion reaching LDL-C ,1.81 mmol/l [,70 mg/dl]) were analysed using multiple imputation approach for handling of missing values followed by logistic regression. The safety analysis of AEs (including adjudicated CVD events and AESIs, laboratory values, and vital signs) was descriptive, based on the safety population (which included randomized patients who received at least 1 dose or part of a dose of study drug during the treatment period). The safety analysis focused on the treatment-emergent AE (TEAE) period, defined as the time from the first double blind dose of study treatment to the last dose of double blind treatment injection 1 70 days (10 weeks).

Study arms

Alirocumab (N = 407)

75 mg every 2 weeksevery 2 weeks; with dose increase to 150 mg every 2 weeks at week 12 if week 8 LDL-C was >1.81 mmol/l [>70 mg/dl])

Ezetimibe (N = 208)

10mg/daily

Characteristics

Arm-level characteristics

Characteristic	Alirocumab (N = 407)	Ezetimibe (N = 208)
% Female	n = 92 ; % = 22.6	n = 62 ; % = 29.8

Characteristic	Alirocumab (N = 407)	Ezetimibe (N = 208)
Sample size		
Mean age (SD) Mean (SD)	58.8 (10.7)	58.3 (11.2)
Ethnicity Asian Sample size	n = 407 ; % = 100	n = 208 ; % = 100
Existing CVD diagnoses Coronary heart disease Sample size	n = 398 ; % = 97.8	n = 202 ; % = 97.1
Type 2 diabetes Sample size	n = 121 ; % = 29.7	n = 48 ; % = 23.1
LDL cholesterol (mmol/l) calculate LDL-C (Alirocumab= 110.7 (48.5) mg/dl; Ezetimibe=111.2 (49.8) mg/dl) Mean (SD)	2.86 (1.26)	2.88 (1.29)
Non-HDL cholesterol (mmol/l) Alirocumab= 138.3 (50.7) mg/dl; Ezetimibe=140.5 (52.7) mg/dl Mean (SD)	3.58 (1.31)	3.63 (1.36)
Statins used High-intensity statins (atorvastatin 40–80 mg daily or rosuvastatin 20 mg daily) Sample size	n = 277 ; % = 68.1	n = 142 ; % = 68.3

Characteristic	Alirocumab (N = 407)	Ezetimibe (N = 208)
Simvastatin 20 or 40mg Sample size	n = 10 ; % = 2.5	n = 8 ; % = 3.8
Other lipid-lowering medication used Sample size	n = 1 ; % = 0.2	n = 3 ; % = 1.4

Outcomes

Study timepoints

- 24 week (For Treatment related adverse effects, period was defined as the time from the first double-blind dose of study treatment to the last dose of double-blind treatment injection 1 70 days (10 weeks).)

Change from baseline to week 24 in lipid parameters

Outcome	Alirocumab, 24 week, N = 403	Ezetimibe, 24 week, N = 208
Change in calculated LDL-C from baseline (%) LS mean (SE) Mean (SE)	-56 (1.5)	-20.3 (2)
Change in non-HDL-C from baseline (%) LS mean (SE) Mean (SE)	-47 (1.2)	-19.4 (1.7)

Change in calculated LDL-C from baseline - Polarity - Higher values are better (greater reduction is better)

Change in non-HDL-C from baseline - Polarity - Higher values are better (greater reduction is better)

ITT population: including all randomized patients with an LDL-C measurement available at baseline and at least one of the post randomisation time points between weeks 4 and 24, regardless of treatment adherence.

Difference in lipid parameters (Alirocumab vs Ezetimibe) at week 24

Outcome	Alirocumab vs Ezetimibe, 24 week, N2 = 208, N1 = 403
Difference in calculated LDL-C change from baseline (%) Difference (95% CI); SE=2.5 Mean (95% CI)	-35.6 (-40.6 to -30.7)
Difference in non-HDL-C change from baseline (%) Difference in LS mean (95% CI); SE=2.1 Mean (95% CI)	-27.7 (-31.8 to -23.6)

Difference in calculated LDL-C change from baseline - Polarity - Higher values are better (greater reduction is better)

Difference in non-HDL-C change from baseline - Polarity - Higher values are better (greater reduction is better)

Treatment-emergent adverse events

Outcome	Alirocumab, 24 week, N = 406	Ezetimibe, 24 week, N = 206
Positively adjudicated CVD events (n (%)) number of participants No of events	n = 13 ; % = 3.2	n = 10 ; % = 4.9
Local injection site reactions (n (%)) number of participants	n = 11 ; % = 2.7	n = 2 ; % = 1

Outcome	Alirocumab, 24 week, N = 406	Ezetimibe, 24 week, N = 206
No of events		
New onset diabetes in people without diabetes (n (%)) number of participants No of events	n = 4 ; % = 1.4	n = 5 ; % = 3.2
Type 2 diabetes mellitus No of events	n = 5 ; % = 1.8	n = 2 ; % = 1.3

Positively adjudicated CVD events - Polarity - Lower values are better

Local injection site reactions - Polarity - Lower values are better

New onset diabetes in people without diabetes - Polarity - Lower values are better

Analysis used safety population: included randomized patients who received at least 1 dose or part of a dose of study drug during the treatment period; Time-point from the first double-blind dose of study treatment to the last dose of double-blind treatment injection 1 70 days (10 weeks).

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Absolute change in calculated LDL-C

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Absolute change non-HDL-C

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Difference in calculated LDL-C absolute change from baseline

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Difference in calculated non-HDL-C absolute change from baseline

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Positively adjudicated CVD events

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Local injection site reactions

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

New-onset diabetes in people without diabetes

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

New-onset type 2 diabetes in people without diabetes

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Hao, 2022

Bibliographic Reference	Hao, Yan; Yang, Yu-Lin; Wang, Yong-Chao; Li, Jian; Effect of the Early Application of Evolocumab on Blood Lipid Profile and Cardiovascular Prognosis in Patients with Extremely High-Risk Acute Coronary Syndrome.; International heart journal; 2022; vol. 63 (no. 4); 669-677

Study details

Study type	Randomised controlled trial (RCT)
Study location	China
Study setting	Primary care
Study dates	Patients were screened from May 2019 to October 2021. 3-month follow-up
Sources of funding	Shandong Provincial Natural Science Foundation (ZR2017MH056)
Inclusion criteria	Patients with extremely high-risk coronary heart disease diagnosed with acute coronary syndrome (ACS) and receiving percutaneous coronary intervention (PCI) treatment and LDL-C ≥ 3.0 mmol/l after statin therapy. Extremely high risk patients were defined as follows: 1) myocardial infarction recurrence + previous vascular events in the past 2 years; 2) ACS + multivessel disease; 3) ACS + multivascular disease and 4) ACS + diabetes + one additional risk factor, CRP ≥3 g/L and/or chronic kidney disease eGFR <60 ml/minute/1.73 m2 and or lipoprotein a ≥50 mg/dl. ACS was defined as unstable angina, non-ST-segment elevation myocardial infarction and ST-segment elevation myocardial infarction.
Exclusion criteria	Patients (1) with a history of coronary artery bypass grafting; (2) who are intolerant to statins, ezetimibe, or PCSK9 inhibitors; (3) who have used PCSK9 inhibitors in the past 12 months; or (4) with severe liver and kidney dysfunction. Severe hepatic dysfunction was defined as an increase in bilirubin that exceeded 10 times the normal value, prothrombin activity < 40%, or the presence of hepatic encephalopathy. Severe renal insufficiency is defined as a glomerular filtration rate of < 30%.
Recruitment / selection of participants	Recruitment method not specified
Population subgroups	Not applicable
Intervention(s)	Evolocumab (140 mg, every 2 weeks), injected subcutaneously within 48 hours after PCI

Comparator	Control: Atorvastatin 40mg/day + Ezetimibe 10mg/d
Background treatment	All patients received standard PCI treatment and were implanted with drug-eluting stents. For patients with multivessel disease, investigators adopted staged interventional procedures, prioritizing the treatment of criminal vessels and allowing interventional treatment of noncriminal vessels to be completed during hospitalization. Both control and evolocumab groups received atorvastatin 40 mg/day and ezetimibe 10 mg/day to lower lipids after PCI. The rest of the treatment drugs were used in accordance with the current guidelines. Blood samples were collected during the baseline examination to assess fasting blood lipids. After that, patient follow-ups and blood tests were performed at the first and third months. During the follow-up, treatment was adjusted according to lipid control.
Number of participants	136
Duration of follow-up	3 months
Additional comments	The incidence of MACEs in the evolocumab group is approximately 10%.7) In patients with an extremely high risk of coronary heart disease, even if ezetimibe combined with statins lowers lipids, the incidence of long-term adverse cardiovascular prognosis is still as high as 40%.8) The estimated incidence of MACEs in the control group is approximately 25%, and a total sample size of 136 patients will provide 90% statistical power at the 5% significance level. Continuous variables are expressed as the mean ± standard deviation or median (Q1, Q3), and categorical variables are expressed as frequencies and proportions. Independent sample t tests were used for continuous variables, and the chi-square test or Fisher's exact test was used to compare categorical data. Kaplan-Meier analysis was used to evaluate the differences in MACEs between the evolocumab and control groups. All analyses used two-sided tests, and $P < 0.05$ was considered significantly different between the two groups. SPSS software 25.0 was used for all analyses. Blood samples were obtained from the cubital vein after at least 12 hours of fasting in the present study. LDL-C, was measured in an enzymatic assay. MACE outcomes were reported within 3 months of treatment so did not meet review protocol and adverse reactions reported also did not meet review protocol and hence were not extracted in the present data extraction table.

Study arms

Evolocumab (N = 68)

Evolocumab (140 mg, every 2 weeks), injected subcutaneously within 48 hours after PCI

Control (N = 68)

atorvastatin 40 mg/day and ezetimibe 10 mg/day

Characteristics

Arm-level characteristics

Characteristic	Evolocumab (N = 68)	Control (N = 68)
% Female Sample size	n = 23 ; % = 33.8	n = 20 ; % = 29.4
Mean age (SD) Mean (SD)	62.21 (12.31)	62.22 (11.44)
Index ACS event: STEMI Sample size	n = 27 ; % = 39.71	n = 28 ; % = 41.18
Index ACS event: NSTEMI Sample size	n = 34 ; % = 50	n = 31 ; % = 45.59

Characteristic	Evolocumab (N = 68)	Control (N = 68)
Index ACS event: Unstable angina Sample size	n = 7 ; % = 10.29	n = 9 ; % = 13.24
LDL cholesterol (mmol/l) Mean (SD)	3.54 (0.58)	3.52 (0.41)
Aspirin Sample size	n = 63 ; % = 92.65	n = 66 ; % = 97.06
P2Y12 inhibitor Sample size	n = 67 ; % = 98.53	n = 68 ; % = 100
ACEI/ARB Sample size	n = 57 ; % = 83.82	n = 62 ; % = 91.18
Beta-blockers Sample size	n = 52 ; % = 76.47	n = 49 ; % = 72.06
Diabetes mellitus Sample size	n = 27 ; % = 39.71	n = 23 ; % = 33.8
Hypertension Sample size	n = 48 ; % = 70.59	n = 41 ; % = 60.29
History of stroke Sample size	n = 4 ; % = 5.88	n = 3 ; % = 4.41

Outcomes

Study timepoints

- 3 month

LDL-C

Outcome	Evolocumab, 3 month, N = 68	Control, 3 month, N = 61
LDL-C at 3 months (mmol/l) Blood samples were obtained from the cubital vein after at least 12 hours of fasting; LDL-C was measured in an enzymatic assay Mean (SD)	0.58 (0.26)	1.27 (0.54)

LDL-C at 3 months - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

LDL-C-at 3 months

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(due to recruitment and randomisation method not specified (leading to potential selection bias), treatment being adjusted according to lipid control during follow-up and this in combination with lack of blinding could have introduced bias)*

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

Hiro, 2014

Bibliographic Reference	Hiro, Takafumi; Hirayama, Atsushi; Ueda, Yasunori; Komatsu, Sei; Matsuoka, Hiroshi; Takayama, Tadateru; Ishihara, Masaharu; Hayashi, Takatoshi; Saito, Satoshi; Kodama, Kazuhisa; ZIPANGU, investigators; Rationale and design of a randomized clinical study to investigate the effect of ezetimibe, a cholesterol absorption inhibitor, on the regression of intracoronary plaque evaluated by non-obstructive angioscopy and ultrasound: The ZIPANGU study.; Journal of cardiology; 2014; vol. 64 (no. 6); 501-7

Study details

Secondary publication of another included study- see primary study for details	Study rationale and design for ZIPANGU trial. Full trial details reported in main study entry (Ueda 2017).

Hougaard, 2017

Bibliographic Reference	Hougaard, Mikkel; Hansen, Henrik Steen; Thayssen, Per; Antonsen, Lisbeth; Junker, Anders; Veien, Karsten; Jensen, Lisette Okkels; Influence of ezetimibe in addition to high-dose atorvastatin therapy on plaque composition in patients with ST-segment elevation myocardial infarction assessed by serial: Intravascular ultrasound with iMap: the OCTIVUS trial.; Cardiovascular revascularization medicine : including molecular interventions; 2017; vol. 18 (no. 2); 110-117

Study details

Trial name / registration number	OCTIVUS trial (NCT01385631).
Study type	Randomised controlled trial (RCT)
Study location	Denmark
Study setting	Odense University Hospital, Denmark.
Study dates	June 2011 to June 2013.
Sources of funding	Danish Heart Foundation.
Inclusion criteria	Patients with first time STEMI, no prior treatment with statins or other lipid lowering drugs and a non-significant lesion in one of the two non-culprit coronary arteries (angiographic diameter stenosis >20% and < 50%).
Exclusion criteria	People aged below 18 years or over 81 years, who had a serum creatinine greater than176 µmol/l and women with child-bearing potential and not using chemical or mechanical contraception. People with a history of malignancy (unless 5 years disease free), participation in another RCT or people undergoing treatment with cyclosporine or fibrates.
Recruitment / selection of participants	Patients admitted with STEMI.
Intervention(s)	Atorvastatin 80 mg/day (high intensity) with additional ezetimibe 10 mg/day.
Comparator	Atorvastatin 80 mg/day (high intensity) and placebo.
Background treatment	Prior cardiovascular medications (unclear if continued during trial): Ezetimibe group: B-Blockers: 0 (0%)

	Calcium antagonists: 4 (9.3%) ACE inhibitors: 4 (9.3%) ATII inhibitors: 0 (0%) Diuretics: 1 (2.3%) Current smoking: 25 (58.1%) Hypertension: 7 (16.3%) Placebo group: B-Blockers: 2 (4.5%) Calcium antagonists: 3 (6.8%) ACE inhibitors: 3 (6.8%) ATII inhibitors: 1 (2.3%) Diuretics: 3 (6.8%) Current smoking: 23 (52.3%) Hypertension: 8 (18.2%)
Number of participants	N=87
Duration of follow-up	1 year. Mean follow-up time was 353 ±14 days in the intervention group and 356 ±13 days in the placebo group.

Indirectness	No indirectness.
Additional comments	All patients were maintained in their designated treatment arm (Intention to treat analysis).

Study arms

Ezetimibe (N = 43)

Atorvastatin 80 mg/day (high intensity) and ezetimibe 10 mg/day.

Placebo (N = 44)

Atorvastatin 80 mg/day (high intensity) and placebo.

Characteristics

Arm-level characteristics

Characteristic	Ezetimibe (N = 43)	Placebo (N = 44)
% Female Sample size	n = 4 ; % = 9.3	n = 8 ; % = 18.2
Mean age (SD) Mean (SD)	55.3 (11)	57.2 (9.1)
Ethnicity	NR	NR

Characteristic	Ezetimibe (N = 43)	Placebo (N = 44)
Nominal		
Existing CVD diagnosis	NR	NR
Type 2 diabetes Type not specified Sample size	n = 1 ; % = 2.3	n = 1 ; % = 2.3
Chronic kidney disease Nominal	NR	NR
LDL (mmol/l) Mean (SD)	3.7 (0.7)	4.1 (0.9)
Statins used Nominal	0	0

Outcomes

Study timepoints

- Baseline
- 1 year

Continuous outcomes - lipids at 1 year

Outcome	Ezetimibe, Baseline, N = 43	Ezetimibe, 1 year, N = 39	Placebo, Baseline, N = 44	Placebo, 1 year, N = 41
LDL (mmol/l) (mmol/l) Mean (SD)	3.7 (0.7)	1.4 (0.8)	4.1 (0.9)	2 (0.5)
LDL Cholesterol (% change) (mmol/l) Mean (SD)	NA (NA)	-62 (19.2)	NA (NA)	-52.4 (10.9)
Change in LDL (mmol/l) (mmol/l) Change from baseline Mean (SD)	NA (NA)	-2.3 (0.9)	NA (NA)	-2.2 (0.7)

LDL (mmol/l) - Polarity - Lower values are better

LDL Cholesterol (% change) - Polarity - Higher values are better (greater reduction is better)

Change in LDL (mmol/l) - Polarity - Higher values are better (greater reduction is better)

Dichotomous outcomes - adverse events at 3 months

Outcome	Ezetimibe, Baseline, N = 43	Ezetimibe, 1 year, N = 43	Placebo, Baseline, N = 44	Placebo, 1 year, N = 44
Elevated liver enzymes at 3 months Definition of outcome not provided. Participant switched to a low dose of a different statin due to elevated liver enzymes. No of events	n = NA ; % = NA	n = 1 ; % = 2.3	n = NA ; % = NA	n = 0 ; % = 0

Elevated liver enzymes at 3 months - Polarity - Lower values are better

Participant changed to low dose rosuvastatin due to elevated liver enzymes at 3 months.

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

LDL-C final score

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Bias from randomisation process and different baseline LDL between groups)*
Overall bias and Directness	Overall Directness	Directly applicable

LDL-C (% change)

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Bias from randomisation process and different baseline LDL between groups)*
Overall bias and Directness	Overall Directness	Directly applicable

LDL-C absolute change

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Bias from randomisation process and different baseline LDL between groups)*

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

Dichotomous outcomes- -Elevated liver enzymes at 3 months

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Joshi, 2017

Bibliographic Reference	Joshi, S.; Sharma, R.; Rao, H.K.; Narang, U.; Gupta, N.; Efficacy of combination therapy of rosuvastatin and ezetimibe vs rosuvastatin monotherapy on lipid profile of patients with coronary artery disease; Journal of Clinical and Diagnostic Research; 2017; vol. 11 (no. 12); oc28-oc31

Study details

Study type	Randomised controlled trial (RCT)
Study location	Northern India.
Study setting	Department of Medicine at Government Medical College, Patiala.
Study dates	2007-2008.
Sources of funding	No financial or competing interests reported.
Inclusion criteria	18 years old and with informed written consent.

Exclusion criteria	People with liver disease, renal disease, history of seizures, pregnant or lactating females were excluded.
Recruitment / selection of participants	Consecutive patients of coronary artery disease reporting to a single unit of Medicine Department.
Intervention(s)	Ezetimibe 10 mg/day and rosuvastatin 10 mg/day (high intensity statin).
Comparator	Rosuvastatin 10 mg/day (high intensity statin).
Background treatment	Advised to follow lifestyle modifications, stop smoking, exercise regularly, avoid alcohol and have a low fat diet. Adequate counselling about lifestyle modifications was given to all patients. Regular treatment of coronary artery disease including antiplatelets, beta-blockers, ACE inhibitors, Nitrates was continued. Patients were followed fortnightly and examined for any side effects of drugs.
Number of participants	80.
Duration of follow-up	24 weeks.
Indirectness	No indirectness.
Additional comments	Intention to treat analysis.

Study arms

Ezetimibe and rosuvastatin (N = 40)

Ezetimibe 10 mg/day and rosuvastatin 10 mg/day (high intensity statin).

Rosuvastatin (N = 40)

Rosuvastatin 10 mg/day (high intensity statin).

Characteristics

Arm-level characteristics

Characteristic	Ezetimibe and rosuvastatin (N = 40)	Rosuvastatin (N = 40)
% Female Sample size	n = 18 ; % = 45	n = 15 ; % = 37.5
Mean age (SD) Mean (SD)	60.33 (9.83)	59.78 (11.12)
Ethnicity Nominal	NR	NR
Existing CVD diagnosis Nominal	NR	NR
Diabetes diabetes (type not specified) Sample size	n = 11 ; % = 27.5	n = 9 ; % = 22.5
Chronic kidney disease Nominal	NR	NR
LDL cholesterol	162.68 (23.13)	153.38 (24.78)

Characteristic	Ezetimibe and rosuvastatin (N = 40)	Rosuvastatin (N = 40)
Mean (SD)		
Non-HDL cholesterol Nominal	NR	NR
Statins used Nominal	NR	NR
Other lipid lowering medication used Nominal	NR	NR

Outcomes

Study timepoints

- Baseline
- 24 week

Continuous outcomes - lipids at 24 weeks

Outcome	Ezetimibe and rosuvastatin, Baseline, N = 40	Ezetimibe and rosuvastatin, 24 week, N = 40	Rosuvastatin, Baseline, N = 40	Rosuvastatin, 24 week, N = 40
LDL (mg/dl) Mean (SD)	162.68 (23.13)	70.58 (8.97)	153.38 (24.78)	83.15 (14.03)

Outcome	Ezetimibe and rosuvastatin, Baseline, N = 40	Ezetimibe and rosuvastatin, 24 week, N = 40	Rosuvastatin, Baseline, N = 40	Rosuvastatin, 24 week, N = 40
LDL Cholesterol (% change) (mg/dl) Nominal	NA	-57.39	NA	-45.54

LDL - Polarity - Lower values are better

LDL Cholesterol (% change) - Polarity - Higher values are better (greater reduction is better)

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

LDL-C at 24 weeks

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Unclear allocation concealment)*
Overall bias and Directness	Overall Directness	Directly applicable

% change in LDL-C

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Unclear allocation concealment)*
Overall bias and Directness	Overall Directness	Directly applicable

Kereiakes, 2015

Bibliographic Reference	Kereiakes, Dean J; Robinson, Jennifer G; Cannon, Christopher P; Lorenzato, Christelle; Pordy, Robert; Chaudhari, Umesh; Colhoun, Helen M; Efficacy and safety of the proprotein convertase subtilisin/kexin type 9 inhibitor alirocumab among high cardiovascular risk patients on maximally tolerated statin therapy: The ODYSSEY COMBO I study.; American heart journal; 2015; vol. 169 (no. 6); 906-915e13

Study details

Other publications associated with this study included in review	Colhoun 2014 - Study design and rationale
Trial name / registration number	ODYSSEY COMBO I NCT01644175
Study type	Randomised controlled trial (RCT)
Study location	USA - 76 sites
Study setting	Outpatient care
Study dates	July 2012 and April 2014
Sources of funding	Sanofi and Regeneron
Inclusion criteria	Hypercholesterolemia and established CHD or CHD risk equivalents (PAD, ischaemic stroke or diabetes mellitus and two or more additional risk factors)

	LDL-C poorly controlled despite maximally tolerated daily dose of statin with or without other LLT, both at stable dose for at least 4 weeks prior to screening LDL-C criteria: LDL-C ≥70 mg/dl (≥1.81 mmol/l) if documented CVD LDL-C ≥100 mg/dl (≥2.59 mmol/l) if no documented CVD
Exclusion criteria	Age <18 years Fasting serum triglycerides >400 mg/dl during screening Currently taking a statin other than a registered dose of simvastatin, atorvastatin, or rosuvastatin Use of fibrates, other than fenofibrate, within the 6 weeks before screening
Recruitment / selection of participants	Screening period of up to 2 weeks to check laboratory values and provide training for self-administration of study drugs.
Population subgroups	Statin intensity
Intervention(s)	Alirocumab 75-mg every 2 weeks, self-administered via subcutaneous injection using a prefilled pen. If LDL-C level was ≥70 mg/dl at week 8, alirocumab dose was increased to 150 mg at week 12.
Comparator	Matching placebo injection
Background treatment	All patients were receiving a stable, maximally tolerated statin dose: atorvastatin, 40-80 mg; rosuvastatin, 20-40 mg; simvastatin, 80 mg daily; or

	lower doses in cases of intolerance Other lipid-lowering therapy also permitted: bile acid sequestrant, ezetimibe, niacin or omega-3 ≥1000 mg/day with stable dose ≥4 weeks; or fenofibrate with stable dose ≥6 weeks before enrollment.
Number of participants	316
Duration of follow-up	52 weeks treatment + 8 weeks off treatment
Indirectness	Not serious
Additional comments	ITT

Study arms

Alirocumab (N = 209)

Alirocumab 75mg every 2 weeks starting dose (could be increased to 150 mg) self-administered subcutaneously via 1 mL prefilled pen

Placebo (N = 107)

Characteristics

Arm-level characteristics

Characteristic	Alirocumab (N = 209)	Placebo (N = 107)
% Female	n = 78 ; % = 37.3	n = 30 ; % = 28

Characteristic	Alirocumab (N = 209)	Placebo (N = 107)
Sample size		
Mean age (SD) Mean (SD)	63 (9.5)	63 (8.8)
Ethnicity		
White Sample size	n = 170 ; % = 81.3	n = 88 ; % = 82.2
Black or African American Sample size	n = 34 ; % = 16.3	n = 17 ; % = 15.9
Existing CVD diagnoses Sample size	n = 179 ; % = 85.6	n = 87 ; % = 81.3
CHD history Sample size	n = 164 ; % = 78.5	n = 83 ; % = 77.6
Type 2 diabetes Sample size	n = 94 ; % = 45	n = 42 ; % = 39.3
Chronic kidney disease Nominal	NR	NR
Measured LDL-C (N= 138 alirocumab and 70 placebo) Measurement of LDL-C was not planned in initial protocol so not available for all	94.8 (29.3)	100.2 (34.4)

Characteristic	Alirocumab (N = 209)	Placebo (N = 107)
Mean (SD), mg/dl		
Calculated LDL-C (based all randomised) Friedewald formula Mean (SD)	100.2 (29.5)	106 (35.3)
Non-HDL cholesterol, mg/dl Mean (SD)	130 (34)	133.4 (39.8)
Any statin Sample size	n = 208 ; % = 99.5	n = 107 ; % = 100
High dose statin atorvastatin 40-80mg, rosuvastatin 20-40mg or simvastatin 80mg Sample size	n = 129 ; % = 61.7	n = 69 ; % = 64.5
Any other LLT Sample size	n = 80 ; % = 38	n = 53 ; % = 49.5
Ezetimibe Sample size	n = 15 ; % = 7.2	n = 11 ; % = 10.3

Outcomes

Study timepoints

- Baseline

- 24 week
- 52 week

Continuous

Outcome	Alirocumab, Baseline, N = 205	Alirocumab, 24 week, N = 189	Alirocumab, 52 week, N = 167	Placebo, Baseline, N = 106	Placebo, 24 week, N = 97	Placebo, 52 week, N = 79
% change LDL-C Mean (SD)	100.3 (29.7)	-	-	104.6 (32.3)	-	-
% change LDL-C Primary analysis - least squares estimated mean; ITT Mean (95% CI)	-	-48.2 (-52 to -44.4)	-	-	-2.3 (-7.6 to 3.1)	-
% change LDL-C Raw data - ITT Mean (SD)	-	-47.9 (29.1)	-42.4 (35.2)	-	-2.5 (24.9)	-1.4 (27.7)
Absolute change LDL-C (mg/dl) Raw data - ITT Mean (SD)	100.3 (29.7)	-49.3 (33.4)	-43.8 (37.3)	104.6 (32.3)	-5.3 (30.2)	-1.4 (25.8)

Outcome	Alirocumab, Baseline, N = 205	Alirocumab, 24 week, N = 189	Alirocumab, 52 week, N = 167	Placebo, Baseline, N = 106	Placebo, 24 week, N = 97	Placebo, 52 week, N = 79
Absolute change LDL-C (mg/dl) Primary analysis - least sqaures estimated mean; ITT Mean (95% CI)	-	-39.1 (-42.6 to -35.6)	-	-	-1.6 (-6.6 to 3.3)	-
Absolute change LDL-C (mg/dl) Raw data - ITT Mean (SD)	-	-39 (25.8)	-32.5 (32.8)	-	-1.6 (25.1)	-3.4 (25)
non-HDL-C final value (mg/dl) Raw data - ITT Mean (SD)	130.1 (34.3)	77.3 (34)	85.4 (42.8)	131.7 (36.3)	128 (41.7)	128.8 (29.6)
High-intensity statin; n = 121 vs 62 atorvastatin 40-80 mg or rosuvastatin 20-40 mg Mean (95% CI)	-	-46.8 (-51.7 to 41.9)	-	-	-0.2 (-7.3 to 6.9)	-
No high-intensity statin = 84 vs 44	-	-50.2 (-56.3 to -44)	-	-	-5.2 (-13.7 to 2.3)	-

Outcome	Alirocumab, Baseline, N = 205	Alirocumab, 24 week, N = 189	Alirocumab, 52 week, N = 167	Placebo, Baseline, N = 106	Placebo, 24 week, N = 97	Placebo, 52 week, N = 79
Mean (95% CI)						

% change LDL-C - Polarity - Higher values are better (greater reduction is better)

Absolute change LDL-C - Polarity - Lower values are better

% change non-HDL-C - Polarity - Higher values are better (greater reduction is better)

non-HDL-C final value - Polarity - Lower values are better

% change LDL-C: statin intensity sensitivity analysis - Polarity - Higher values are better (greater reduction is better)

Dichotomous

Outcome	Alirocumab, Baseline, N =	Alirocumab, 24 week, N =	Alirocumab, 52 week, N = 205	Placebo, Baseline, N =	Placebo, 24 week, N =	Placebo, 52 week, N = 106
Major adverse CVD events **CHD death, non-fatal MI or fatal/non-fatal stroke** No of events	-	-	n = 4 ; % = 2	-	-	n = 2 ; % = 1.9
Injection-site reaction No of events	-	-	n = 11 ; % = 5.3	-	-	n = 3 ; % = 2.8
Nausea	-	-	n = 8 ; % = 3.9	-	-	n = 0 ; % = 0

Outcome	Alirocumab, Baseline, N =	Alirocumab, 24 week, N =	Alirocumab, 52 week, N = 205	Placebo, Baseline, N =	Placebo, 24 week, N =	Placebo, 52 week, N = 106
No of events						
Influenza No of events	-	-	n = 6 ; % = 2.9	-	-	n = 0 ; % = 0

Major adverse CVD events - Polarity - Lower values are better

Injection-site reaction - Polarity - Lower values are better

Nausea - Polarity - Lower values are better

Influenza - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

% change LDL-C 52 weeks

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

% change LDL-C 24 weeks

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Absolute change LDL-C 24 weeks

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Absolute change LDL-C 52 weeks

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

% change non-HDL-C 24 weeks

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

non-HDL-C final value at 24 weeks

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

non-HDL-C final value at 52 weeks

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Statin sensitivity analysis - % change LDL-C

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

MACE 52 weeks

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Injection site reaction

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Nausea

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Influenza

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Koh, 2018

Bibliographic Reference	Koh, Kwang Kon; Nam, Chang Wook; Chao, Ting-Hsing; Liu, Ming-En; Wu, Chiung-Jen; Kim, Dong-Soo; Kim, Chong-Jin; Li, Ivy; Li, Jianyong; Baccara-Dinet, Marie T.; Hsiao, Pi-Jung; Chiang, Chern-En; A randomized trial evaluating the efficacy and

safety of alirocumab in South Korea and Taiwan (ODYSSEY KT); Journal of Clinical Lipidology; 2018; vol. 12 (no. 1); 162-172e6

Study details

Trial name / registration number	ODYSSEY-KT/ NCT02289963
Study type	Randomised controlled trial (RCT)
Study location	Multicentre study conducted in 27 active centres (which screened at least 1 patient) from 16 study centres in South Korea and 11 in Taiwan.
Study setting	Primary/secondary care
Study dates	The study comprised an up to 3-week screening period, followed by 24 weeks of double-blind treatment and 8 weeks of follow-up
Sources of funding	Sanofi and Regeneron Pharmaceuticals, Inc.
Inclusion criteria	Patients (aged ≥18 years) with high CV risk who had inadequately controlled hypercholesterolemia on maximally tolerated statin therapy at a stable dose for at least 4 weeks before screening. High CV risk was defined as history of CV disease (CVD), moderate chronic kidney disease, or diabetes with multiple risk factors. Inadequately controlled hypercholesterolemia was defined as LDL-C ≥70 mg/dl in patients with a history of documented CVD, or LDL-C ≥100 mg/dl in patients without such history. Maximally tolerated statin therapy was defined as atorvastatin 40 to 80 mg daily, rosuvastatin 20 mg daily, or simvastatin 40 mg daily. Patients were also eligible if they were receiving a daily dose of atorvastatin, rosuvastatin, or simvastatin considered appropriate by the investigator. Background treatment with LLTs other than statins was allowed for all patients, provided that they had been on a stable dose for at least 4 weeks before the screening visit.

Exclusion criteria	Patients without established CHD or CHD risk equivalents 2 LDL-C ,<70 mg/dl at the screening visit (week –3) in patients with a history of documented CVD 3 LDL-C , <100 mg/dl at the screening visit (week –3) in patients without history of documented CVD 4 Not on a stable dose of LTT (including statin) for ≥4 wk before the screening visit (week –3) or between screening and randomization visit; Receiving statins other than atorvastatin, rosuvastatin, or simvastatin; fibrates other than fenofibrate; or red yeast rice products. Patients were required to be on a stable diet (the National Cholesterol Education Program Adult Treatment Panel III Therapeutic Lifestyle Changes diet or equivalent) from screening visit to the end of study; atorvastatin, rosuvastatin, or simvastatin is not taken daily or not taken at a registered dose. Use of fibrates, other than fenofibrate in the past 4 wk before screening visit (week –3) or between screening and randomization visits 9 Use of nutraceutical products or over-the-counter therapies that may affect lipids which have not been at a stable dose/ amount for >4 wk before the screening visit (week –3) or between screening and randomization visits 10 Use of red yeast rice products within 4 wk of the screening visit (week –3) or between screening and randomization visits 11 Patient who has received plasmapheresis treatment within 2 mo before the screening visit (week –3) or has plans to receive this during the study; History of an MI, unstable angina leading to hospitalization, CABG, PCI, uncontrolled cardiac arrhythmia, carotid surgery or stenting, stroke, transient ischemic attack, carotid revascularization, endovascular procedure, or surgical intervention for peripheral vascular disease within 3 mo before the screening visit (week –3, visit 1) 13 Planned to undergo scheduled PCI or CABG, or carotid or peripheral revascularization, during the study 14 Systolic blood pressure .160 mm Hg or diastolic blood pressure .100 mm Hg at screening visit or randomization visit 15 History of New York Heart Association Class III or IV heart failure within the past 12 mo 16 Known history of haemorrhagic stroke 17 Age ,18 y or legal age of majority at the screening visit (week –3), whichever is greater 18 Patients not previously instructed on a cholesterol-lowering diet before the screening visit (week –3) 19 Newly diagnosed (within 3 mo before randomization visit [week 0]) or poorly controlled (HbA1c .9% at the screening visit [week –3]) diabetes 20 Presence of any clinically significant uncontrolled endocrine disease known to influence serum lipids or lipoproteins 21 History of bariatric surgery within 12 mo before the screening visit (week –3) 22 Unstable weight defined by a variation .5 kg within 2 mo before the screening visit (week –3) 23 Known history of homozygous or heterozygous familial hypercholesterolemia 24 Known history of loss of function of PCSK9 (ie, genetic mutation or sequence variation) 25 Use of systemic corticosteroids, unless used as replacement therapy for pituitary/adrenal disease with a stable regimen for at least 6 wk before randomization (week 0) 26 Use of continuous oestrogen or testosterone hormone replacement therapy unless the regimen has been stable in the past 6 wk before the screening visit (week –3) and no plans to change the regimen during the study 27 History of cancer within the past 5 y, except for adequately treated basal cell skin cancer, squamous cell skin cancer, or in situ cervical cancer 28 Known history of a positive HIV test 29 Patient who has taken any investigational drugs other than the alirocumab training placebo kits within 1 mo or 5 half-lives, whichever is longer 30 Patient who has been previously treated with at least 1 dose of alirocumab or any other anti-PCSK9 monoclonal antibody in other clinical trials 31 Patient

	who withdraws consent during the screening period (patient who is not willing to continue or fails to return) 32 Conditions/situations such as: Any clinically significant abnormality identified at the time of screening that in the judgment of the investigator or any subinvestigator would preclude safe completion of the study or constrain endpoints assessment such as major systemic diseases or patients with a short life expectancy. Considered by the investigator or any subinvestigator as inappropriate for this study for any reason, e.g. Deemed unable to meet specific protocol requirements, such as scheduled visits Deemed unable to administer or tolerate long-term injections as per the patient or the investigator; Investigator or any subinvestigator, pharmacist, study coordinator, other study staff, or relative thereof directly involved in the conduct of the protocol, etc. Presence of any other conditions (eg, geographic, social), actual or anticipated, that the investigator feels would restrict or limit the patient's participation for the duration of the study (continued on next page) Koh et al Alirocumab and ODY
Recruitment / selection of participants	Meeting inclusion criteria; Randomization was stratified according to history of myocardial infarction or ischemic stroke, statin treatment (atorvastatin 40–80 mg or rosuvastatin 20 mg vs atorvastatin ,40 mg, rosuvastatin ,20 mg, or simvastatin any dose), and country
Population subgroups	None examined; Strata: high-intensity statin/mixed: approximately 20% medium intensity statin in each group
Intervention(s)	alirocumab 75 mg every 2 weeks, administered subcutaneously via auto-injector. The patient or designated carer was trained to self-inject/inject using placebo; Alirocumab-treated patients not achieving LDL-C levels of ,70 mg/dl at week 8 had their dosing regimen changed to 150 mg every 2 weeks from week 12 in a blinded fashion.
Comparator	Plaecbo, administered subcutaneously via auto-injector. The patient or designated carer was trained to self-inject/inject using placebo.
Background treatment	Maximally tolerated statins: atorvastatin 40 to 80 mg daily, rosuvastatin 20 mg daily, or simvastatin 40 mg daily. Patients were also eligible if they were receiving a daily dose of atorvastatin, rosuvastatin, or simvastatin considered appropriate by the investigator. Background treatment with LLTs other than statins was allowed for all patients, provided that they had been on a stable dose for at least 4 weeks before the screening visit.
Number of participants	199
Duration of follow-up	24 weeks

Indirectness	none
Additional comments	Percent change in calculated LDL-C from baseline to week 24 analysed with an intent-to-treat (ITT) approach. The percent change in calculated LDL-C from baseline to week 24 was also assessed using an on-treatment approach. The ITT population included all randomized patients with an LDL-C measurement available at baseline and at least 1 of the post-randomization time points between weeks 4 and 24, regardless of treatment adherence. Safety population included randomized patients who received at least 1 dose or part of a dose of study drug during the treatment period. The safety analysis included all randomized and treated patients. Safety data were analysed by descriptive statistics. All statistical analyses were conducted using SAS (SAS Institute Inc, Cary, NC). Analyses of lipid samples were performed by a central laboratory using standard procedures. LDL-C levels were calculated using the Friedewald formula. LDL-C levels were reflexively measured via beta-quantification when TG levels were >400 mg/dl. In addition, LDL-C levels were systematically measured (via the beta-quantification method) at weeks 0 and 24 for efficacy analysis purposes. Safety was assessed by monitoring treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), laboratory parameters, and vital signs. TEAEs were defined as adverse events that occurred, worsened, or became serious during the period from first to last injection of study drug plus 70 days. Adverse events of special interest included overdose with study drug, local injection-site reactions, allergy events, ophthalmologic events, neurologic events, neurocognitive events, pregnancy of female patient, increase in alanine aminotransferase (≥3 x upper limit of normal), and haemolytic anaemia.

Study arms

Alirocumab + Statin (N = 97)

Alirocumab 75mg every 2 weeks, increased to 150mg every 2 weeks at week 12 if LDL-C >70mg/dl at week 8

Placebo + statin (N = 102)

Characteristics

Arm-level characteristics

Characteristic	Alirocumab + Statin (N = 97)	Placebo + statin (N = 102)
% Female Sample size	n = 14 ; % = 14.4	n = 21 ; % = 20.6
Mean age (SD) Mean (SD)	61.2 (10.4)	60.1 (9.1)
Existing CVD diagnoses Coronary heart disease (CHD) Sample size	n = 96 ; % = 99	n = 95 ; % = 93.1
LDL cholesterol (mg/dl) Calculated Mean (SD)	97 (27.8)	99.3 (25.2)
Non-HDL cholesterol (mg/dl) Mean (SD)	123.9 (29)	128.4 (30.3)
Statins used Sample size	n = 97 ; % = 100	n = 102 ; % = 100
High-intensity statin use atorvastatin 40 to 80 mg daily or rosuvastatin 20 mg daily Sample size	n = 71 ; % = 73.2	n = 73 ; % = 71.6
Simvastatin 40 mg	n = 17 ; % = 17.5	n = 22 ; % = 21.6

Characteristic	Alirocumab + Statin (N = 97)	Placebo + statin (N = 102)
Sample size		
Other lipid-lowering medication used Sample size	n = 22 ; % = 22.7	n = 24 ; % = 23.5
Ezetimibe use Sample size	n = 14 ; % = 14.4	n = 12 ; % = 11.8
Nutraceuticals Sample size	n = 0 ; % = 0	n = 0 ; % = 0
Diabetes Sample size	n = 32 ; % = 33	n = 38 ; % = 37.3

Outcomes

Study timepoints

- 24 week (For adverse events, analysis concerns period from the first to last injection plus 70 days)

Continuous

Outcome	Alirocumab + Statin, 24 week, N = 97	Placebo + statin, 24 week, N = 102
Absolute change in calculated LDL-C from baseline (mg/dl) LS mean (SE)	-55.5 (3.1)	4.7 (3)

Outcome	Alirocumab + Statin, 24 week, N = 97	Placebo + statin, 24 week, N = 102
Mean (SE)		
% Change in calculated LDL-C from baseline (%) LS mean (SE) Mean (SE)	-57.1 (3)	6.3 (2.9)
% change in non-HDL-C from baseline (%) Mean (SD)	-47.2 (24.62)	4.3 (24.24)

Absolute change in calculated LDL-C from baseline - Polarity - Lower values are better

% Change in calculated LDL-C from baseline - Polarity - Higher values are better (greater reduction in better)

% change in non-HDL-C from baseline - Polarity - Higher values are better (greater reduction is better)

ITT analysis

Calculated LDL-C (difference vs placebo)

Outcome	Alirocumab + Statin vs Placebo + statin, 24 week, N2 = 102, N1 = 97
Absolute change in calculate LDL-C from baseline (mg/dl) LS mean (SE=4.3) Mean (95% CI)	-60.1 (-68.6 to -51.65)
Change in calculated LDL-C from baseline (%) LS mean (SD=4.2) Mean (95% CI)	-63.4 (-71.6 to -55.2)

Absolute change in calculate LDL-C from baseline - Polarity - Higher values are better (greater reduction is better)

Change in calculated LDL-C from baseline - Polarity - Higher values are better (greater reduction is better)

Treatment-related-adverse events

Outcome	Alirocumab + Statin, 24 week, N = 97	Placebo + statin, 24 week, N = 102
Injection site reactions (n (%)) number of people No of events	n = 2 ; % = 2.1	n = 3 ; % = 2.9
New-onset diabetes at 52 weeks (n (%)) number of people No of events	n = 9 ; % = 9.27	n = 5 ; % = 4.9

Injection site reactions - Polarity - Lower values are better

New-onset diabetes at 52 weeks - Polarity - Lower values are better

Safety population used for this analysis included randomized patients who received at least 1 dose or part of a dose of study drug during the treatment period.

Positively adjudicated CVD events

Outcome	Alirocumab + Statin, 24 week, N = 97	Placebo + statin, 24 week, N = 102
Positively adjudicated CVD events (n (%)) **number of people** No of events	n = 3 ; % = 3.1	n = 5 ; % = 4.9

Positively adjudicated CVD events - Polarity - Lower values are better

Safety population used for this analysis included randomized patients who received at least 1 dose or part of a dose of study drug during the treatment period.

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Absolute change LDL-C

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

% change LDL-C

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

% change non-HDL-C

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Absolute change LDL-C (difference vs placebo)

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

% change LDL-C (difference vs placebo)

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Injection-site reactions

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

New-onset diabetes

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Positively adjudicated CVD events

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Kohli, 2012

Bibliographic Reference	Kohli, Payal; Desai, Nihar R; Giugliano, Robert P; Kim, Jae B; Somaratne, Ransi; Huang, Fannie; Knusel, Beat; McDonald, Shannon; Abrahamsen, Timothy; Wasserman, Scott M; Scott, Robert; Sabatine, Marc S; Design and rationale of the LAPLACE-TIMI 57 trial: a phase II, double-blind, placebo-controlled study of the efficacy and tolerability of a monoclonal antibody inhibitor of PCSK9 in subjects with hypercholesterolemia on background statin therapy.; Clinical cardiology; 2012; vol. 35 (no. 7); 385-91

Study details

Secondary publication of another included study- see primary study for details	Design and rationale of the LAPLACE-TIMI 57 trial. Full details available in the main study entry (Giugliano, 2012)

Kouvelos, 2013

Bibliographic Reference	Kouvelos, George N; Arnaoutoglou, Eleni M; Matsagkas, Miltiadis I; Kostara, Christina; Gartzonika, Constantina; Bairaktari, Eleni T; Milionis, Haralampos J; 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; vol. 18 (no. 1); 5-12

Study details

Study type	Randomised controlled trial (RCT)
Study location	Greece
Study setting	School of Medicine, University of Ioannina, Ioannina, Greece
Study dates	Recruitment: January 2007 to June 2009 and 12 month follow-up
Sources of funding	The author(s) received no financial support for the research, authorship, and/or publication of this article.
Inclusion criteria	Patients who underwent elective vascular surgery from January 2007 to June 2009
Exclusion criteria	Patients were excluded if they had: any contraindication to the use of statins; emergency surgery; a reoperation within 30 days after a previous procedure; liver disease; a history of a cardiovascular event within the previous 6 months prior to randomization (myocardial infarction [MI] or stroke).
Recruitment / selection of participants	All undergoing elective vascular surgery at the hospital between January 2007 to June 2009
Population subgroups	None examined; study falls under high-intensity statin strata
Intervention(s)	Combination of rosuvastatin 10 mg/d plus ezetimibe 10 mg/d (RSV/EZT), starting 2 weeks prior to the vascular surgery procedure. All regimens were prescribed by the institution and were continued by the patients during the follow-up period. Because of the commercial unavailability of a single drug combining the 2 substances (RSV and EZT), the patients of the RSV/EZT group were given 2 different regimens.
Comparator	Rosuvastatin (RSV) 10 mg/d starting 2 weeks prior to the vascular surgery procedure

Background treatment	In patients already on statin, there was an 8-week washout period between different drug treatments. Initiation of lipid therapy before surgery was decided to enhance compliance afterward. All patients were under antiplatelet therapy for at least 3 weeks prior to the procedure. Preoperative medications were continued immediately after surgery. Patients who were enrolled and were already receiving b-blocker therapy continued their medication. For patients not already on a b-blocker, bisoprolol (2.5 mg once daily) was initiated at the screening visit. Anaesthetic management and surgical technique were at the discretion of the same surgical and anaesthesiologic team, who were unaware of patient group assignment.
Number of participants	262
Duration of follow-up	12 months (after surgery)
Additional comments	The analysis of serum lipid parameters was carried out on an Olympus AU2700 analyser (Olympus Diagnostica, Hamburg, Germany). The LDL-C was calculated by the Friedewald formula and non-HDL-C was calculated as total HDL-C. Comparisons of continuous variables were performed by Student t test for normally distributed variables and Mann-Whitney U test for non-normally distributed variables, while chi-square test was used for categorical variables. Differences between the groups in the rate of occurrence of primary end points were evaluated with the Fisher exact test. Event rates were further examined with the Kaplan-Meier method, while Kaplan-Meier survival curves were compared using the log-rank test. Univariate and multivariate Cox proportional hazard regression analyses were used to evaluate the effect of each therapy.

Study arms

Ezetimibe 10mg/d + Rosuvastatin 10mg/d (N = 126)

starting 2 weeks prior to the vascular surgery procedure

Rosuvastatin 10 mg/d (N = 136)

Characteristics

Arm-level characteristics

Characteristic	Ezetimibe 10mg/d + Rosuvastatin 10mg/d (N = 126)	Rosuvastatin 10 mg/d (N = 136)
% Female Sample size	n = 13 ; % = 10.3	n = 14 ; % = 10.3
Mean age (SD) Median (IQR)	70 (41 to 89)	72 (46 to 88)
Existing CVD diagnoses (n (%)) Coronary artery disease (CAD) Sample size	n = 62 ; % = 49.2	n = 67 ; % = 49.3
Cardiac failure Sample size	n = 20 ; % = 15.9	n = 29 ; % = 21.3
Chronic kidney disease Stage 1 at baseline Sample size	n = 9 ; % = 7.14	n = 15 ; % = 11
Stage 2 Sample size	n = 75 ; % = 59.5	n = 84 ; % = 62
Stage 3 Sample size	n = 41 ; % = 32.5	n = 33 ; % = 24

Characteristic	Ezetimibe 10mg/d + Rosuvastatin 10mg/d (N = 126)	Rosuvastatin 10 mg/d (N = 136)
Stage 4 Sample size	n = 0 ; % = 0	n = 1 ; % = 0.7
LDL cholesterol (mg/dl) Mean (SD)	148.2 (58.1)	143 (54.1)
Beta-blocker Sample size	n = 126 ; % = 100	n = 136 ; % = 100
Anti-platelet Sample size	n = 81 ; % = 24.3	n = 91 ; % = 66.9
Anticoagulant Sample size	n = 23 ; % = 18.3	n = 27 ; % = 19.9
Calcium antagonist Sample size	n = 20 ; % = 23.8	n = 31 ; % = 22.8
ACE inhibitor Sample size	n = 42 ; % = 33.3	n = 44 ; % = 32.3
Angiotensin II receptor antagonist Sample size	n = 20 ; % = 15.8	n = 19 ; % = 13.9
Nitrate Sample size	n = 7 ; % = 5.6	n = 8 ; % = 5.9

Characteristic	Ezetimibe 10mg/d + Rosuvastatin 10mg/d (N = 126)	Rosuvastatin 10 mg/d (N = 136)
Diuretic Sample size	n = 31 ; % = 24.6	n = 34 ; % = 25
Existing CVD		
Aneurysm disease Sample size	n = 72 ; % = 57.1	n = 70 ; % = 51.5
Carotid disease Sample size	n = 37 ; % = 29.4	n = 32 ; % = 23.5
Peripheral disease Sample size	n = 17 ; % = 13.5	n = 34 ; % = 25
Open surgery (n (%)) Sample size	n = 38 ; % = 30.2	n = 40 ; % = 20.4
Endovascular surgery (n (%)) Sample size	n = 88 ; % = 69.8	n = 96 ; % = 70.6
Diabetes (n (%)) Sample size	n = 40 ; % = 31.7	n = 39 ; % = 28.7

Outcomes

Study timepoints

- 1 year

LDL-C

Outcome	Ezetimibe 10mg/d + Rosuvastatin 10mg/d, 1 year, N = 126	Rosuvastatin 10 mg/d, 1 year, N = 136
Calculated LDL-C (mg/dl) at 1 year after surgery Mean (SD)	75.9 (31.6)	87.2 (31.7)

Calculated LDL-C - Polarity - Lower values are better

Cardiovascular events

Outcome	Ezetimibe 10mg/d + Rosuvastatin 10mg/d, 1 year, N = 126	Rosuvastatin 10 mg/d, 1 year, N = 136
Composite of death from cardiac causes, nonfatal acute MI, ischemic stroke, and unstable angina (n (%)- number of people) From month 1 to 12 of the follow-up No of events	n = 9 ; % = 7.1	n = 18 ; % = 13.2
Cardiac death number of people No of events	n = 0 ; % = 0	n = 5 ; % = 3.7
non-fatal MI No of events	n = 0 ; % = 0	n = 1 ; % = 0.7

Outcome	Ezetimibe 10mg/d + Rosuvastatin 10mg/d, 1 year, N = 126	Rosuvastatin 10 mg/d, 1 year, N = 136
Ischemic Stroke No of events	n = 1 ; % = 0.79	n = 1 ; % = 0.7
Unstable angina No of events	n = 1 ; % = 0.79	n = 2 ; % = 1.47

Composite of death from cardiac causes, nonfatal acute MI, ischemic stroke, and unstable angina - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

LDL-C

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Composite of death from cardiac causes, nonfatal acute MI, ischemic stroke, and unstable angina

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Leiter, 2017

Bibliographic Reference	Leiter, Lawrence A; Zamorano, Jose Luis; Bujas-Bobanovic, Maja; Louie, Michael J; Lecorps, Guillaume; Cannon, Christopher P; Handelsman, Yehuda; Lipid-lowering efficacy and safety of alirocumab in patients with or without diabetes: A sub-analysis of ODYSSEY COMBO II.; Diabetes, obesity & metabolism; 2017; vol. 19 (no. 7); 989-996

Study details

Secondary publication of another included study- see primary study for details	**Influenza outcome data from ODYSSEY COMBO II. Full details reported in main trial entry (Cannon 2015).**
Other publications associated with this study included in review	Colhoun 2014 - Study design and rationale El Shahawy 2017 - 104 week data
Study type	Randomised controlled trial (RCT)

Study arms

Alirocumab (+ oral placebo) (N = 479)

75 mg every 2 weeks with increase to 150 mg (with background statin)

Ezetimibe (+ subcutaneous placebo) (N = 241)

10 mg/day (with background statin)

Outcomes

Study timepoints

- 104 week

Dichotomous

Outcome	Alirocumab (+ oral placebo) , 104 week, N = 479	Ezetimibe (+ subcutaneous placebo), 104 week, N = 241
Influenza No of events	n = 22 % = 4.6	n = 16 % = 6.6

Influenza - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Influenza-104 weeks

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Unclear if the outcome was consistently recorded)*
Overall bias and Directness	Overall Directness	Directly applicable

Luo, 2014

Bibliographic Reference	Luo P; Li L; Wang LX; Zhu HH; Du S; Wu SL; Han YG; Wang GG; Effects of atorvastatin in combination with ezetimibe on carotid atherosclerosis in elderly patients with hypercholesterolemia.; Genetics and molecular research : GMR; 2014; vol. 13 (no. 2)

Study details

Study type	Randomised controlled trial (RCT)
Study location	China
Study setting	Secondary care
Study dates	July 2010 - December 2011
Sources of funding	None reported
Inclusion criteria	Patients with hypercholesterolaemia who had an LDL-C ≥2.6 mM after undergoing lipid reduction therapy for three months
Exclusion criteria	Patients with hypertension, blood diseases, hepatorenal dysfunction, severe infectious disease and heart failure
Recruitment / selection of participants	Method not reported
Population subgroups	No additional information
Intervention(s)	Atorvastatin (Lipitor, 20 mg) plus ezetimibe (Zetia, 10 mg) once per day
Comparator	Atorvastatin (Lipitor, 20 mg) once per day
Background treatment	No additional information

Number of participants	84 randomised 40 assigned to atorvastatin plus ezetimibe group 44 assigned to atorvastatin monotherapy group
Duration of follow-up	12 months
Indirectness	None
Additional comments	Not reported

Study arms

Atorvastatin (N = 44)

Atorvastatin (Lipitor, 20 mg) once per night

Ezetimibe + atorvastatin (N = 40)

Atorvastatin (Lipitor, 20 mg) once per night and ezetimibe (Zetia, 10 mg) once per day

Characteristics

Arm-level characteristics

Characteristic	Atorvastatin (N = 44)	Ezetimibe + atorvastatin (N = 40)
% Female	n = 22 ; % = 50	n = 18 ; % = 45

Characteristic	Atorvastatin (N = 44)	Ezetimibe + atorvastatin (N = 40)
Sample size		
Mean age (SD) Mean (SD)	66.31 (5.82)	67.21 (6.4)
Ethnicity Nominal	NR	NR
Existing CVD diagnoses Coronary heart disease Sample size	n = 34 ; % = 77.3	n = 36 ; % = 90
Type 2 diabetes Sample size	n = 16 ; % = 36.4	n = 12 ; % = 30
Chronic kidney disease Nominal	NR	NR
LDL cholesterol (mmol/l) Mean (SD)	3.31 (0.46)	3.27 (0.36)
Non-HDL cholesterol (mmol/l) Nominal	NR	NR
Statins used Nominal	NR	NR

Characteristic	Atorvastatin (N = 44)	Ezetimibe + atorvastatin (N = 40)
Other lipid-lowering medication used Nominal	NR	NR

Outcomes

Study timepoints

- Baseline
- 12 month

Continuous Outcomes

Outcome	Atorvastatin, Baseline, N = 44	Atorvastatin, 12 month, N = 44	Ezetimibe + atorvastatin , Baseline, N = 40	Ezetimibe + atorvastatin , 12 month, N = 40
LDL-c (mmol/l) Final values Mean (SD)	3.31 (0.46)	2.75 (0.58)	3.27 (0.36)	2.31 (0.54)

LDL-c - Polarity - Lower values are better

Dichotomous Outcomes

Outcome	Atorvastatin, Baseline, N = 44	Atorvastatin, 12 month, N = 44	Ezetimibe + atorvastatin , Baseline, N = 40	Ezetimibe + atorvastatin , 12 month, N = 40
Combined major cardiovascular events Final values No of events	n = NA ; % = NA	n = 0 ; % = 0	n = NA ; % = NA	n = 0 ; % = 0

Combined major cardiovascular events - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

LDL-C

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Unclear method of randomisation and no information about allocation concealment or adherence to treatment)*
Overall bias and Directness	Overall Directness	Directly applicable

Combined major cardiovascular events

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Unclear method of randomisation and no information about allocation concealment or adherence to treatment)*

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

Luo, 2016

Bibliographic Reference	Luo, P.; Wang, L.; Zhu, H.; Du, S.; Wang, G.; Ding, S.; Impact of atorvastatin combined with ezetimibe for the treatment of carotid atherosclerosis in patients with coronary heart disease; Acta Cardiologica Sinica; 2016; vol. 32 (no. 5); 578-585

Study details

Study type	Randomised controlled trial (RCT)
Study location	China
Study setting	Secondary care
Sources of funding	None reported
Inclusion criteria	Patients with coronary heart disease, confirmed by coronary angiography. Patients had received lipid lowering therapy for 3 months prior to enrolment, but not achieved LDL-C levels ≤2.6 mmol/l
Exclusion criteria	Patients with blood diseases, hepatonephric dysfunction, severe infectious diseases and heart failure
Recruitment / selection of participants	Method not reported
Population subgroups	No additional information

Intervention(s)	Ezetimibe (Ezetrol, 10 mg) in the morning and atorvastatin (Lipitor) (dose not specified - can be assumed to be same as comparator group (20 mg)) in the evening
Comparator	Atorvastatin (Lipitor, 20 mg) once per night
Background treatment	Secondary prevention drugs, such as aspirin, angiotensin II receptor antagonists, and hypoglycaemic drugs were routinely administered to both groups
Number of participants	148 randomised 74 assigned to ezetimibe + atorvastatin group 74 assigned to atorvastatin monotherapy group
Duration of follow-up	12 months
Indirectness	None
Additional comments	Not reported

Study arms

Ezetimibe + atorvastatin (N = 74)

Ezetimibe in the morning (10 mg) plus atorvastatin in the evening (dose not specified - likely the same as comparator)

Atorvastatin (N = 74)

Atorvastatin once a night (20 mg)

Characteristics

Arm-level characteristics

Characteristic	Ezetimibe + atorvastatin (N = 74)	Atorvastatin (N = 74)
% Female Sample size	n = 30 ; % = 40.5	n = 34 ; % = 46
Mean age (SD) Mean (SD)	60.76 (11.56)	61.55 (9.72)
Ethnicity Nominal	NR	-
Existing CVD diagnoses Sample size	n = NA ; % = NA	n = NA ; % = NA
Stroke Sample size	n = 14 ; % = 18.9	n = 12 ; % = 16.2
1-vessel CHD Sample size	n = 35 ; % = 47.3	n = 37 ; % = 50
2-vessel CHD Sample size	n = 17 ; % = 23	n = 16 ; % = 21.6
3-vessel CHD Sample size	n = 22 ; % = 29.7	n = 21 ; % = 28.4

Characteristic	Ezetimibe + atorvastatin (N = 74)	Atorvastatin (N = 74)
Type 2 diabetes Sample size	n = 34 ; % = 46	n = 30 ; % = 40.5
Chronic kidney disease Nominal	NR	NR
LDL cholesterol (mmol/l) Mean (SD)	3.57 (0.38)	3.52 (0.46)
Non-HDL cholesterol Nominal	NR	NR
Statins used Nominal	NR	NR
Other lipid-lowering medication used Nominal	NR	NR

Outcomes

Study timepoints

- Baseline
- 12 month

Continuous Outcomes

Outcome	Ezetimibe + atorvastatin , Baseline, N = 74	Ezetimibe + atorvastatin , 12 month, N = 74	Atorvastatin, Baseline, N = 74	Atorvastatin, 12 month, N = 74
LDL-C (mmol/l) Final values Mean (SD)	3.57 (0.38)	2.12 (0.58)	3.52 (0.46)	2.63 (0.56)

LDL-c - Polarity - Lower values are better

Dichotomous Outcomes

Outcome	Ezetimibe + atorvastatin , Baseline, N = 74	Ezetimibe + atorvastatin , 12 month, N = 74	Atorvastatin, Baseline, N = 74	Atorvastatin, 12 month, N = 74
Combined major cardiovascular events (cardiac death, hospitalization for unstable angina, nonfatal myocardial infarction, coronary revascularization, and stroke) Final values No of events	n = NA ; % = NA	n = 6 ; % = 8.1	n = NA ; % = NA	n = 5 ; % = 6.8
Myopathy/rhabdomyolysis (muscle pain or weakness with CK changes) Final values No of events	n = NA ; % = NA	n = 0 ; % = 0	n = NA ; % = NA	n = 0 ; % = 0

Combined major cardiovascular events - Polarity - Lower values are better

Myopathy/rhabdomyolysis (muscle pain) - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

LDL-C

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(no information on adherence)*
Overall bias and Directness	Overall Directness	Directly applicable

Combined major cardiovascular events

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(no information on adherence)*
Overall bias and Directness	Overall Directness	Indirectly applicable *(Paper reports number of events, not time to event as specified in protocol)*

Myopathy/rhabdomyolysis (muscle pain or weakness with CK changes)

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(no information on adherence)*
Overall bias and Directness	Overall Directness	Directly applicable

Masuda, 2015

Bibliographic Reference	Masuda, Jun; Tanigawa, Takashi; Yamada, Tomomi; Nishimura, Yuki; Sasou, Takashi; Nakata, Tomoyuki; Sawai, Toshiki; Fujimoto, Naoki; Dohi, Kaoru; Miyahara, Masatoshi; Nishikawa, Masakatsu; Nakamura, Mashio; Ito, Masaaki; Effect of combination therapy of ezetimibe and rosuvastatin on regression of coronary atherosclerosis in patients with coronary artery disease.; International heart journal; 2015; vol. 56 (no. 3); 278-85

Study details

Trial name / registration number	UMIN ID: 000010323
Study location	Japan.
Study setting	No additional information.
Study dates	October 2008 and September 2012.
Sources of funding	Not reported
Inclusion criteria	People aged 20 to 80 years old with clinically stable angina pectoris if they were undergoing elective percutaneous coronary intervention (PCI) for at least one significant obstructive lesion with more than 75% angiographic luminal diameter narrowing and had more than one untouched non-culprit target lesion for imaging with less than 50% luminal diameter narrowing that could be clearly imaged by intravascular ultrasound (IVUS). LDL-C level higher than 100 mg/dl (2.6 mmol/l) at entry, regardless to prior administration of statins.
Exclusion criteria	If they had any one of the following: history of acute coronary syndrome with in 3 months prior to study entry heart failure (NYHA class III or IV)

	secondary hyperlipidemia left main CAD of more than 50% stenosis chronic total occlusion uncontrolled hypertension uncontrolled diabetes persistent liver dysfunction with 2 or more times the upper limit of normal of serum transaminase serum creatine level of > 2.0 mg/dl or creatinine clearance of < 30 mL/minute unexplained serum creatine kinase level of > 3x ULN history of allergy /sensitivity reaction to any statin and/or ezetimibe were already taking rosuvastatin or ezetimibe before enrolment were recommended for coronary artery bypass graft surgery.
Recruitment / selection of participants	People with stable coronary artery disease who underwent percutaneous coronary intervention (PCI) were enrolled. They were recruited within 72 hours of a successful PCI under IVUS guidance.
Population subgroups	No additional information.
Intervention(s)	Ezetimibe 10 mg/day and rosuvastatin 5 mg/day (medium intensity).
Comparator	Rosuvastatin 5 mg/day (medium intensity).
Background treatment	After PCI of the culprit lesion, baseline IVUS examination was performed. Follow up visits scheduled at 1, 3 and 6 months after administration of allocated drugs and repeated IVUS and coronary angiography (CAG) examinations were performed at the 6-month follow-up.

	Baseline characteristics: **Ezetimibe and rosuvastatin group** Beta-blocker: 9 (42.9%) ARB: 9 (42.9%) ACE inhibitor: 2 (9.8%) Oral glycaemic agent: 8 (38.1%) Insulin:1 (4.8%) Current smoking: 9 (42.9%) Hypertension: 13 (61.9%) **Rosuvastatin group** Beta-blocker: 9 (47.4%) ARB: 10 (52.6%) ACE inhibitor: 3 (15.8%) Oral glycaemic agent: 7 (36.8%) Insulin: 0 (0%) Current smoking: 4 (21.1%) Hypertension: 17 (89.5%)
Number of participants	51 randomised but only 40 included in analysis. Ezetimibe and rosuvastatin group: n=19 and rosuvastatin group: n=21.

Duration of follow-up	6 months.
Indirectness	No indirectness.
Additional comments	Primary analysis only included participants that had IVUS examination at baseline and 6 month follow-up. Safety analysis included all participants that received study drug.

Study arms

Ezetimibe and rosuvastatin (N = 26)

Ezetimibe 10 mg and rosuvastatin 5 mg (medium intensity) daily

Rosuvastatin (N = 25)

Rosuvastatin 5 mg (medium intensity) daily.

Characteristics

Arm-level characteristics

Characteristic	Ezetimibe and rosuvastatin (N = 26)	Rosuvastatin (N = 25)
% Female Sample size	n = 2 ; % = 9.5	n = 3 ; % = 14.2
Mean age (SD)	64 (7.9)	70.2 (7.6)

Characteristic	Ezetimibe and rosuvastatin (N = 26)	Rosuvastatin (N = 25)
Mean (SD)		
Ethnicity Nominal	NR	NR
Existing CVD diagnosis		
Previous MI Sample size	n = 5 ; % = 23.8	n = 4 ; % = 21.1
Type 2 diabetes Diabetes (type not specified) Sample size	n = 11 ; % = 52.4	n = 8 ; % = 42.1
Chronic kidney disease Nominal	NR	NR
LDL cholesterol (mg/dl) Mean (SD)	131.8 (25.6)	123 (27)
Non-HDL cholesterol (mg/dl) Mean (SD)	151.4 (29.4)	146.2 (35.6)
Statins used Sample size	n = 9 ; % = 42.9	n = 7 ; % = 36.8
Other lipid lowering medication used	NR	NR

Characteristic	Ezetimibe and rosuvastatin (N = 26)	Rosuvastatin (N = 25)
Nominal		
Number analysed for baseline characteristics Baseline characteristics only given for participants included in primary analysis and not total randomised. Nominal	21	19

Outcomes

Study timepoints

- Baseline
- 6 month

Continuous outcomes - lipid levels at 6 months

Outcome	Ezetimibe and rosuvastatin, Baseline, N = 26	Ezetimibe and rosuvastatin, 6 month, N = 21	Rosuvastatin, Baseline, N = 25	Rosuvastatin, 6 month, N = 19
LDL cholesterol (mg/dl) Mean (SD)	131.8 (25.6)	57.3 (20.2)	123 (27)	75.1 (21.4)
LDL Cholesterol (% change) Study reported p<0.05 for combination group	NA (NA)	-55.8 (18.9)	NA (NA)	-36.8 (18.9)

Outcome	Ezetimibe and rosuvastatin, Baseline, N = 26	Ezetimibe and rosuvastatin, 6 month, N = 21	Rosuvastatin, Baseline, N = 25	Rosuvastatin, 6 month, N = 19
versus statin group calculated with the use of analysis of covariance with age as a covariate. Mean (SD)				
Non-HDL cholesterol (mg/dl) Mean (SD)	151.4 (29.4)	74.3 (23.4)	146.2 (35.6)	92.8 (24.7)
Non-HDL cholesterol (% change) Study reported p<0.05 for combination group versus statin group calculated with the use of analysis of covariance with age as a covariate. Mean (SD)	NA (NA)	-50.3 (17.9)	NA (NA)	-34.8 (17.9)

LDL cholesterol - Polarity - Lower values are better

LDL Cholesterol (% change) - Polarity - Higher values are better (greater reduction is better)

Non-HDL cholesterol - Polarity - Lower values are better

Non-HDL cholesterol (% change) - Polarity - Higher values are better (greater reduction is better)

Dichotomous outcomes - adverse events at 6 months

Outcome	Ezetimibe and rosuvastatin, Baseline, N = 26	Ezetimibe and rosuvastatin, 6 month, N = 21	Rosuvastatin, Baseline, N = 25	Rosuvastatin, 6 month, N = 19
Rhabdomyolysis	n = NA ; % = NA	n = 0 ; % = 0	n = NA ; % = NA	n = 0 ; % = 0

Outcome	Ezetimibe and rosuvastatin, Baseline, N = 26	Ezetimibe and rosuvastatin, 6 month, N = 21	Rosuvastatin, Baseline, N = 25	Rosuvastatin, 6 month, N = 19
No of events				
AST or ALT > 3 x upper limit of normal No of events	n = NA ; % = NA	n = 0 ; % = 0	n = NA ; % = NA	n = 0 ; % = 0

Rhabdomyolysis - Polarity - Lower values are better

AST or ALT > 3 x upper limit of normal - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

LDL-C

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Baseline differences in age between groups and high rate of missing outcome data.)*
Overall bias and Directness	Overall Directness	Directly applicable

LDL Cholesterol (% change)

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Baseline differences in age between groups and high rate of missing outcome data.)*

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

Non-HDL cholesterol value

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Baseline differences in age between groups and high rate of missing outcome data.)*
Overall bias and Directness	Overall Directness	Directly applicable

Non-HDL cholesterol (% change)

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Baseline differences in age between groups and high rate of missing outcome data.)*
Overall bias and Directness	Overall Directness	Directly applicable

Rhabdomyolysis

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Baseline differences in age between groups.)*
Overall bias and Directness	Overall Directness	Directly applicable

AST or ALT>3xULN

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Baseline differences in age between groups and high rate of missing outcome data.)*
Overall bias and Directness	Overall Directness	Directly applicable

McCullough, 2018

Bibliographic Reference	McCullough, Peter A; Ballantyne, Christie M; Sanganalmath, Santosh K; Langslet, Gisle; Baum, Seth J; Shah, Prediman K; Koren, Andrew; Mandel, Jonas; Davidson, Michael H; Efficacy and Safety of Alirocumab in High-Risk Patients With Clinical Atherosclerotic Cardiovascular Disease and/or Heterozygous Familial Hypercholesterolemia (from 5 Placebo-Controlled ODYSSEY Trials).; The American journal of cardiology; 2018; vol. 121 (no. 8); 940-948

Study details

Other publications associated with this study included in review	**Robinson 2015: Primary trial report for ODYSSEY LONG TERM without details of CVD subgroup.**
Trial name / registration number	Analysis extracted includes data from the ASCVD subgroup of ODYSSEY LONG TERM (97% of analysis sample) and ODYSSEY HIGH FH (3% of analysis sample) ODYSSEY LONG TERM: NCT01507831 ODYSSEY HIGH FH: NCT01617655
Study type	Randomised controlled trial (RCT)
Study location	ODYSSEY LONG TERM: 27 countries throughout Africa, Europe, and North and South America ODYSSEY HIGH FH: 33 sites across Canada, the United States, the Netherlands, Russia, and South Africa
Study setting	Outpatient care
Study dates	ODYSSEY LONG TERM: January 2012 to November 2014 ODYSSEY HIGH FH: December 2012 to January 2015
Sources of funding	Sanofi and Regeneron Pharmaceuticals.
Inclusion criteria	This sub analysis limited to people included in the ODYSSEY trials who had clinical ASCVD, defined as: coronary heart disease, stroke, and peripheral arterial disease, all of presumed atherosclerotic origin ODYSSEY LONG TERM inclusion criteria: Adult patients (≥18 years of age) with heterozygous familial hypercholesterolemia or with established coronary heart disease or a coronary heart disease risk equivalent and LDL cholesterol 70 mg per deciliter (1.8 mmol/l) or more.

Other publications associated with this study included in review	**Robinson 2015: Primary trial report for ODYSSEY LONG TERM without details of CVD subgroup.**
	Receiving either high-dose statin therapy or statin therapy at the maximum tolerated dose, with or without other lipid-lowering therapy, for at least 4 weeks before screening (6 weeks for fenofibrate) ODYSSEY HIGH FH inclusion criteria: Patients with heFH and LDL-C ≥ 160 mg/dl On a maximally tolerated stable daily dose of statin, with or without other lipid-lowering therapy, for at least 4 weeks (6 weeks for fenofibrate) before screening.
Exclusion criteria	ODYSSEY LONG TERM exclusion criteria: LDL-C <70 mg/dl (< 1.81 mmol/l) at the screening visit. Not on a stable dose of LMT (including statin) for at least 4 weeks and/or fenofibrate for at least 6 weeks, as applicable, prior to the screening visit and from screening to randomisation. Currently taking a statin that is not simvastatin, atorvastatin, or rosuvastatin. Simvastatin, atorvastatin, or rosuvastatin is not taken daily or not taken at a registered dose. Daily doses above atorvastatin 80 mg, rosuvastatin 40 mg or simvastatin 40 mg (except for patients on simvastatin 80 mg for more than one year, who are eligible). Fasting serum TG >400 mg/dl (>4.52 mmol/l) at the screening visit Use of fibrates other than fenofibrate within 6 weeks prior to screening visit or plan to receive it. ODYSSEY HIGH FH exclusion criteria:

Other publications associated with this study included in review	**Robinson 2015: Primary trial report for ODYSSEY LONG TERM without details of CVD subgroup.**
	Patients with heFH who are not adequately controlled with a maximally-tolerated stable daily dose of statin for at least 4 weeks prior to the screening visit, with or without other LLT Principal exclusion criteria Not on a stable dose of LLT (including statin) for at least 4 weeks and/or fenofibrate for at least 6 weeks, as applicable, prior to the screening visit or from screening to randomization Currently taking a statin that is not simvastatin, atorvastatin or rosuvastatin taken daily at a registered dose Receiving daily doses above atorvastatin 80 mg, rosuvastatin 40 mg or simvastatin 40 mg (except for patients on simvastatin 80 mg for more than 1 year, who are eligible) Use of fibrates, other than fenofibrate, within 6 weeks of the screening visit Fasting serum triglycerides >400 mg/dl (>4.52 mmol/l) at the screening visit Known history of homozygous FH LDL-C <160 mg/dl (<4.14 mmol/l) at screening and patient only on statin monotherapy without additional LLT
Recruitment / selection of participants	3 week screening period to identify those eligible
Population subgroups	This study reports a post-hoc analysis of the ASCVD subgroup using individual participant data.
Intervention(s)	Fixed dose alirocumab 150 mg every 2 weeks (self-administered single 1-ml subcutaneous injection, in a prefilled syringe).
Comparator	Placebo (self-administered single 1-ml subcutaneous injection, in a prefilled syringe).

Other publications associated with this study included in review	**Robinson 2015: Primary trial report for ODYSSEY LONG TERM without details of CVD subgroup.**
Background treatment	Maximally tolerated stain with or without additional lipid-lowering therapies.
Number of participants	1827
Duration of follow-up	24 weeks
Indirectness	None
Additional comments	An intention-to-treat approach was used that included all data, regardless of adherence to treatment. Least squares mean lipid values were calculated from a mixed-effects model with repeated measures to account for missing data.

Study arms

Alirocumab (N = 1219)

150 mg every 2 weeks Background of maximally tolerated statin

Placebo (N = 634)

Background of maximally tolerated statin

Characteristics

Arm-level characteristics

Characteristic	Alirocumab (N = 1615)	Placebo (N = 834)
% Female n=1615 vs 834 Sample size	n = 542; % = 33.6	n = 282; % = 33.8
Mean age (SD) n=1615 vs 834 Mean (SD)	61.3 (9.9)	61.3 (9.6)
Ethnicity (n=1615 vs 834) White Sample size	n = 1499; % = 92.8	n = 780; % = 93.5
Existing CVD diagnosis		
ACS Sample size	n = 980; % = 60.7	n = 528; % = 63.3
Coronary revascularization procedure Sample size	n = 1006; % = 62.3	n = 522; % = 62.6
Other clinically significant coronary heart disease Sample size	n = 622; % = 38.5	n = 322; % = 38.6
PAD	n = 97; % = 6	n = 56; % = 6.7

Characteristic	Alirocumab (N = 1615)	Placebo (N = 834)
Sample size		
Ischaemic stroke Sample size	n = 199; % = 12.3	n = 86; % = 10.3
Type 2 diabetes 'Diabetes mellitus' Sample size	n = 440; % = 27.2	n = 223; % = 26.7
Chronic kidney disease Nominal	NR	NR
LDL cholesterol (mg/dl) Mean (SD)	120.1 (41.3)	122.8 (44.5)
Non-HDL cholesterol (mg/dl) Mean (SD)	149.4 (45)	152.2 (48.9)
High-intensity statin Sample size	n = 910; % = 56.3	n = 492; % = 59
Moderate-intensity statin Sample size	n = 471; % = 29.2	n = 227; % = 27.2
Other lipid-lowering medication used Nominal	NR	NR

Only reported for all 5 studies - only 2 of which, contributing 75% of total sample, were included in this review analysis

Outcomes

Study timepoints

- 24 week

Continuous

Outcome	Alirocumab , 24 week, N = 1201	Placebo, 24 week, N = 626
% change LDL-C (%) least squares mean (baseline values not provided) Mean (SE)	-61.9 (0.8)	-0.1 (1.2)
High-intensity statin n=914 Mean (SE)	-64.3 (1.5)	-1.2 (2.1)
Moderate-intensity statin n=605 Mean (SE)	-52.7 (0.7)	-0.6 (1)
% change non-HDL-C (%) least squares mean (baseline values not provided) Mean (SE)	-52.7 (0.7)	-0.6 (1)

Outcome	Alirocumab , 24 week, N = 1201	Placebo, 24 week, N = 626
High-intensity statin n=914 Mean (SE)	-52.1 (1)	-0.5 (1.4)
Moderate-intensity statin n=605 Mean (SE)	-54.4 (1.2)	-1.1 (1.8)

% change LDL-C - Polarity - Higher values are better (greater reduction is better)

% change non-HDL-C - Polarity - Higher values are better (greater reduction is better)

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

% change LDL-C

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Post hoc analysis but using IPD data and pre-specified endpoint)*
Overall bias and Directness	Overall Directness	Directly applicable

% change non-HDL-C

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Post hoc analysis but using IPD data and pre-specified endpoint)*

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

Muller-Wieland, 2017

Bibliographic Reference	Muller-Wieland, Dirk; Leiter, Lawrence A; Cariou, Bertrand; Letierce, Alexia; Colhoun, Helen M; Del Prato, Stefano; Henry, Robert R; Tinahones, Francisco J; Aurand, Lisa; Maroni, Jaman; Ray, Kausik K; Bujas-Bobanovic, Maja; Design and rationale of the ODYSSEY DM-DYSLIPIDEMIA trial: lipid-lowering efficacy and safety of alirocumab in individuals with type 2 diabetes and mixed dyslipidaemia at high cardiovascular risk.; Cardiovascular diabetology; 2017; vol. 16 (no. 1); 70

Study details

Secondary publication of another included study- see primary study for details	Design and rationale for Ray 2019 analysis of the ODYSSEY DM-DYSLIPIDEMIA and DM-INSULIN studies. Full details available in main study entry (Ray 2019).
Other publications associated with this study included in review	Ray 2019 analysis of the ODYSSEY DM-DYSLIPIDEMIA and DM-INSULIN studies

Nicholls, 2022

Bibliographic Reference	Nicholls, Stephen J; Kataoka, Yu; Nissen, Steven E; Prati, Francesco; Windecker, Stephan; Puri, Rishi; Hucko, Thomas; Aradi, Daniel; Herrman, Jean-Paul R; Hermanides, Renicus S; Wang, Bei; Wang, Huei; Butters, Julie; Di Giovanni, Giuseppe; Jones,

Stephen; Pompili, Gianluca; Psaltis, Peter J; Effect of Evolocumab on Coronary Plaque Phenotype and Burden in Statin-Treated Patients Following Myocardial Infarction.; JACC. Cardiovascular imaging; 2022; vol. 15 (no. 7); 1308-1321

Study details

Other publications associated with this study included in review	Nicholls 2021, Assessing the impact of PCSK9 inhibition on coronary plaque phenotype with optical coherence tomography: rationale and design of the randomized, placebo-controlled HUYGENS study (study protocol)
Trial name / registration number	HUYGENS/ NCT03570697
Study type	Randomised controlled trial (RCT)
Study location	Multicentre trial (27 centres countries including: USA, Australia, Italy, Netherlands, Hungary)
Study setting	Primary care clinic
Study dates	November 19, 2018 to December 27, 2019
Sources of funding	Amgen Inc.
Inclusion criteria	Patients aged ≥18 years were eligible if they demonstrated at least 1 nonculprit epicardial coronary stenosis ≥20% on angiography during non– ST-segment elevation myocardial infarction (NSTEMI) with interventional treatment of the culprit lesion and a target vessel suitable for imaging with ≤50% visual obstruction. Patients were required to be treated with maximally tolerated statin therapy and have a qualifying LDL-C level at the time of presentation with NSTEMI ≥130 mg/dl if not taking a statin, ≥80 mg/dl if taking low- or moderate-intensity statin, or ≥60 mg/dl if taking a high-intensity statin. Patients were required to have at least 1 OCT image with an FCT ≤120 mm and 1 image with a lipid arc >90o in a segment at least 40 mm in length.
Exclusion criteria	renal dysfunction (estimated glomerular filtration rate <30 mL/min/1.73 m2), statin intolerance, or prior use of PCSK9 inhibitors.

Recruitment / selection of participants	All patients who met all of the inclusion criteria, none of the exclusion criteria and who tolerate the placebo run-in injection at the time of screening were deemed eligible.
Population subgroups	None applicable; randomization stratified by use of statin therapy for more than 4 weeks before screening; Mean (SD) LDL-C at baseline was 141.3 (33.1) mg/dl.
Intervention(s)	Evolocumab 420 mg administered monthly via subcutaneous injection for 52 weeks.
Comparator	Placebo administered monthly via subcutaneous injection for 52 weeks.
Background treatment	Statins: overall 95% of study population taking statins at baseline; 80.7% high intensity statins, 13.7% moderate intensity and 0.6% low intensity statins. . High-intensity statins: atorvastatin ≥40 mg, rosuvastatin ≥20 mg, simvastatin ≥80 mg daily. Moderate-intensity statins: atorvastatin 10 to <40 mg, rosuvastatin 5 to <20 mg, simvastatin 20 to <80 mg daily. Low-intensity statins: atorvastatin <10 mg, rosuvastatin <5 mg, simvastatin <20 mg daily. Also 4.9% were treated with Ezetimibe at time of screening; 99% were on antiplatelet therapy; 84% on beta-blockers; 72.7% on ACE inhibitor; 14.2% on angiotensin receptor blocker
Number of participants	161
Duration of follow-up	52 weeks
Indirectness	Population indirectness as part of the participants (unclear how many) were receiving Simvastatin ≥80mg/d as part of being on high-intensity statins.
Additional comments	All analyses were performed using SAS version 9.4 (SAS Inc). All efficacy and safety analyses were performed on patients who received at least 1 dose of study drug; Step-down and Hochberg statistical approaches of multiplicity adjustment were applied to investigate the primary and secondary endpoints.

Study arms

Evolocumab (N = 80)

420 mg administered monthly via subcutaneous injection

Placebo (N = 81)

Characteristics

Arm-level characteristics

Characteristic	**Evolocumab (N = 80)**	**Placebo (N = 81)**
% Female Sample size	n = 20 ; % = 25	n = 26 ; % = 32.1
Mean age (SD) Mean (SD)	60.9 (10)	60.2 (9.2)
Ethnicity White Sample size	n = 77 ; % = 96.3	n = 79 ; % = 97.6
Diabetes White Sample size	n = 13 ; % = 16.3	n = 14 ; % = 17.3
LDL cholesterol (mg/dl)	140.4 (34)	142.1 (32.3)

Characteristic	Evolocumab (N = 80)	Placebo (N = 81)
Mean (SD)		
Non-HDL cholesterol (mg/dl) Mean (SD)	130.9 (36.6)	133.4 (38.7)
Statins used Sample size	n = 75 ; % = 93.8	n = 78 ; % = 96.3
High intensity Baseline statin use Sample size	n = 63 ; % = 78.8	n = 67 ; % = 82.7
Moderate intensity Sample size	n = 11 ; % = 13.8	n = 11 ; % = 13.6
Low intensity Sample size	n = 1 ; % = 1.3	n = 0 ; % = 0
Ezetimibe Sample size	n = 1 ; % = 1.3	n = 2 ; % = 2.5
Existing CVD diagnosis		
Previous Myocardial infarction (MI)	n = 5 ; % = 6.3	n = 9 ; % = 11.1

Characteristic	Evolocumab (N = 80)	Placebo (N = 81)
Sample size		
Percutaneous coronary intervention Sample size	n = 9 ; % = 11.3	n = 12 ; % = 14.8
Baseline antiplatelet therapy Sample size	n = 79 ; % = 98.8	n = 81 ; % = 100
Baseline Beta-blocker use Sample size	n = 64 ; % = 80	n = 72 ; % = 88.9
Baseline angiotensin-converting enzyme-inhibitor use Sample size	n = 59 ; % = 73.8	n = 58 ; % = 71.6
Baseline angiotensin receptor blocker use Sample size	n = 14 ; % = 17.5	n = 9 ; % = 11.1

Outcomes

Study timepoints

- 50 week

Absolute change at week 50 (mg/dl)

Outcome	Evolocumab, 50 week, N = 80	Placebo, 50 week, N = 81
LDL-c (mg/dl) absolute change from baseline Mean (SD)	-114.2 (41.7)	-55.3 (47.1)
Non-HDL cholesterol (mg/dl) absolute change from baseline Mean (SD)	-86.5 (45.6)	-20.8 (47.1)

LDL-c - Polarity - Lower values are better

Non-HDL cholesterol - Polarity - Lower values are better

Adverse events

Outcome	Evolocumab, 50 week, N = 80	Placebo, 50 week, N = 81
Injection site reaction No of events	n = 0 ; % = 0	n = 1 ; % = 1.2

Injection site reaction - Polarity - Lower values are better

Analysis included patients who received at least 1 dose of study drug.

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Absolute change LDL-C

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Partially applicable *(Some of the participants were on simvastatin >80mg/dl)*

Absolute change non-HDL-C

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Partially applicable *(Some of the participants were on simvastatin >80mg/dl)*

Injection site reaction

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Partially applicable *(Some of the participants were on simvastatin >80mg/dl)*

Nicholls, 2021

Bibliographic Reference	Nicholls, Stephen J; Nissen, Steven E; Prati, Francesco; Windecker, Stephan; Kataoka, Yu; Puri, Rishi; Hucko, Thomas; Kassahun, Helina; Liao, Jason; Somaratne, Ransi; Butters, Julie; Di Giovanni, Giuseppe; Jones, Stephen; Psaltis, Peter J; Assessing the impact of PCSK9 inhibition on coronary plaque phenotype with optical coherence tomography: rationale and design of the randomized, placebo-controlled HUYGENS study.; Cardiovascular diagnosis and therapy; 2021; vol. 11 (no. 1); 120-129

Study details

Secondary publication of another included study- see primary study for details	Nicholls 2022; HUYGENS trial, full details in main trial entry
Other publications associated with this study included in review	Nicholls 2022; HUYGENS trial, full details in main trial entry
Study type	Randomised controlled trial (RCT)

Nicholls, 2016

Bibliographic Reference	Nicholls, Stephen J; Puri, Rishi; Anderson, Todd; Ballantyne, Christie M; Cho, Leslie; Kastelein, John J P; Koenig, Wolfgang; Somaratne, Ransi; Kassahun, Helina; Yang, Jingyuan; Wasserman, Scott M; Scott, Robert; Ungi, Imre; Podolec, Jakub; Ophuis, Antonius Oude; Cornel, Jan H; Borgman, Marilyn; Brennan, Danielle M; Nissen, Steven E; Effect of Evolocumab on Progression of Coronary Disease in Statin-Treated Patients: The GLAGOV Randomized Clinical Trial.; JAMA; 2016; vol. 316 (no. 22); 2373-2384

Study details

Other publications associated with this study included in review	Study protocol: Impact of PCSK9 inhibition on coronary atheroma progression: Rationale and design of Global Assessment of Plaque Regression with a PCSK9 Antibody as Measured by Intravascular Ultrasound (GLAGOV), 2016
Trial name / registration number	Global Assessment of Plaque Regression With a PCSK9 Antibody as Measured by Intravascular Ultrasound (GLAGOV) Clinicaltrials.gov identifier: NCT01813422
Study type	Randomised controlled trial (RCT)
Study location	Global
Study setting	Secondary care
Study dates	May 2013 - January 2015
Sources of funding	Sponsored by Amgen Inc.
Inclusion criteria	Men or women aged >18 years Clinically indicated coronary angiogram, evidence of coronary disease, stable statin dose for ≥4 wk prior to screening

	LDL-C criteria met within 4 wk of screening visit or, if applicable, at the end of lipid stabilization period: (LDL-C ≥80 mg/dl, OR LDL-C ≥60 but ≥80 mg/dl in the presence of 1 major or 3 minor risk factors - major risk factors: noncoronary atherosclerotic vascular disease as evidenced by documented peripheral arterial disease, documented abdominal aortic aneurysm, or documented cerebrovascular disease) Documented myocardial infarction or hospitalization for unstable angina within the last 2 years Documented type 2 diabetes mellitus Minor risk factors (3 required): cigarette smoking (current), hypertension (blood pressure ≥140/90 mm Hg or current use of antihypertensive medications), low HDL-C (men: b40 mg/dl; women b50 mg/dl), family history of premature coronary heart disease (1st-degree male relative aged ≥55 y or 1st-degree female relative aged ≥65 y), age (men ≥50 y; women ≥55 y), hs-CRP ≥2 mg/L
Exclusion criteria	Clinically significant heart disease which, in the opinion of the Principal Investigator, is likely to require coronary bypass surgery, percutaneous coronary intervention, cardiac transplantation, surgical valve repair, and/or replacement during the course of the study Heart failure of New York Heart Failure Association class III or IV or last known left ventricular ejection fraction <30% Coronary artery bypass surgery <6 wk prior to the qualifying IVUS Cardiac arrhythmia within 3 mo prior to randomization that is not controlled by medication Uncontrolled hypertension at day 1, defined as a resting systolic blood pressure of ≥180 mm Hg Triglyceride level >400 mg/dl at screening Type 1 diabetes mellitus or poorly controlled type 2 diabetes (glycosylated haemoglobin >9%) at screening Thyroid-stimulating hormone <lower limit of normal or >1.5× upper limit of normal Estimated glomerular filtration rate <30 mL/min per 1.73 m2 Aspartate aminotransferase or alanine aminotransferase >2× ULN

	Creatine kinase >3× ULN Use of cholesterylester transfer protein inhibition treatment within 12 mo prior to randomization Any prior use of PCSK9 inhibitor therapy Consumption of any of the following drugs for more than 2 wk in the last 3 mo prior to LDL-C screening: systemic cyclosporine, systemic steroids, isotretinoin History of malignancy (except nonmelanoma skin cancers, cervical in situ carcinoma, breast ductal carcinoma in situ, or stage 1 prostate carcinoma) Known major active infection, or major hematologic, renal, metabolic, gastrointestinal, or endocrine dysfunction Pregnant or breast-feeding. Premenopausal females must have been willing to use at least 1 highly effective method of birth control during treatment and for an additional 15 wk after the end of treatment
Recruitment / selection of participants	Method not reported
Population subgroups	No additional information
Intervention(s)	Evolocumab (420 mg) administered subcutaneously on a monthly basis
Comparator	Placebo administered subcutaneously on a monthly basis
Background treatment	No additional information
Number of participants	968 randomised

	484 assigned to evolocumab group, 423 completed 484 assigned to placebo group, 423 completed
Duration of follow-up	78 weeks
Indirectness	All outcomes downgraded by one increment due to intervention duration of 18 months - protocol specified 12 months
Additional comments	ITT with multiple imputation of missing data

Study arms

Evolocumab (N = 484)

Monthly subcutaneous injections (420 mg) (423 completed trial)

Placebo (N = 484)

(423 completed trial)

Characteristics

Arm-level characteristics

Characteristic	Evolocumab (N = 484)	Placebo (N = 484)
% Female Sample size	n = 135 ; % = 27.9	n = 134 ; % = 27.7
Mean age (SD) Mean (SD)	59.8 (9.6)	59.8 (8.8)
Ethnicity		
White Sample size	n = 456 ; % = 94.2	n = 452 ; % = 93.4
Black or African American Sample size	n = 4 ; % = 0.8	n = 5 ; % = 1
Asian Sample size	n = 14 ; % = 2.9	n = 16 ; % = 3.3
Native Hawaiian or other Pacific Islander Sample size	n = 1 ; % = 0.2	n = 0 ; % = 0
American Indian or Alaska Native Sample size	n = 0 ; % = 0	n = 2 ; % = 0.4

Characteristic	Evolocumab (N = 484)	Placebo (N = 484)
Multiple Sample size	n = 7 ; % = 1.4	n = 6 ; % = 1.2
Other Sample size	n = 2 ; % = 0.4	n = 3 ; % = 0.6
Existing CVD diagnoses		
Previous percutaneous coronary intervention Sample size	n = 189 ; % = 39	n = 188 ; % = 38.8
Previous myocardial infarction Sample size	n = 169 ; % = 34.9	n = 171 ; % = 35.3
Type 2 diabetes Sample size	n = 98 ; % = 20.2	n = 104 ; % = 21.5
Chronic kidney disease Nominal	NR	NR
LDL cholesterol (mg/dl) Mean (95% CI)	92.6 (90.1 to 95)	92.4 (90 to 94.6)

Characteristic	Evolocumab (N = 484)	Placebo (N = 484)
Non-HDL cholesterol (mg/dl) Mean (95% CI)	119.4 (116.5 to 122.3)	120.8 (117.9 to 123.7)
Statins used Sample size	n = 478 ; % = 98.8	n = 476 ; % = 98.3
High intensity: atorvastatin (≥40 mg), rosuvastatin (≥20 mg), simvastatin (≥80 mg) Sample size	n = 280 ; % = 57.9	n = 290 ; % = 59.9
Moderate intensity: atorvastatin (10-40 mg), rosuvastatin (5-20 mg), simvastatin (20-80 mg), pravastatin (≥40 mg), lovastatin (≥40 mg), fluvastatin (80 mg), pitavastatin (≥2 mg) Sample size	n = 196 ; % = 40.5	n = 185 ; % = 38.2
Low intensity: atorvastatin (<10 mg), rosuvastatin (<5 mg), simvastatin (<20 mg), pravastatin (<40 mg), lovastatin (<40 mg) Sample size	n = 2 ; % = 0.4	n = 1 ; % = 0.2
Other lipid-lowering medication used Sample size	n = NA ; % = NA	n = NA ; % = NA
Ezetimibe Sample size	n = 9 ; % = 2.1	n = 9 ; % = 2.1

Outcomes

Study timepoints

- Baseline
- 18 month

Continuous Outcomes

Outcome	Evolocumab , Baseline, N = 484	Evolocumab , 18 month, N = 484	Placebo, Baseline, N = 484	Placebo, 18 month, N = 484
LDL-C (mg/dl) Time weighted average over 18 months (SD calculated from 95%CI reported in paper) Mean (SD)	92.6 (27.5)	36.6 (24.1)	92.4 (26.9)	93 (27.5)
LDL-C (mg/dl) Change scores (least square means, SD calculated from 95%CI reported in paper) Mean (SD)	NA (-)	-56.3 (35.6)	NA (NA)	0.2 (35.4)
LDL-C (mg/dl) Change scores (least square means, SD calculated from 95%CI reported in paper) Mean (95% CI)	-	-56.3 (-59.4 to -53.1)	-	0.2 (-2.9 to 3.4)

Outcome	Evolocumab , Baseline, N = 484	Evolocumab , 18 month, N = 484	Placebo, Baseline, N = 484	Placebo, 18 month, N = 484
non-HDL-C (mg/dl) Time weighted average over 18 months (SD calculated from 95%CI reported in paper) Mean (SD)	119.4 (32.6)	57.7 (28.1)	120.8 (32.6)	122 (30.3)
non-HDL-C (mg/dl) Time weighted average over 18 months (SD calculated from 95%CI reported in paper) Mean (95% CI)	119.4 (116.5 to 122.3)	57.7 (55.2 to 60.2)	120.8 (117.9 to 123.7)	122 (119.3 to 124.7)
non-HDL-C (mg/dl) Change scores (least square means, SD calculated from 95%CI reported in paper) Mean (SD)	NA (NA)	-62.3 (41.99)	NA (NA)	1.1 (41.99)
non-HDL-C (mg/dl) Change scores (least square means, SD calculated from 95%CI reported in paper) Mean (95% CI)	-	-62.3 (-66 to -58.5)	-	1.1 (-2.7 to 4.8)

LDL-C - Polarity - Lower values are better

LDL-C - Polarity - Lower values are better

non-HDL-C - Polarity - Lower values are better

non-HDL-C - Polarity - Lower values are better

Dichotomous Outcomes

Outcome	Evolocumab , Baseline, N = 484	Evolocumab , 18 month, N = 484	Placebo, Baseline, N = 484	Placebo, 18 month, N = 484
Combined major cardiovascular events (study definition: first major adverse CV event) Final values No of events	n = NA ; % = NA	n = 59 ; % = 12.2	n = NA ; % = NA	n = 74 ; % = 15.3
New-onset diabetes Final values No of events	n = NA ; % = NA	n = 17 ; % = 3.6	n = NA ; % = NA	n = 18 ; % = 3.7
Increased liver transaminases (ALT or AST 3x ULN) Final values No of events	n = NA ; % = NA	n = 2 ; % = 0.5	n = NA ; % = NA	n = 2 ; % = 0.5
Injection site reactions Final values No of events	n = NA ; % = NA	n = 2 ; % = 0.4	n = NA ; % = NA	n = 0 ; % = 0

Combined major cardiovascular events (study definition: first major adverse CV event) - Polarity - Lower values are better

New-onset diabetes - Polarity - Lower values are better

Increased liver transaminases (ALT or AST 3x ULN) - Polarity - Lower values are better

Injection site reactions - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

LDL-C

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(due to proportion of missing outcome data)*
Overall bias and Directness	Overall Directness	Partially applicable *(Weighted mean over an 18-month treatment period, protocol specified 12 months)*

non-HDL-C

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(due to proportion of missing outcome data)*
Overall bias and Directness	Overall Directness	Partially applicable *(Weighted mean over an 18-month treatment period, protocol specified 12 months)*

LDL-C-change

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(due to proportion of missing outcome data)*

Section	Question	Answer
Overall bias and Directness	Overall Directness	Partially applicable *(Outcome assessed at 18 months, protocol specified 12 months)*

non-HDL-C-change scores

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(due to proportion of missing outcome data)*
Overall bias and Directness	Overall Directness	Partially applicable *(Outcome assessed at 18 months, protocol specified 12 months)*

MACE

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

New-onset diabetes

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Increased liver transaminases (ALT or AST3xULN)

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Injection-site reactions

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Oyama, 2021

Bibliographic Reference	Oyama, Kazuma; Giugliano, Robert P; Blazing, Michael A; Park, Jeong-Gun; Tershakovec, Andrew M; Sabatine, Marc S; Cannon, Christopher P; Braunwald, Eugene; Baseline Low-Density Lipoprotein Cholesterol and Clinical Outcomes of

Combining Ezetimibe With Statin Therapy in IMPROVE-IT.; Journal of the American College of Cardiology; 2021; vol. 78 (no. 15); 1499-1507

Study details

Secondary publication of another included study- see primary study for details	Baseline LDL-C subgroup analysis of IMPROVE-IT. Full trial details available in main study entry (Cannon 2015)
Other publications associated with this study included in review	Blazing 2014 (used for ethnicity data for population characteristics); Cannon 2008 (study rationale and design).
Trial name / registration number	IMPROVE-IT
Study type	Randomised controlled trial (RCT)
Population subgroups	17,999 patients were stratified by LDL-C at qualifying event into 3 groups (50-<70, 70-<100, and 100-125 mg/dl).

Study arms

Ezetimibe + simvastatin (N = 8990)

Once daily simvastatin (40 mg; medium intensity) plus ezetimibe (10 mg)

Simvastatin + placebo (N = 9009)

Simvastatin (40 mg; medium intensity)

Characteristics

Arm-level characteristics

Characteristic	Ezetimibe + simvastatin (N = 8990)	Simvastatin + placebo (N = 9009)
% Female		
Baseline LDL-C 50-<70 mg/dl (N=2480; 1202 vs 1278) Sample size	n = 939; % = 78	n = 988; % = 77
Baseline LDL-C 70-<100mg/dl (N=8097; 4081 vs 4016) Sample size	n = 3040; % = 75	n = 3009; % =75
Baseline LDL-C 100-125 mg/dl (N=7422; 3707 vs 3715) Sample size	n = 2812; % = 76	n = 2833; % = 76
Mean age (SD)		
Baseline LDL-C 50-<70 mg/dl (N=2480; 1202 vs 1278)	67 (59 to 73)	66 (59 to 74)

Characteristic	Ezetimibe + simvastatin (N = 8990)	Simvastatin + placebo (N = 9009)
Median (IQR)		
Baseline LDL-C 70-<100mg/dl (N=8097; 4081 vs 4016) Median (IQR)	64 (58 to 71)	64 (57 to 72)
Baseline LDL-C 100-125 mg/dl (N=7422; 3707 vs 3715) Median (IQR)	62 (55 to 69)	62 (56 to 70)
Ethnicity: White		
Baseline LDL-C 50-<70 mg/dl (N=2480; 1202 vs 1278) Sample size	n = 1009; % = 84	n = 1066; % = 83
Baseline LDL-C 70-<100mg/dl (N=8097; 4081 vs 4016) Sample size	n = 3377; % = 83	n = 3339; % = 83
Baseline LDL-C 100-125 mg/dl (N=7422; 3707 vs 3715) Sample size	n = 3128; % = 84	n = 3156; % = 85
Type 2 diabetes		

Characteristic	Ezetimibe + simvastatin (N = 8990)	Simvastatin + placebo (N = 9009)
Baseline LDL-C 50-<70 mg/dl (N=2480; 1202 vs 1278) Sample size	n = 466 ; % = 39	n = 519 ; % = 41
Baseline LDL-C 70-<100mg/dl (N=8097; 4081 vs 4016) Sample size	n = 1245 ; % = 31	n = 1217 ; % = 30
Baseline LDL-C 100-125 mg/dl (N=7422; 3707 vs 3715) Sample size	n = 735 ; % = 20	n = 719 ; % = 19
LDL cholesterol		
Baseline LDL-C 50-<70 mg/dl Median (IQR)	62 (56 to 66)	62 (57 to 66)
Baseline LDL-C 70-<100mg/dl Median (IQR)	86 (79 to 93)	86 (79 to 93)
Baseline LDL-C 100-125 mg/dl Median (IQR)	113 (106 to 120)	113 (107 to 120)
Non-HDL cholesterol		

Characteristic	Ezetimibe + simvastatin (N = 8990)	Simvastatin + placebo (N = 9009)
Baseline LDL-C 50-<70 mg/dl Median (IQR)	85 (77 to 97)	85 (77 to 97)
Baseline LDL-C 70-<100mg/dl Median (IQR)	110 (101 to 122)	111 (101 to 122)
Baseline LDL-C 100-125 mg/dl Median (IQR)	138 (128 to 149)	138 (128 to 149)
Statins used (before ACS event)		
Baseline LDL-C 50-<70 mg/dl Sample size	n = 864; % = 72	n = 908; % = 71
Baseline LDL-C 70-<100mg/dl Sample size	n = 2001; % = 49	n = 1953; % = 49
Baseline LDL-C 100-125 mg/dl Sample size	n = 243; % = 7	n = 234; % = 6
Prior MI (before ACS event)		
Baseline LDL-C 50-<70 mg/dl Sample size	n= 471; % = 39	n=486; % = 38

Characteristic	Ezetimibe + simvastatin (N = 8990)	Simvastatin + placebo (N = 9009)
Baseline LDL-C 70-<100mg/dl Sample size	n = 1085; % = 27	n = 1035; % = 26
Baseline LDL-C 100-125 mg/dl Sample size	n = 353; % = 10	n = 346; % = 9
Prior PCI (before ACS event)		
Baseline LDL-C 50-<70 mg/dl Sample size	n = 441; % = 37	n= 475; % = 37
Baseline LDL-C 70-<100mg/dl Sample size	n = 1034; % = 25	n = 1006; % = 25
Baseline LDL-C 100-125 mg/dl Sample size	n = 277; % = 8	n = 304; % = 8
Prior CABG (before ACS event)		
Baseline LDL-C 50-<70 mg/dl Sample size	n = 215; % = 18	n = 221; % = 17
Baseline LDL-C 70-<100mg/dl Sample size	n = 490; % = 12	n = 484; % = 12

Characteristic	Ezetimibe + simvastatin (N = 8990)	Simvastatin + placebo (N = 9009)
Baseline LDL-C 100-125 mg/dl Sample size	n = 132; % = 4	n = 130; % = 4
Prior stroke/TIA (before ACS event)		
Baseline LDL-C 50-<70 mg/dl Sample size	n = 107; % = 9	n = 123; % = 10
Baseline LDL-C 70-<100mg/dl Sample size	n = 266; % = 7	n = 264; % = 7
Baseline LDL-C 100-125 mg/dl Sample size	n = 150; % = 4	n = 158; % = 4

Outcomes

Study timepoints

- Baseline
- 0 month (at randomisation)
- 4 month
- 6 year
- 7 year

Continuous outcomes

Outcome: Absolute LDL-C	Ezetimibe + simvastatin , Baseline, N = 8990	Ezetimibe + simvastatin , 0 month, N = 8990	Ezetimibe + simvastatin , 4 month, N =	Simvastatin + placebo, 0 month, N = 9009	Simvastatin + placebo, 4 month, N =
Baseline LDL-C (at ACS event): 50-<70 mg/dl Median (IQR)	62 (56 to 66)	61 (51 to 73)	44	61 (50 to 72)	61
Baseline LDL-C (at ACS event): 70-<100 mg/dl Median (IQR)	86 (79 to 93)	76 (64 to 89)	49	76 (64 to 90)	69
Baseline LDL-C (at ACS event): 100-125 mg/dl Median (IQR)	113 (106 to 120)	90 (75 to 106)	52	91 (76 to 107)	71

Absolute LDL-C value - Polarity - Lower values are better

Dichotomous outcomes

Outcome	Ezetimibe + simvastatin , 6 year, N = 8990	Ezetimibe + simvastatin , 7 year, N = 8990	Simvastatin + placebo, 6 year, N = 9009	Simvastatin + placebo, 7 year, N = 9009
CVD death, major coronary events or stroke				

Outcome	Ezetimibe + simvastatin , 6 year, N = 8990	Ezetimibe + simvastatin , 7 year, N = 8990	Simvastatin + placebo, 6 year, N = 9009	Simvastatin + placebo, 7 year, N = 9009
Baseline LDL-C 50-<70 mg/dl (N=2480; 1202 vs 1278) No of events	-	n = 390	-	n = 456
Baseline LDL-C 70-<100mg/dl (N=8097; 4081 vs 4016) No of events	-	n = 1253	-	n = 1307
Baseline LDL-C 100-125 mg/dl (N=7422; 3707 vs 3715) No of events	-	n = 911	-	n = 967
Outcome: Myopathy				
Baseline LDL-C 50-<70 mg/dl (N=2480; 1202 vs 1278) No of events	n = 2	-	n = 1	-
Baseline LDL-C 70-<100mg/dl (N=8097; 4081 vs 4016) No of events	n = 8	-	n = 4	-
Baseline LDL-C 100-125 mg/dl (N=7422; 3707 vs 3715)	n = 5	-	n = 5	-

Outcome	Ezetimibe + simvastatin , 6 year, N = 8990	Ezetimibe + simvastatin , 7 year, N = 8990	Simvastatin + placebo, 6 year, N = 9009	Simvastatin + placebo, 7 year, N = 9009
No of events				
Rhabdomyolysis				
Baseline LDL-C 50-<70 mg/dl (N=2480; 1202 vs 1278) No of events	n = 4	-	n = 2	-
Baseline LDL-C 70-<100mg/dl (N=8097; 4081 vs 4016) No of events	n = 5	-	n = 9	-
Baseline LDL-C 100-125 mg/dl (N=7422; 3707 vs 3715) No of events	n = 3	-	n = 7	-
ALT, AST, or both ≥3× ULN				
Baseline LDL-C 50-<70 mg/dl (N=2480; 1202 vs 1278) No of events	n = 35	-	n = 26	-
Baseline LDL-C 70-<100mg/dl (N=8097; 4081 vs 4016)	n = 101	-	n = 102	-

Outcome	Ezetimibe + simvastatin , 6 year, N = 8990	Ezetimibe + simvastatin , 7 year, N = 8990	Simvastatin + placebo, 6 year, N = 9009	Simvastatin + placebo, 7 year, N = 9009
No of events				
Baseline LDL-C 100-125 mg/dl (N=7422; 3707 vs 3715) No of events	n = 86	-	n = 78	-
Cancer				
Baseline LDL-C 50-<70 mg/dl (N=2480; 1202 vs 1278) No of events	n = 111	-	n = 115	-
Baseline LDL-C 70-<100mg/dl (N=8097; 4081 vs 4016) No of events	n = 328	-	n = 307	-
Baseline LDL-C 100-125 mg/dl (N=7422; 3707 vs 3715) No of events	n = 303	-	n = 306	-
Gall-bladder related adverse events				
Baseline LDL-C 50-<70 mg/dl (N=2480; 1202 vs 1278)	n = 28	-	n = 44	-

Outcome	Ezetimibe + simvastatin , 6 year, N = 8990	Ezetimibe + simvastatin , 7 year, N = 8990	Simvastatin + placebo, 6 year, N = 9009	Simvastatin + placebo, 7 year, N = 9009
No of events				
Baseline LDL-C 70-<100mg/dl (N=8097; 4081 vs 4016) No of events	n = 96	-	n = 91	-
Baseline LDL-C 100-125 mg/dl (N=7422; 3707 vs 3715) No of events	n = 74	-	n = 82	-

Cardiovascular death, major coronary events, or stroke - Polarity - Lower values are better

Myopathy - Polarity - Lower values are better

Rhabdomyolysis - Polarity - Lower values are better

ALT, AST, or both ≥3× ULN - Polarity - Lower values are better

Cancer - Polarity - Lower values are better

Gall-bladder-related adverse events - Polarity - Lower values are better

Hazard ratio

Outcome: Cardiovascular death, major coronary events, or stroke	Ezetimibe + simvastatin vs Simvastatin + placebo, 7 year, N2 = 8990, N1 = 9009
Baseline LDL-C 50-<70 mg/dl (N=2480; 1202 vs 1278) Hazard ratio/95% CI	0.92 (0.8 to 1.05)
Baseline LDL-C 70-<100mg/dl (N=8097; 4081 vs 4016) Hazard ratio/95% CI	0.93 (0.87 to 1.01)
Baseline LDL-C 100-125 mg/dl (N=7422; 3707 vs 3715) Hazard ratio/95% CI	0.94 (0.86 to 1.03)

Cardiovascular death, major coronary events, or stroke - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Absolute LDL-C value -4 months

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Not a prespecified end point and subgroup categories differ from those prespecified)*
Overall bias and Directness	Overall Directness	Ddirectly applicable

MACE - 7 years

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Subgroup categories differ from those prespecified)*
Overall bias and Directness	Overall Directness	Directly applicable

Myopathy

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Subgroup categories differ from those prespecified)*
Overall bias and Directness	Overall Directness	Directly applicable

Rhabdomyolysis

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Subgroup categories differ from those prespecified)*
Overall bias and Directness	Overall Directness	Directly applicable

ALT, AST, or both ≥3×ULN

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Subgroup categories differ from those prespecified)*
Overall bias and Directness	Overall Directness	Directly applicable

Cancer

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Subgroup categories differ from those prespecified)*
Overall bias and Directness	Overall Directness	Directly applicable

Gall-bladder-related adverse events

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Subgroup categories differ from those prespecified)*
Overall bias and Directness	Overall Directness	Directly applicable

MACE - HR

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Subgroup categories differ from those prespecified)*
Overall bias and Directness	Overall Directness	Directly applicable

Puri, 2016

Bibliographic Reference	Puri, Rishi; Nissen, Steven E; Somaratne, Ransi; Cho, Leslie; Kastelein, John J P; Ballantyne, Christie M; Koenig, Wolfgang; Anderson, Todd J; Yang, Jingyuan; Kassahun, Helina; Wasserman, Scott M; Scott, Robert; Borgman, Marilyn; Nicholls, Stephen J; Impact of PCSK9 inhibition on coronary atheroma progression: Rationale and design of Global Assessment of Plaque Regression with a PCSK9 Antibody as Measured by Intravascular Ultrasound (GLAGOV).; American heart journal; 2016; vol. 176; 83-92

Study details

Secondary publication of another included study- see primary study for details	Rationale and design of GLAGOV trial. Full details available in main trial entry (Nicholls 2016)

Raber, 2022

Bibliographic Reference	Raber, Lorenz; Ueki, Yasushi; Otsuka, Tatsuhiko; Losdat, Sylvain; Haner, Jonas D; Lonborg, Jacob; Fahrni, Gregor; Iglesias, Juan F; van Geuns, Robert-Jan; Ondracek, Anna S; Radu Juul Jensen, Maria D; Zanchin, Christian; Stortecky, Stefan; Spirk,

David; Siontis, George C M; Saleh, Lanja; Matter, Christian M; Daemen, Joost; Mach, Francois; Heg, Dik; Windecker, Stephan; Engstrom, Thomas; Lang, Irene M; Koskinas, Konstantinos C; PACMAN-AMI, collaborators; Effect of Alirocumab Added to High-Intensity Statin Therapy on Coronary Atherosclerosis in Patients With Acute Myocardial Infarction: The PACMAN-AMI Randomized Clinical Trial.; JAMA; 2022; vol. 327 (no. 18); 1771-1781

Study details

Other publications associated with this study included in review	Zanchin 2021 (trial rational and design)
Trial name / registration number	PACMAN-AMI/ NCT03067844
Study type	Randomised controlled trial (RCT)
Study location	Multicentre conducted in 9 European centres: Switzerland (5), Austria (1), Denmark (1) and the Netherlands (2)
Study setting	Primary care
Study dates	Enrolment: May 9, 2017, through October 7, 2020; final follow-up: October 13, 2021
Sources of funding	The study is supported by a grant to Bern University Hospital provided by Regeneron, Sanofi, and Infraredx. The grant providers were not involved in protocol writing, data acquisition, storage and analysis. Regeneron provided alirocumab and the matching placebo free of charge. One employee of Sanofi (DS) contributed to the trial conception, and also provided expertise on the investigational medicinal product, study material, and drug-related assay and equipment.

Inclusion criteria	Male or female, age ≥18 y at screening; Acute myocardial infarction: acute ST-segment elevation myocardial infarction (STEMI) with pain onset within ≤24 h, or non-ST segment elevation myocardial infarction (NSTEMI), with at least one coronary segment (culprit lesion) requiring PCI; LDL-C ≥70 mg/dl (≥1.8 mmol/l) assessed prior to, or during PCI in patients who have been receiving any stable statin regimen within ≥4 wk prior to enrolment; OR LDL-C ≥125 mg/dl (≥3.2 mmol/l) in patients who are statin-naïve or have not been on stable statin regimen for ≥4 wk prior to enrollment; At least two major native coronary arteries (“target vessels”) each meeting the following criteria for intracoronary imaging immediately following the qualifying PCI procedure: Angiographic evidence of <50% reduction in lumen diameter by angiographic visual estimation; Target vessel deemed to be accessible to imaging catheters and suitable for intracoronary imaging in the proximal (50mm) segment (“target segment”); Target vessel may not be a bypass (saphenous vein or arterial) graft or a bypassed native vessel; Target vessel must not have undergone previous PCI within the target segment; Target vessel is not candidate for intervention at the time of qualifying PCI or over the following 6 months in the judgment of the Investigator; Hemodynamic stability allowing the repetitive administration of nitroglycerine; Ability to understand the requirements of the study and to provide informed consent; Willingness of patient to undergo follow-up intracoronary imaging.
Exclusion criteria	Left-main disease, defined as ≥50% reduction in lumen diameter of the left main coronary artery by angiographic visual estimation; Three-vessel disease, defined as ≥70% reduction in lumen diameter of three major epicardial coronary arteries by angiographic visual estimation or in major branches of one or more of these arteries, irrespective of the localization (proximal 50mm or more distal localization) of the obstructive lesions; History of coronary artery bypass surgery; TIMI flow <2 of the infarct-related artery after PCI; Unstable clinical status (hemodynamic or electrical instability); Significant coronary calcification or tortuosity deemed to preclude IVUS, NIRS and OCT evaluation; Uncontrolled cardiac arrhythmia, defined as recurrent and symptomatic ventricular tachycardia or atrial fibrillation with rapid ventricular response not controlled by medications in the past 3 months prior to screening; Severe renal dysfunction, defined by estimated glomerular filtration rate <30 ml/min/1.73m2; Active liver disease or hepatic dysfunction; Known intolerance to rosuvastatin OR known statin intolerance; Known allergy to contrast medium, heparin, aspirin, ticagrelor or prasugrel; Known sensitivity to any substances to be administered, including known statin intolerance; Patients who previously received alirocumab or other PCSK9 inhibitor; Patient who received cholesterol ester transfer protein inhibitors in the past 12 months prior to screening; Treatment with systemic steroids or systemic cyclosporine in the past 3 months; Known active infection or major hematologic, metabolic, or endocrine dysfunction in the judgment of the Investigator; Planned surgery within 12 months; Patients who will not be available for study-required visits in the judgment of the Investigator; Current enrolment in another investigational device or drug study; History of cancer within the past 5 y, except for adequately treated basal cell skin cancer, squamous cell skin cancer, or in situ cervical cancer; Estimated life expectancy less than 1 y; Female of

	childbearing potential (age <50 y and last menstruation within the last 12 months), who did not undergo tubal ligation, ovariectomy or hysterectomy.
Recruitment / selection of participants	Patients who underwent clinically indicated percutaneous coronary intervention (PCI) for AMI (ST-elevation or non-ST-elevation myocardial infarction) were screened for clinical and anatomic eligibility for study participation.
Intervention(s)	Alirocumab 150 mg, administered subcutaneously bi-weekly via injection, initiated less than 24 hours after urgent percutaneous coronary intervention of the culprit lesions, as add on to rosuvastatin 20 mg/d (high-intensity-statin); without dose adjustments during the study period.
Comparator	Placebo administered biweekly via subcutaneous injection + rosuvastatin 20 mg/d, without change in type or dose of statin during the course of the study
Background treatment	Rosuvastatin 20 mg/d
Number of participants	300
Duration of follow-up	52 weeks
Additional comments	Blood samples were obtained prior to PCI, at week 4, and week 52. Blood samples were immediately processed and stored at −80 °C locally and subsequently transferred to a central biobank. All central biochemical analyses were conducted by the Department of Clinical Chemistry, University of Zurich, Switzerland. Statistical comparisons between groups were performed using mixed-effect models by fitting the interaction between group (alirocumab or placebo) and time point (baseline or follow-up) as fixed effects and patient identity as the random effect. These models account for repeated measures for a given vessel (baseline and follow-up) and for the multiple vessels imaged per patient. For biomarker secondary end points, statistical comparisons between groups were performed using mixed-effect repeated models at the patient level. The difference between treatments is reported as the marginal difference

	(with 95% CIs) computed from the mixed-effect models. The primary analysis was performed on the full analysis set, which included all patients with available serial IVUS data. Patients were analysed according to their randomization group. Patients with missing data were excluded from the primary analysis. The stratification variables used in the stratified randomization were not included in the model for the primary analysis; stratification variables were included in a post hoc sensitivity analysis, with type of myocardial infarction (STEMI vs NSTEMI) and use of stable (≥4 weeks) statin treatment at presentation (yes vs no) fitted as fixed effects and site identity as a random intercept. Analyses for the secondary end points were performed in the full analysis set excluding patients with missing serial data for the considered end point (imaging or biomarker). For binary outcomes, treatment groups were compared using logistic regression. Analyses of adverse events included patients who received at least 1 administration of the study drug. Adverse events were summarized per treatment group by keeping only the first event of each type per patient.

Study arms

Alirocumab + Statin (N = 148)

150 mg, administered subcutaneously bi-weekly via injection plus rosuvastatin 20mg/d

Placebo + statin (N = 152)

Placebo administered biweekly via subcutaneous injections plus rosuvastatin 20mg/d

Characteristics

Arm-level characteristics

Characteristic	Alirocumab + Statin (N = 148)	Placebo + statin (N = 152)
% Female	n = 24 ; % = 16.2	n = 32 ; % = 21.1
Sample size		

Characteristic	Alirocumab + Statin (N = 148)	Placebo + statin (N = 152)
Mean age (SD) Mean (SD)	58.4 (10)	58.6 (9.4)
Existing CVD diagnosis		
Previous myocardial infarction Sample size	n = 2 ; % = 1.4	n = 5 ; % = 3.3
Previous percutaneous coronary intervention Sample size	n = 2 ; % = 1.4	n = 4 ; % = 2.6
Peripheral arterial disease Sample size	n = 2 ; % = 1.4	n = 4 ; % = 2.6
LDL cholesterol (mg/dl) Alirocumab (n=126)/ Placebo (n=132) in people completing the 52-week follow-up Mean (SD)	154.8 (30.9)	150.9 (36.3)
Non-HDL cholesterol Alirocumab (n=126)/ Placebo (n=132) in people completing the 52-week follow-up Mean (SD)	165.7 (34.5)	162.9 (35.3)
Statins used Sample size	n = 17 ; % = 11.5	n = 20 ; % = 13.2

Characteristic	Alirocumab + Statin (N = 148)	Placebo + statin (N = 152)
High-intensity statin Atorvastatin ≥40 mg or rosuvastatin ≥20 mg Sample size	n = 11 ; % = 7.4	n = 9 ; % = 5.9
Other lipid-lowering medication used Ezetimibe Sample size	n = 0 ; % = 0	n = 1 ; % = 0.7
Diabetes Sample size	n = 12 ; % = 8.1	n = 19 ; % = 12.5
Insulin-dependent diabetes Sample size	n = 4 ; % = 2.7	n = 4 ; % = 2.6
NSTEMI Sample size	n = 70 ; % = 47.3	n = 72 ; % = 47.4
STEMI Sample size	n = 78 ; % = 52.7	n = 80 ; % = 52.6
Angiotensin receptor blocker Sample size	n = 20 ; % = 13.5	n = 21 ; % = 13.8
Antiplatelet therapy	n = 14 ; % = 9.5	n = 17 ; % = 11.2

Characteristic	Alirocumab + Statin (N = 148)	Placebo + statin (N = 152)
Sample size		
β-Blockers Sample size	n = 12 ; % = 8.1	n = 17 ; % = 11.2
Angiotensin converting enzyme inhibitor Sample size	n = 12 ; % = 8.1	n = 12 ; % = 7.9

Outcomes

Study timepoints

- 52 week

Lipid outcomes at 52 weeks

Outcome	Alirocumab + Statin, 52 week, N = 126	Placebo + statin, 52 week, N = 132
LDL-c (mg/dl) Mean (SD)	23.6 (23.8)	74.4 (30.5)
non-HDL-C (mg/dl) Mean (SD)	36.1 (27.3)	94.4 (32.2)

LDL-c - Polarity - Lower values are better

non-HDL-C - Polarity - Lower values are better

In people completing the 52 week follow-up (Alirocumab n=126; Placebo n=132); Blood samples were obtained prior to PCI, at week 4, and week 52. Blood samples were immediately processed and stored at −80 °C locally and subsequently transferred to a central biobank. All central biochemical analyses were conducted by the Department of Clinical Chemistry, University of Zurich, Switzerland.

Absolute change in lipid outcomes from baseline to week 52

Outcome	Alirocumab + Statin, 52 week, N = 126	Placebo + statin, 52 week, N = 132
LDL-c (mg/dl) Mean (95% CI)	-131.2 (-137 to -125.4)	-76.5 (-83.2 to -69.8)
non-HDL-C (mg/dl) Mean (95% CI)	-129.7 (-136 to -123.3)	-68.5 (-75 to -61.9)

LDL-c - Polarity - Lower values are better

non-HDL-C - Polarity - Lower values are better

Analyses were performed on the full analysis set (265 patients), but 7 patients were excluded due to missing serial biomarker data (258 patients included in the biomarker analyses). Difference in change between groups are marginal differences (95% CI) computed from mixed-effect models.

Absolute change in lipid outcomes from baseline to week 52 (between group difference)

Outcome	Alirocumab + Statin vs Placebo + statin, 52 week, N2 = 126, N1 = 131
Difference in absolute change in LDL-C (mg/dl) Mean (95% CI)	-54.7 (-63.5 to -45.9)

Outcome	Alirocumab + Statin vs Placebo + statin, 52 week, N2 = 126, N1 = 131
Difference in absolute change in non-HDL-C (mg/dl) Mean (95% CI)	-61.2 (-70.2 to -52.1)

Difference in absolute change in LDL-C - Polarity - Lower values are better

Difference in absolute change in non-HDL-C - Polarity - Lower values are better

Analyses were performed on the full analysis set (265 patients), but 7 patients were excluded due to missing serial biomarker data (258 patients included in the biomarker analyses). Difference in change between groups are marginal differences (95% CI) computed from mixed-effect models.

Adverse events

Outcome	Alirocumab + Statin, 52 week, N = 147	Placebo + statin, 52 week, N = 151
Local injection-site reactions No of events	n = 9 ; % = 6.1	n = 5 ; % = 3.3

Local injection-site reactions - Polarity - Lower values are better

In population who received at least one dose of the study drug; reported as number of people (%)

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

LDL-c at 52 wk

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

non-HDL-C-at 52 wk

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Absolute change LDL-c

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Absolute change non-HDL-C

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Absolute change (between group difference)-LDL-C

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Absolute change (between group difference) non-HDL-C

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Local injection-site reactions

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Ran, 2017

Bibliographic Reference	Ran, Dan; Nie, Hui-Juan; Gao, Yu-Lin; Deng, Song-Bai; Du, Jian-Lin; Liu, Ya-Jie; Jing, Xiao-Dong; She, Qiang; A randomized, controlled comparison of different intensive lipid-lowering therapies in Chinese patients with non-ST-elevation acute coronary

syndrome (NSTE-ACS): Ezetimibe and rosuvastatin versus high-dose rosuvastatin.; International journal of cardiology; 2017; vol. 235; 49-55

Study details

Trial name / registration number	ChiCTR-IPR-15006636.
Study type	Randomised controlled trial (RCT)
Study location	China
Study setting	Second Affiliated Hospital of Chongqing Medical University.
Study dates	July 2015 to June 2016.
Sources of funding	No funding support.
Inclusion criteria	At least 18 years old and hospitalised within the last 10 days for non-ST segment elevation acute coronary syndrome (including unstable angina and no -ST-elevation myocardial infarction). Diagnosis based on the AHA/ACC guideline and the specific diagnostic criteria were: resting state angina with a duration of 10 to more than 20 minutes ; newly discovered angina within one month, angina deterioration within 1 month with more frequent seizure, more serious pain, or longer duration of pain, variant angina pectoris, angina attack (electrocardiogram decreases ≥ 0.1mV for at least 2 adjacent ST segments or transient ST-segment elevation). Non-ST segment elevation myocardial infarction is angina with increased biomarkers of myocardial necrosis (≥ 2 times the upper limit of normal in the blood)
Exclusion criteria	Has received lipid-lowering therapy within 6 months, severe congestive heart failure, alanine transaminase and aspartate aminotransferase ≥ 3 upper limit of normal, renal insufficiency (serum creatinine > 176 mmol/l), unexplained elevated creatinine kinase ≥1 upper limit of normal, current use of medication that interacts with statins and /or ezetimibe.

Recruitment / selection of participants	Consecutive patients undergoing percutaneous coronary intervention for non-ST-elevation acute coronary syndrome (NSTE-ACS) at the hospital were screened.
Population subgroups	No additional information.
Intervention(s)	Ezetimibe 10 mg/day and rosuvastatin 10 mg/day (high intensity statin).
Comparator	Rosuvastatin 10 mg/day (high intensity statin).
Background treatment	There was another arm that received rosuvastatin 20 mg/day that was not extracted or included in the analysis. All eligible participants were treated with standard non-ST-elevation acute coronary syndrome drugs including aspirin, clopidogrel, B-blocker and angiotensin-converting enzyme inhibitors/angiotensin II receptor antagonists. Lipid lowering therapies started the day after percutaneous coronary intervention within 24 hours. Laboratory tests including lipid levels, high sensitivity C-reactive protein, liver and renal function tests, and CK were performed prior to intervention and at week 4 and 12. Baseline: **Ezetimibe and rosuvastatin:** Aspirin: 41 (97.6%) Clopidogrel: 37 (88.1%) ACEI and ARB: 29 (69.0%) B-Blocker: 39 (92.9%) Smoking: 23 (54.8%) Hypertension: 21 (50.0%)

	Rosuvastatin: Aspirin: 40 (95.2%) Clopidogrel: 38 (90.5%) ACEI and ARB: 32 (76.2%) B-Blocker: 38 (90.5%) Smoking: 21 (50.0%) Hypertension: 19 (45.2%)
Number of participants	125 (analysed 84)
Duration of follow-up	12 weeks.
Indirectness	No indirectness.
Additional comments	Intention to treat analysis.

Study arms

Ezetimibe and Rosuvastatin (N = 42)

Ezetimibe 10 mg/day and rosuvastatin 10 mg/day (high intensity statin).

Rosuvastatin (N = 42)

Rosuvastatin 10 mg/day (high intensity statin).

Characteristics

Arm-level characteristics

Characteristic	Ezetimibe and Rosuvastatin (N = 42)	Rosuvastatin (N = 42)
% Female Sample size	n = 10 ; % = 23.8	n = 11 ; % = 26.2
Mean age (SD) Mean (SD)	60.4 (8.2)	60.6 (6.7)
Ethnicity Nominal	NR	NR
Existing CVD disease		
Non-ST elevate myocardial infarction Sample size	n = 14 ; % = 33.3	n = 10 ; % = 23.8
Unstable angina Sample size	n = 28 ; % = 66.7	n = 32 ; % = 76.2

Characteristic	Ezetimibe and Rosuvastatin (N = 42)	Rosuvastatin (N = 42)
Stroke Sample size	n = 5 ; % = 11.9	n = 3 ; % = 7.1
Type 2 diabetes Actual outcome: Diabetes (type not specified) Sample size	n = 11 ; % = 26.2	n = 10 ; % = 23.8
Chronic kidney disease Sample size	n = NR ; % = NR	n = NR ; % = NR
Statins used Sample size	n = NR ; % = NR	n = NR ; % = NR
Other lipid lowering drugs Sample size	n = NR ; % = NR	n = NR ; % = NR

Outcomes

Study timepoints

- Baseline
- 12 week

Continuous - lipids at 12 weeks

Outcome	Ezetimibe and Rosuvastatin, Baseline, N = 42	Ezetimibe and Rosuvastatin, 12 week, N = 42	Rosuvastatin , Baseline, N = 42	Rosuvastatin , 12 week, N = 42
LDL cholesterol (mg/dl) Mean (SD)	141 (27)	46 (17)	141 (33)	77 (17)
Non-HDL cholesterol (mg/dl) Mean (SD)	166 (30)	68 (30)	165 (35)	108 (23)
% Change LDL Cholesterol (mg/dl) (%) Adjusted mean Nominal	NA	-67.28	NA	43.89

LDL cholesterol - Polarity - Lower values are better

Non-HDL cholesterol - Polarity - Lower values are better

% Change LDL Cholesterol (mg/dl) - Polarity - Higher values are better (greater reduction is better)

Dichotomous - adverse events at 12 weeks

Outcome	Ezetimibe and Rosuvastatin, Baseline, N = 42	Ezetimibe and Rosuvastatin, 12 week, N = 42	Rosuvastatin , Baseline, N = 42	Rosuvastatin , 12 week, N = 42
Rhabdomyolysis No of events	n = NA ; % = NA	n = 0 ; % = 0	n = NA ; % = NA	n = 0 ; % = 0

Outcome	Ezetimibe and Rosuvastatin, Baseline, N = 42	Ezetimibe and Rosuvastatin, 12 week, N = 42	Rosuvastatin , Baseline, N = 42	Rosuvastatin , 12 week, N = 42
Liver enzyme elevation No of events	n = NA ; % = NA	n = 0 ; % = 0	n = NA ; % = NA	n = 0 ; % = 0

Rhabdomyolysis - Polarity - Lower values are better

Liver enzyme elevation - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

LDL cholesterol

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Bias due to randomisation process – unclear allocation concealment)*
Overall bias and Directness	Overall Directness	Directly applicable

Non-HDL cholesterol

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Bias due to randomisation process – unclear allocation concealment)*
Overall bias and Directness	Overall Directness	Directly applicable

% Change LDL Cholesterol

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Bias due to randomisation process – unclear allocation concealment)*
Overall bias and Directness	Overall Directness	Directly applicable

Rhabdomyolysis

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Bias due to randomisation process – unclear allocation concealment)*
Overall bias and Directness	Overall Directness	Directly applicable

GI discomfort

Liver enzyme elevation

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Bias due to randomisation process – unclear allocation concealment)*
Overall bias and Directness	Overall Directness	Directly applicable

Ray, 2019

Bibliographic Reference	Ray, Kausik K; Del Prato, Stefano; Muller-Wieland, Dirk; Cariou, Bertrand; Colhoun, Helen M; Tinahones, Francisco J; Domenger, Catherine; Letierce, Alexia; Mandel, Jonas; Samuel, Rita; Bujas-Bobanovic, Maja; Leiter, Lawrence A; Alirocumab therapy in individuals with type 2 diabetes mellitus and atherosclerotic cardiovascular disease: analysis of the ODYSSEY DM-DYSLIPIDEMIA and DM-INSULIN studies.; Cardiovascular diabetology; 2019; vol. 18 (no. 1); 149

Study details

Other publications associated with this study included in review	Muller-Wieland 2017 (trial design and rationale)
Trial name / registration number	ODYSSEY DM-DYSLIPIDEMIA (NCT02642159) and DM-INSULIN (NCT02585778).

Study type	Randomised controlled trial (RCT)
Study location	DM-INSULIN: multicentre trial
Study setting	Primary/secondary care
Study dates	DM-DYSLIPIDEMIA: recruitment began in March 2016
Sources of funding	Sanofi and Regeneron Pharmaceuticals, Inc
Inclusion criteria	Individuals with established ASCVD receiving maximally tolerated statin who were enrolled in the DM-DYSLIPIDEMIA and DM-INSULIN studies. ASCVD was defined as coronary heart disease (CHD; acute and silent MI, and unstable angina), ischemic stroke, or peripheral artery disease (PAD). DM-DYSLIPIDEMIA: Individuals (n=413) aged≥18 years with T2DM and mixed dyslipidemia whose non-HDL-C level was not adequately controlled (≥100 mg/dl [>2.59 mmol/l]) despite stable maximally tolerated statin dose for≥4 weeks prior to screening visit, without other lipid-lowering therapies (LLTs), and who had either a documented history of ASCVD and/or at least one additional CV risk factor were included. Mixed dyslipidaemia was defined as non-HDL-C≥100 mg/dl (≥2.59 mmol/l) and triglycerides≥150 mg/dl (≥1.70 mmol/l) and<500 mg/dl (<5.65 mmol/l). Study participants were also required to have a glycated haemoglobin (HbA1c) level of<9% (74.9 mmol/mol). DM-INSULIN: insulin-treated individuals aged≥18 years with T2DM (n=441) or type 1 diabetes mellitus (T1DM; n=76) diagnosed≥1 year prior to screening, and who had either a documented history of ASCVD and/or at least one additional CV risk factor; HbA1c level<10% (86 mmol/mol).
Exclusion criteria	DM-INSLUNI: Participants with T1DM were not included in the current analysis due to the low number of individuals with established ASCVD in this group (alirocumab: n=11; placebo: n=5).
Recruitment / selection of participants	Meeting inclusion criteria

Population subgroups	None explore; Majority no LLTs other than statins, Statin intensity mixed: majority had been on high-intensity statins except for one Alirocumab group where 50% were on moderate intensity statins.
Intervention(s)	1) Alirocumab 75 mg (with blinded dose increase to 150 mg at week 12 if week 8 non-HDL-C was≥100 mg/dl [≥2.59 mmol/l]) administered subcutaneously every 2 weeks. 2) Alirocumab 75 mg every 2 weeksevery 2 weeks, with blinded dose increase to 150 mg every 2 weeks at week 12 if week 8 LDL-C was≥70 mg/ dL (≥1.81 mmol/l).
Comparator	1) usual care (UC) every 2 weeks; with UC options selected before stratified randomization based on the investigator's preference for each participant. The following five UC options were included in the study: continued use of maximally tolerated statin therapy with no additional LLT, fenofibrate, ezetimibe, omega-3 fatty acid, and nicotinic acid, reflecting variability in regional practice and therapeutic options available at the time the study was conducted. 2) Placebo
Background treatment	DM-DYSLIPIDEMIA: stable maximally tolerated statin dose for≥4 weeks prior to screening visit, without other lipid-lowering therapies (LLTs), DM-INSULIN: Statins and other LLTs remained stable throughout the duration of the study.
Number of participants	142 individuals from the DM-DYSLIPIDEMIA trial and 177 individuals from the DM-INSULIN trial (all of whom had established ASCVD and T2DM)
Duration of follow-up	24 weeks in each trial
Indirectness	Small % (less than 10% in each group) was on low intensity statins
Additional comments	Due to the substantial differences in the patient populations from DM-DYSLIPIDEMIA and DM-INSULIN, as well as the methodological differences between the two studies, efficacy was analysed separately. The efficacy analysis included week 24 percentage reduction from baseline in non-HDL-C, calculated LDL-C, ApoB, triglyceride-rich lipoproteins (TGRL), and

	LDL-PN; the percentage of individuals achieving non-HDL-C<100 mg/dl (<2.59 mmol/l), LDL-C<70 mg/dl (<1.81 mmol/l), and ApoB<80 mg/dl at week 24. TGRL was defined as non-HDL-C minus measured LDL-C if measured LDL-C not missing; non-HDL-C minus calculated LDL-C if measured LDL-C missing and calculated LDL-C not missing, using fasting samples first, or if fasting sample missing using non-fasting measurements. Efficacy data were analysed with an intention-to-treat approach, including all randomized individuals with a non-HDL-C (DM-DYSLIPIDEMIA) or LDL-C (DM-INSULIN) value at baseline and at least one value post-baseline up to week 24. Safety data were pooled due to the small sample size, however, separate adverse event outcomes are also reported. Percent changes from baseline in non-HDL-C, HDL-C, LDL-C, Apo-B and LDL-PN at week 24 were derived and compared between treatment groups using a mixed-effects model with repeated measures (MMRM), which accounts for missing data and utilizes every lipid values at week 0, 8, 12, 20 and 24. For TGRL, as normal distribution assumption wasn't satisfied, their percent changes from baseline were estimated by robust regressions preceded by multiple imputations to handle missing data: combined estimates for means and standard errors (SE) are obtained by combining adjusted means and SE from robust regression model analyses of the different imputed datasets, using Rubin formulae. The proportion of individuals achieving the different goals at week 24 were analysed by multiple imputation followed by a logistic regression: the logistic regression included the treatment group and the UC stratum (for DM-DYSLIPIDEMIA) as main effects and the corresponding baseline value as covariate. Missing values were addressed using a multiple imputation approach and the logistic regressions were repeatedly performed in the datasets containing both observed and imputed lipid values and combined using Rubin formulae to allow for the treatment comparison. Analyses were in the intention-to-treat populations and for DM-DYSLIPIDEMIA, analyses are adjusted on the UC stratum. Descriptive analyses were performed for baseline, other efficacy, and safety analyses.

Study arms

Alirocumab DM-DYSLIPIDEMIA (N = 95)

Alirocumab 75 mg (with blinded dose increase to 150 mg at week 12 if week 8 non-HDL-C was≥100 mg/dl [≥2.59 mmol/l])

Usual care DM-DYSLIPIDEMIA (N = 47)

Alirocumab DM-INSULIN (N = 119)

Placebo DM-INSULIN (N = 58)

Characteristics

Arm-level characteristics

Characteristic	Alirocumab DM-DYSLIPIDEMIA (N = 95)	Usual care DM-DYSLIPIDEMIA (N = 47)	Alirocumab DM-INSULIN (N = 119)	Placebo DM-INSULIN (N = 58)
% Female Sample size	n = 30 ; % = 31.6	n = 16 ; % = 34	n = 40 ; % = 33.6	n = 26 ; % = 44.8
Mean age (SD) Mean (SD)	64.9 (9.1)	65.4 (8.1)	66.2 (8.7)	64.9 (8.9)
Existing CVD diagnoses Coronary heart disease Sample size	n = 90 ; % = 94.7	n = 45 ; % = 95.7	n = 102 ; % = 85.7	n = 51 ; % = 87.9
Acute MI Sample size	n = 43 ; % = 45.3	n = 20 ; % = 42.6	n = 59 ; % = 49.6	n = 18 ; % = 31
Silent MI Sample size	n = 5 ; % = 5.3	n = 1 ; % = 2.1	n = 4 ; % = 3.4	n = 4 ; % = 6.9

Characteristic	Alirocumab DM-DYSLIPIDEMIA (N = 95)	Usual care DM-DYSLIPIDEMIA (N = 47)	Alirocumab DM-INSULIN (N = 119)	Placebo DM-INSULIN (N = 58)
Unstable angina Sample size	n = 15 ; % = 15.8	n = 9 ; % = 19.1	n = 15 ; % = 12.6	n = 4 ; % = 6.9
Coronary revascularisation Sample size	n = 77 ; % = 81.1	n = 35 ; % = 74.5	n = 80 ; % = 67.2	n = 37 ; % = 63.8
Other clinically significant CHD Sample size	n = 20 ; % = 21.1	n = 14 ; % = 29.8	n = 31 ; % = 26.1	n = 15 ; % = 25.9
Ischemic Stroke Sample size	n = 14 ; % = 14.7	n = 5 ; % = 10.6	n = 27 ; % = 22.7	n = 9 ; % = 15.5
Peripheral artery disease Sample size	n = 6 ; % = 6.3	n = 4 ; % = 8.5	n = 13 ; % = 10.9	n = 6 ; % = 10.3
Chronic kidney disease Sample size	n = 15 ; % = 15.8	n = 11 ; % = 23.4	n = 37 ; % = 31.1	n = 13 ; % = 22.4
Type 2 diabetes Sample size	n = 95 ; % = 100	n = 47 ; % = 100	n = 119 ; % = 100	n = 58 ; % = 100

Characteristic	Alirocumab DM-DYSLIPIDEMIA (N = 95)	Usual care DM-DYSLIPIDEMIA (N = 47)	Alirocumab DM-INSULIN (N = 119)	Placebo DM-INSULIN (N = 58)
LDL cholesterol mg/dl Mean (SD)	108.3 (46.3)	109.4 (44)	107.2 (35.1)	111.9 (46.4)
Non-HDL cholesterol (mg/dl) Mean (SD)	156.5 (48.4)	156.8 (43.3)	142.8 (41.5)	147 (54.9)
Statins used Sample size	n = 80 ; % = 84.8	n = 41 ; % = 87.2	n = 92 ; % = 77.3	n = 42 ; % = 72.4
Low intensity Sample size	n = 6 ; % = 7.5	n = 0 ; % = 0	n = 3 ; % = 3.3	n = 1 ; % = 2.4
Moderate intensity Sample size	n = 21 ; % = 26.3	n = 20 ; % = 48.8	n = 46 ; % = 50	n = 24 ; % = 57.1
High-intensity statin Sample size	n = 53 ; % = 66.3	n = 21 ; % = 51.2	n = 43 ; % = 46.7	n = 16 ; % = 38.1
Other lipid-lowering medication used Sample size	n = 0 ; % = 0	n = 2 ; % = 4.3	n = 34 ; % = 28.6	n = 11 ; % = 19

Outcomes

Study timepoints

- 24 week (Treatment-emergent adverse events were defined as any event that developed, worsened or became serious during the period from first to last open-label dose of alirocumab plus 70 days (if randomized to alirocumab) or, if randomized to UC, 70 days after the last UC treatment or study day 225 (whichever came first).)

Adverse events

Outcome	Alirocumab DM-DYSLIPIDEMIA, 24 week, N = 95	Usual care DM-DYSLIPIDEMIA, 24 week, N = 47	Alirocumab DM-INSULIN, 24 week, N = 118	Placebo DM-INSULIN, 24 week, N = 57
Influenza number of people No of events	n = 3 ; % = 3.2	n = 3 ; % = 6.4	n = 4 ; % = 3.4	n = 1 ; % = 1.8
Nausea number of people No of events	n = 2 ; % = 2.1	n = 1 ; % = 2.1	n = 2 ; % = 1.7	n = 2 ; % = 3.5

Influenza - Polarity - Lower values are better

Nausea - Polarity - Lower values are better

Lipid outcomes

Outcome	Alirocumab DM-DYSLIPIDEMIA vs Usual care DM-DYSLIPIDEMIA, 24 week, N2 = 94, N1 = 47	Alirocumab DM-INSULIN vs Placebo DM-INSULIN, 24 week, N2 = 115, N1 = 55
LDL-C % change from baseline LS mean difference (SE; 95% CI) vs control Custom value	-45.9 (5.8; 95% CI -57.2 to -34.6)	-48.5 (4.4; 95% CI -57.1 to 39.9)
LDL-C % change from baseline LS mean difference (SE; 95% CI) vs control Mean (SE)	-45.9 (5.8)	-48.5 (4.4)
Non-HDL-C % change from baseline LS mean (SE; 95% CI) vs control Custom value	-31.1 (4.3; 95% CI -39.6 to -22.7)	-37.4 (3.9; 95% CI -4.5 to 29.8)
Non-HDL-C % change from baseline LS mean (SE; 95% CI) vs control Mean (SE)	-31.1 (4.3)	-37.4 (3.9)

LDL-C % change from baseline - Polarity - Higher values are better (greater reduction is better)

Non-HDL-C % change from baseline - Polarity - Higher values are better (greater reduction is better)

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Influenza

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(In DM DYSLIPIDEMIA study, usual care was based on investigators preference and this was an open-label study; However this was determined before randomisation but info on randomisation process is also limited)*
Overall bias and Directness	Overall Directness	Partially applicable *(<10% on low intensity statins)*

Nausea

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(In DM DYSLIPIDEMIA study, usual care was based on investigators preference and this was an open-label study; However this was determined before randomisation but info on randomisation process is also limited)*
Overall bias and Directness	Overall Directness	Partially applicable *(<10% on low intensity statins)*

LDL-C % change from baseline

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(In DM DYSLIPIDEMIA study, usual care was based on investigators preference and this was an open-label study; However this was determined before randomisation but info on randomisation process is also limited)*
Overall bias and Directness	Overall Directness	Partially applicable *(<10% on low intensity statins)*

Non-HDL-C % change from baseline

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(In DM DYSLIPIDEMIA study, usual care was based on investigators preference and this was an open-label study; However this was determined before randomisation but info on randomisation process is also limited)*
Overall bias and Directness	Overall Directness	Partially applicable *(<10% on low intensity statins)*

Ray, 2020

Bibliographic Reference	Ray, Kausik K; Wright, R Scott; Kallend, David; Koenig, Wolfgang; Leiter, Lawrence A; Raal, Frederick J; Bisch, Jenna A; Richardson, Tara; Jaros, Mark; Wijngaard, Peter L J; Kastelein, John J P; ORION-10 and ORION-11, Investigators; Two Phase 3 Trials of Inclisiran in Patients with Elevated LDL Cholesterol.; The New England journal of medicine; 2020; vol. 382 (no. 16); 1507-1519

Study details

Trial name / registration number	ORION-10: NCT03399370 ORION-11: NCT03400800
Study type	Randomised controlled trial (RCT)
Study location	ORION-10: USA ORION-11: Czech Republic, Germany, Hungary, Poland, South Africa, Ukraine and the United Kingdom
Study setting	Outpatient care
Study dates	ORION-10: Dec 2017 - Sept 2019 ORION-11: Nov 2017 - Aug 2019
Sources of funding	The Medicines Company
Inclusion criteria	• Age ≥18 years • History of ASCVD (CHD, CVD or PAD) or, in ORION-11, ASCVD-risk equivalents (type 2 diabetes, familial hypercholesterolemia, and 10-year risk of a CV event by Framingham Risk Score for Cardiovascular Disease or equivalent with a target LDL-C of <100 mg/dl). • Serum LDL-C ≥1.8 mmol/l (≥70 mg/dl) for ASCVD subjects or ≥2.6 mmol/l (≥100 mg/dl) for ASCVD-risk equivalent subjects at screening • Fasting triglyceride <4.52 mmol/l (<400 mg/dl) at screening • Calculated glomerular filtration rate >30 mL/min/ 1.73 m2 by eGFR. • Maximum tolerated dose of statin.

	• Any lipid-lowering therapies (such as a statin and/or ezetimibe) should be at a stable dose for ≥30 days before screening.
Exclusion criteria	• New York Heart Association (NYHA) class IV heart failure or last known left ventricular ejection fraction <25%. • Cardiac arrhythmia within 3 months prior to randomization that is not controlled by medication or via ablation. • Major adverse cardiovascular event within 3 months prior to randomization • Uncontrolled severe hypertension • Active liver disease • Patients receiving treatment with monoclonal antibodies directed toward PCSK9 within 90 days before screening were excluded.
Recruitment / selection of participants	Meeting inclusion criteria and none of the exclusion criteria
Intervention(s)	Inclisiran (284 mg) as a 1.5-ml subcutaneous injection - four injections: day 1, day 90, day 270, and day 450
Comparator	Matching placebo
Background treatment	ORION-10: 89% on statins and 9.9% ezetimibe ORION-11: 95% on statins and 7.1% ezetimibe The majority of patients received high-intensity statins (68.0% and 78.6%, respectively).
Number of participants	ORION-10: 1561 ORION-11: 1617

Duration of follow-up	Patients attended the clinic on days 1, 30, 90, 150, 270, 330, 450 and 510 for follow- up and laboratory assessments. The end-of-trial visit was on day 540.
Indirectness	
Additional comments	ITT Calculated LDL cholesterol was derived from the Friedewald formula

Study arms

ORION-10: inclisiran (N = 781)

ORION-10: placebo (N = 780)

ORION-11: inclisiran (N = 810)

ORION-11: placebo (N = 807)

Characteristics

Arm-level characteristics

Characteristic	ORION-10: inclisiran (N = 781)	ORION-10: placebo (N = 780)	ORION-11: inclisiran (N = 810)	ORION-11: placebo (N = 807)
% Female Sample size	n = 246 ; % = 31.5	n = 232 ; % = 29.7	n = 231 ; % = 28.5	n = 226 ; % = 28
Mean age (SD) Mean (SD)	66.4 (8.9)	65.7 (8.9)	64.8 (8.3)	64.8 (8.7)
Ethnicity **White** Sample size	n = 653 ; % = 83.6	n = 685 ; % = 87.8	n = 791 ; % = 97.7	n = 796 ; % = 98.6
Any ASCVD Sample size	n = 781 ; % = 100	n = 780 ; % = 100	n = 712 ; % = 87.9	n = 702 ; % = 87
Type 2 diabetes **'diabetes'** Sample size	n = 371 ; % = 47.5	n = 331 ; % = 42.4	n = 296 ; % = 36.5	n = 272 ; % = 33.7
LDL cholesterol (mg/dl) **mean of the values at screening and before receipt of first trial dose** Mean (SD)	104.5 (39.6)	104.8 (37)	107.2 (41.8)	103.7 (36.4)

Non-HDL cholesterol (mg/dl) **mean of the values at screening and before receipt of first trial dose** Mean (SD)	134 (44.5)	134.7 (43.5)	137.6 (46.9)	133.9 (41)
Any statin Sample size	n = 701 ; % = 89.8	n = 692 ; % = 88.7	n = 766 ; % = 94.6	n = 766 ; % = 94.9
High intensity statin **Atorvastatin 40 – 80 mg; Rosuvastatin 20 – 40 mg; Simvastatin 80mg** Sample size	n = 525 ; % = 67.2	n = 537 ; % = 68.8	n = 640 ; % = 79	n = 631 ; % = 78.2
Other lipid-lowering medication used **Ezetimibe** Sample size	n = 80 ; % = 10.2	n = 74 ; % = 9.5	n = 52 ; % = 6.3	n = 62 ; % = 7.7

Outcomes

Study timepoints

- Baseline
- 510 day
- 540 day (Time-adjusted change after day 90 up to day 540; used as primary analysis for lipid outcomes)

Between-group difference

Outcome	ORION-10: inclisiran vs ORION-10: placebo, 510 day, N2 = 781, N1 = 780	ORION-10: inclisiran vs ORION-10: placebo, 540 day, N2 = 781, N1 = 780	ORION-11: inclisiran vs ORION-11: placebo, 510 day, N2 = 810, N1 = 807	ORION-11: inclisiran vs ORION-11: placebo, 540 day, N2 = 810, N1 = 807
% change LDL-C 540 day is the time-adjusted change in LDL-C after day 90 and up to day 540 Mean (95% CI)	-52.3 (-55.7 to -48.8)	-53.8 (-56.2 to -51.3)	-49.9 (-53.1 to -46.6)	-49.2 (-51.6 to -46.8)
High intensity statin ORION-10: N=538 vs 546; ORION-11: N=734 vs 729; Atorvastatin 40 – 80 mg; Rosuvastatin 20 – 40 mg; Simvastatin 80mg Least squares mean difference (95% CI)	-58.2 (-62.1 to -54)	-NR	-53.4 (-56.6 to -50.2)	-NR
Not high intensity statin ORION-10: N=243 vs 234; ORION-11: N=76 vs 79 Least squares mean difference (95% CI)	-54.9 (-59.7 to -50.1)	NR	-45.5 (-55 to -35.8)	NR

Outcome	ORION-10: inclisiran vs ORION-10: placebo, 510 day, N2 = 781, N1 = 780	ORION-10: inclisiran vs ORION-10: placebo, 540 day, N2 = 781, N1 = 780	ORION-11: inclisiran vs ORION-11: placebo, 510 day, N2 = 810, N1 = 807	ORION-11: inclisiran vs ORION-11: placebo, 540 day, N2 = 810, N1 = 807
Absolute change LDL-C (mg/dl) 540 day is the time-adjusted change in LDL-C after day 90 and up to day 540 Least squares mean difference (95% CI)	-54.1 (-57.4 to -50.9)	-53.3 (-55.8 to -50.8)	-51.9 (-55 to -48.7)	-48.9 (-51.4 to -46.5)

% change LDL-C - Polarity - Higher values are better (greater reduction is better)

Absolute change LDL-C - Polarity - Higher values are better (greater reduction is better)

Continuous

Outcome	ORION-10: inclisiran, 510 day, N = 781	ORION-10: inclisiran, 540 day, N = 780	ORION-10: placebo, 510 day, N = 780	ORION-10: placebo, 540 day, N = 780	ORION-11: inclisiran, 510 day, N = 810	ORION-11: inclisiran, 540 day, N = 810	ORION-11: placebo, 510 day, N = 807	ORION-11: placebo, 540 day, N = 807
Mean % change LDL-C 540 day is the time-adjusted change in LDL-C after day 90 and up to day 540 Nominal	-51.3	-51.3	1	2.5	-45.8	-45.8	4	3.4

Outcome	ORION-10: inclisiran, 510 day, N = 781	ORION-10: inclisiran, 540 day, N = 780	ORION-10: placebo, 510 day, N = 780	ORION-10: placebo, 540 day, N = 780	ORION-11: inclisiran, 510 day, N = 810	ORION-11: inclisiran, 540 day, N = 810	ORION-11: placebo, 510 day, N = 807	ORION-11: placebo, 540 day, N = 807
Mean absolute change LDL-C (mg/dl) 540 day is the time-adjusted change in LDL-C after day 90 and up to day 540 Nominal	-56.2	-53.7	-2.1	-0.4	-50.9	-48.6	1	0.3
Mean % change non-HDL-C Nominal	-47.4	- NR	-0.1	- NR	-41.2	- NR	2.2	-

Mean % change LDL-C - Polarity - Higher values are better (greater reduction is better)

Mean absolute change LDL-C - Polarity - Higher values are better (greater reduction is better)

Mean % change non-HDL-C - Polarity - Higher values are better (greater reduction is better)

Dichotomous

Outcome	ORION-10: inclisiran, 540 day, N = 781	ORION-10: placebo, 540 day, N = 778	ORION-11: inclisiran, 540 day, N = 811	ORION-11: placebo, 540 day, N = 804
MACE CV death, resuscitated cardiac arrest, non-fatal myocardial infarction (MI),	n = 58	n = 79	n = 63	n = 83

Outcome	ORION-10: inclisiran, 540 day, N = 781	ORION-10: placebo, 540 day, N = 778	ORION-11: inclisiran, 540 day, N = 811	ORION-11: placebo, 540 day, N = 804
and non-fatal stroke (ischemic and haemorrhagic No of events				
Injection-site reaction No of events	n = 20	n = 7	n = 38	n = 4
Alanine aminotransferase >3× ULN No of events	n = 2	n = 2	n = 4	n = 4
Aspartate aminotransferase >3× ULN No of events	n = 4	n = 5	n = 2	n = 4

MACE - Polarity - Lower values are better

Injection-site reaction - Polarity - Lower values are better

Increased liver transaminases - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

ORION-10&11: Between-group difference-% change LDL-C

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Indirectly applicable *(510 days is beyond the 12 month time point in the protocol)*

ORION-10&11: Between-group difference-% change LDL-C (90-540 days time weighted)

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Partially applicable (Some data beyond 12 months included in analysis)

Between-group difference-% change LDL-C -Statin intensity sensitivity analysis

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Indirectly applicable *(510 days is beyond the 12 month time point in the protocol; and statin intensity definition differs from protocol)*

Between-group difference-Absolute change LDL-C-510d

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Indirectly applicable *(510 days is beyond the 12 month time point in the protocol)*

Between-group difference-Absolute change LDL-C-90-540 days

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Partially applicable (Some data beyond 12 months included in analysis)

% change non-HDL-C-510 day

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(No measure of variance reported)*
Overall bias and Directness	Overall Directness	Indirectly applicable *(510 days is beyond the 12 month time point in the protocol)*

MACE

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Injection-site reaction

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Event rate in control arm less than number lost to follow up)*
Overall bias and Directness	Overall Directness	Directly applicable

Alanine aminotransferase>3×ULN

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Event rate less than number lost to follow up)*
Overall bias and Directness	Overall Directness	Directly applicable

Aspartate aminotransferase>3×ULN

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Event rate less than number lost to follow up)*
Overall bias and Directness	Overall Directness	Directly applicable

Rehberger Likozar, 2022

Bibliographic Reference	Rehberger Likozar, A.; Sebestjen, M.; Smoking and diabetes attenuate beneficial effects of PSCK9 inhibitors on arterial wall properties in patients with very high lipoprotein (a) levels; Atherosclerosis Plus; 2022; vol. 50; 1-9

Study details

Study type	Randomised controlled trial (RCT)
Study location	Slovenia
Study setting	Primary care
Study dates	Recruitment period: November 2020 to May 2021 and 6 month follow-up
Sources of funding	Amgen, Sanofi, Research Programs P3- 0308 of the Slovenian Research Agency, and University Medical Centre Ljubljana (Funding number: 20210022).
Inclusion criteria	Patients aged between 18 and 65 years with clinically stable coronary artery disease (CAD) of at least 6 months after myocardial infarction. Only patients who had a myocardial infarction before the age of 55 years and showed serum Lp(a) levels of 1000 mg/L irrespective of LDL-C levels or showed serum Lp(a) levels >600 mg/L and LDL-C >2.6 mmol/l were

	eligible. All of the patients had been prescribed beta blockers and antiplatelet drugs and were taking angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers and statins at the highest tolerated doses, along with ezetimibe where needed. Their therapies had not been changed for at least 8 weeks before entering the study.
Exclusion criteria	Elevated liver transaminases by more than three times the normal levels; severe renal impairment and serum creatinine >200 mmol/l; or history of acute illness in the previous 6 weeks.
Recruitment / selection of participants	Senior investigator enrolled all patients and performed the randomization using the online programme Research randomizer (www.randomizer.org) to generate the random allocation sequences. Both the laboratory and ultrasound examinations were repeated after 6 months of the treatments. Population: clinically stable CAD of at least 6 months after myocardial infarction, with mean age at first coronary event <55 years.
Population subgroups	None investigated; study falls under high-intensity statin strata (maximally tolerated dose) along with other lipid lowering medication where needed.
Intervention(s)	1) Alirocumab 150 mg SC, every two weeks 2) Evolocumab 140 mg SC, every two weeks.
Comparator	Control: standard lipid-lowering therapy with no PCSK9 inhibitors
Background treatment	All the patients were treated with statins at the highest tolerated doses with or without ezetimibe, and all were treated with angiotensin-converting enzyme inhibitors, beta blockers and acetylsalicylic acid. One patient in each group received a calcium channel blocker. One patient in the alirocumab group did not finish the study due to problems associated with COVID-19 disease.
Number of participants	100

Duration of follow-up	6 months
Indirectness	Type of statin received was not specified
Additional comments	The blood for laboratory analysis was collected in the morning after 12 h overnight fasting. Samples were drawn from the antecubital vein into vacuum 5 mL tubes containing a clot activator (Vacutubes; LT Burnik, Slovenia). Total cholesterol, high-density lipoprotein-cholesterol (HDL-C), triglycerides, apoA1 and apoB were determined in the fresh serum by standard colorimetric or immunologic assays on an automated biochemistry analyser (Fusion 5.1; Ortho-Clinical Diagnostics, USA). Kolmogorov Smirnov tests were used to define variables showing normal distributions, with these data expressed as means ± standard deviations. The non-normally distributed variables are expressed as medians and range (lower and upper quartiles). Pearson and Spearman correlation analysis was performed to determine the correlation of ultrasound parameters and lipid risk factors. General linear model analyses using delta values of the lipids (LDL-C, Lp(a), apoB) as covariates were performed to test the influence of the treatment and risk factors (smoking and diabetes) on the delta values of the vascular parameters. The differences between the three groups were calculated with one-way ANOVA or Kruskal-Wallis test for non-normally distributed variables. The differences in parameters between the treated and the placebo groups were compared using the delta values of the parameters (values at 6 months - values at baseline). The difference between the parameters at baseline and after 6 months of treatment were calculated using paired samples t-test. The differences between the two groups of patients with specific risk factor were calculated using Student’s t-test. P values < 0.05 or adequately lower in the case of multiple comparisons, were considered statistically significant. Statistical analysis was performed using IBM SPSS Statistics

Study arms

Alirocumab (N = 35)

Alirocumab 150 mg SC, every two weeks

Evolocumab (N = 34)

Evolocumab 140 mg SC, every two weeks.

Control (N = 31)

standard lipid-lowering therapy with no PCSK9 inhibitors

Characteristics

Arm-level characteristics

Characteristic	Alirocumab (N = 35)	Evolocumab (N = 34)	Control (N = 31)
Mean age (SD) Mean (SD)	52.8 (8.2)	49.9 (8.9)	47.5 (9.5)
Type 2 diabetes Sample size	n = 6 ; % = 17.1	n = 1 ; % = 2.9	n = 7 ; % = 20
LDL cholesterol (mmol/l) Mean (SD)	2.2 (0.6)	2.4 (0.8)	2.4 (0.9)

Outcomes

Study timepoints

- 6 month

LDL-C

Outcome	Alirocumab, 6 month, N = 35	Evolocumab, 6 month, N = 34	Control, 6 month, N = 31
LDL-C (mmol/l) Mean (SD)	0.8 (0.6)	0.9 (0.9)	2.4 (0.8)

LDL-C - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

LDL-C

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Very limited information on baseline characteristics to assess adequacy of randomisation, no data on difference in statins and other background medication between the treatment groups, no information on missing data)*
Overall bias and Directness	Overall Directness	Partially applicable *(No information on type of statin received to assess if it met review protocol; final value not change score)*

Ren, 2017

Bibliographic Reference	Ren, Yizhi; Zhu, Hao; Fan, Zhongguo; Gao, Yali; Tian, Nailiang; Comparison of the effect of rosuvastatin versus rosuvastatin/ezetimibe on markers of inflammation in patients with acute myocardial infarction.; Experimental and therapeutic medicine; 2017; vol. 14 (no. 5); 4942-4950

Study details

Study type	Randomised controlled trial (RCT)
Study location	China.
Study setting	Department of Cardiology, Nanjing First hospital Affiliated with Nanjing Medical University.
Study dates	January 2015 to June 2016.
Sources of funding	No information.
Inclusion criteria	Aged 18-80 years and hospitalised within preceding 24 hours acute myocardial infarction (AMI), including ST-segment elevation myocardial infarction (STEMI) with or without ST-segment elevation myocardial infarction. STEMI defined as an AMI with dynamic changes in the electrocardiogram and at least one instance of elevated levels of cardiac enzymes or myocardial necrosis biomarkers, defined as total creatine phosphokinase or creatine kinase major basic fraction >2 fold the upper limit of the normal range an/or positive troponin I or troponin T.
Exclusion criteria	Contraindications for the intervention, statin use was contraindicated, severe cardiac dysfunction, severe renal insufficiency and other comorbidities including infection, systemic immune diseases, pericarditis and malicious tumours.
Recruitment / selection of participants	Hospital inpatients at the Department of Cardiology, Nanjing First hospital Affiliated with Nanjing Medical University.
Intervention(s)	Ezetimibe 10 mg plus rosuvastatin 10 mg per day (high intensity statin).
Comparator	Rosuvastatin 10 mg per day (high intensity statin).

Background treatment	Instructed to take tablets once daily in the evening and to pay attention to the side effects. Participants received treatment according to common guidelines, including appropriate use of antiplatelet agents, anticoagulants, statins, B-blockers and revascularization. **Ezetimibe and rosuvastatin:** Hypertension: 31 (56.4%) Current smoker: 39 (70.9%) Aspirin: 12 (21.8%) Thienopyridine: 5 (9.1%) Calcium channel blockers: 5 (9.1%) Diuretics: 4 (7.3%) ACEI/ARB: 9 (16.4%) **Rosuvastatin**: Hypertension: 35 (60.3%) Current smoker: 38 (65.5%) Aspirin: 10 (17.5%) Thienopyridine: 3 (5.3%) Calcium channel blockers: 11 (19.3%) Diuretics: 3 (5.3%) ACEI/ARB: 4 (7.0%)

Number of participants	113 randomised (135 initially enrolled).
Duration of follow-up	12 months.
Indirectness	No indirectness.
Additional comments	Available case analysis. No details about dropouts at 12 months.

Study arms

Ezetimibe and rosuvastatin (N = 55)

Ezetimibe 10 mg plus rosuvastatin 10 mg per day (high intensity statin).

Rosuvastatin (N = 58)

Rosuvastatin 10 mg per day (high intensity statin)..

Characteristics

Arm-level characteristics

Characteristic	Ezetimibe and rosuvastatin (N = 55)	Rosuvastatin (N = 58)
% Female	n = 7 ; % = 12.7	n = 12 ; % = 20.7

Characteristic	Ezetimibe and rosuvastatin (N = 55)	Rosuvastatin (N = 58)
Sample size		
Mean age (SD) Mean (SD)	57.3 (1.5)	60.7 (1.3)
Ethnicity Nominal	NR	NR
Existing CVD diagnosis Sample size		
Previous MI Sample size	n = 2 ; % = 3.6	n = 1 ; % = 1.7
Type 2 diabetes Diabetes type not specified Sample size	n = 10 ; % = 18.2	n = 10 ; % = 17.2
Chronic kidney disease Nominal	NR	NR
LDL-cholesterol (mmol/l) Mean (SD)	3 (0.96)	2.93 (1.02)

Characteristic	Ezetimibe and rosuvastatin (N = 55)	Rosuvastatin (N = 58)
Non-HDL cholesterol Nominal	NR	NR
Statins used Sample size	n = 5 ; % = 9.1	n = 6 ; % = 10.5

Outcomes

Study timepoints

- Baseline
- 1 year

Continuous outcomes - lipids at 1 year

Outcome	Ezetimibe and rosuvastatin, Baseline, N = 55	Ezetimibe and rosuvastatin, 1 year, N = 50	Rosuvastatin, Baseline, N = 58	Rosuvastatin, 1 year, N = 53
LDL cholesterol (mmol/l) Mean (SD)	3 (0.96)	1.19 (0.43)	2.93 (1.02)	1.49 (0.51)
LDL Cholesterol (change) (mmol/l) Change from baseline	NA (NA)	-1.81 (0.88)	NA (NA)	-1.44 (0.98)

Outcome	Ezetimibe and rosuvastatin, Baseline, N = 55	Ezetimibe and rosuvastatin, 1 year, N = 50	Rosuvastatin, Baseline, N = 58	Rosuvastatin, 1 year, N = 53
Mean (SD)				

LDL cholesterol - Polarity - Lower values are better

LDL Cholesterol (change) - Polarity - Higher values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

LDL cholesterol

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Bias due to randomisation process)*
Overall bias and Directness	Overall Directness	Directly applicable

LDL Cholesterol (change)

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Bias due to randomisation process)*
Overall bias and Directness	Overall Directness	Directly applicable

Robinson, 2015

Bibliographic Reference	Robinson, Jennifer G; Farnier, Michel; Krempf, Michel; Bergeron, Jean; Luc, Gerald; Averna, Maurizio; Stroes, Erik S; Langslet, Gisle; Raal, Frederick J; El Shahawy, Mahfouz; Koren, Michael J; Lepor, Norman E; Lorenzato, Christelle; Pordy, Robert; Chaudhari, Umesh; Kastelein, John J P; ODYSSEY LONG TERM, Investigators; Efficacy and safety of alirocumab in reducing lipids and cardiovascular events.; The New England journal of medicine; 2015; vol. 372 (no. 16); 1489-99

Study details

Other publications associated with this study included in review	Primary trial report for ODYSSEY LONG TERM. Results reported from IPD meta analysis of CVD subgroup. See McCullough 2018 for details.

Sabatine, 2016

Bibliographic Reference	Sabatine, Marc S; Giugliano, Robert P; Keech, Anthony; Honarpour, Narimon; Wang, Huei; Liu, Thomas; Wasserman, Scott M; Scott, Robert; Sever, Peter S; Pedersen, Terje R; Rationale and design of the Further cardiovascular OUtcomes Research with PCSK9 Inhibition in subjects with Elevated Risk trial.; American heart journal; 2016; vol. 173; 94-101

Study details

Secondary publication of another included	FOURIER trial design and rationale See Sabatine 2017 for full details

study- see primary study for details	

Sabatine, 2017

Bibliographic Reference	Sabatine, MS; Giugliano, RP; Keech, AC; Honarpour, N; Wiviott, SD; Murphy, SA; Evolocumab and clinical outcomes in patients with cardiovascular disease; New England journal of medicine; 2017; vol. online; 1-10

Study details

Other publications associated with this study included in review	Sabatine 2016 - trial design and rationale
Trial name / registration number	FOURIER NCT01764633
Study type	Randomised controlled trial (RCT)
Study location	1242 sites in 49 countries: Argentina, Australia, Austria, Belgium, Brazil, Bulgaria, Canada, Chile, China, Colombia, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hong Kong, Hungary, Iceland, India, Ireland, Israel, Italy, Japan, Latvia, Lithuania, Malaysia, Mexico, Netherlands, New Zealand, Norway, Philippines, Poland, Portugal, Romania, Russia, Singapore, Slovakia, South Africa, South Korea, Spain, Sweden, Switzerland, Taiwan, Turkey, Ukraine, United Kingdom, United States.

Study setting	Outpatient care
Study dates	February 2013 to November 2016
Sources of funding	Amgen
Inclusion criteria	• Age 40–85 years • Clinically evident CVD (history of myocardial infarction, non-haemorrhagic stroke, or symptomatic peripheral artery disease) • Additional risk factors, indicating high risk for a recurrent event • Fasting LDL-C ≥70 mg/dl or non-HDL-C ≥100 mg/dl after ≥2 weeks of optimised stable lipid-lowering therapy (at least atorvastatin 20 mg daily or equivalent), with or without ezetimibe • Fasting TGs ≤400 mg/dl
Exclusion criteria	• NYHA class III or IV, or left ventricular ejection fraction <30% • Prior haemorrhagic stroke • Uncontrolled hypertension • Uncontrolled or recurrent ventricular tachycardia • Untreated hyperthyroidism or hypothyroidism • Homozygous familial hypercholesterolemia • Low-density lipoprotein or plasma apheresis within previous 12 months

Recruitment / selection of participants	Prospective
Population subgroups	• Baseline LDL-C • Baseline statin intensity: high defined as atorvastatin ≥40 mg, rosuvastatin ≥20 mg or simvastatin 80 mg - does not match protocol defintion
Intervention(s)	Evolocumab 140 mg SC every 2 weeks or 420 mg SC every month, according to patient preference
Comparator	Matching placebo injections
Background treatment	Optimised stable lipid-lowering therapy (at least atorvastatin 20 mg daily or equivalent), with or without ezetimibe. At baseline, 69.3% of the patients were taking high-intensity statin therapy (defined as atorvastatin ≥40 mg, rosuvastatin ≥20 mg or simvastatin 80 mg)
Number of participants	27,564 (39 did not receive treatment)
Duration of follow-up	Median duration of follow-up was 26 months (IQR: 22 - 30)
Indirectness	Not serious
Additional comments	ITT

Study arms

Evolocumab (N = 13784)

Background high intensity statins (at least atorvastatin 20 mg or equivalent)

Placebo (N = 13780)

Background high intensity statins (at least atorvastatin 20 mg or equivalent)

Characteristics

Arm-level characteristics

Characteristic	Evolocumab (N = 13784)	Placebo (N = 13780)
% Female Sample size	n = 3387 ; % = 24.6	n = 3382 ; % = 24.5
Mean age (SD) Mean (SD)	62.5 (9.1)	62.5 (8.9)
Ethnicity **White** Sample size	n = 11748 ; % = 85.2	n = 11710 ; % = 85
Existing CVD diagnoses		
MI Sample size	n = 11145 ; % = 80.9	n = 11206 ; % = 81.3
Non-haemorrhagic stroke Sample size	n = 2686 ; % = 19.5	n = 2651 ; % = 19.2
PAD Sample size	n = 1858 ; % = 13.5	n = 1784 ; % = 12.9

Type 2 diabetes **'Diabetes mellitus'** Sample size	n = 5054 ; % = 36.7	n = 5027 ; % = 36.5
Chronic kidney disease Nominal	NR	NR
LDL cholesterol Median (IQR)	92 (80 to 109)	92 (80 to 109)
Statin use		
High-intensity statin **atorvastatin ≥40 mg, rosuvastatin ≥20 mg or simvastatin 80 mg** Sample size	n = 9585 ; % = 69.5	n = 9518 ; % = 69.1
Moderate-intensity statin **Atorvastatin 10 to <40 mg, Rosuvastatin 5 to <20 mg, Simvastatin 20 to <80 mg, Pravastatin ≥40 mg, Lovastatin ≥40 mg, Fluvastatin 80 mg, Pitavastatin ≥2 mg** Sample size	n = 4161 ; % = 30.2	n = 4231 ; % = 30.7
Low intensity or unknown Sample size	n = 38 ; % = 0.3	n = 31 ; % = 0.2

Other lipid-lowering medication used ezetimibe Sample size	n = 726 ; % = 5.3	n = 714 ; % = 5.2

Outcomes

Study timepoints

- Baseline
- 48 week
- 36 month (End of follow-up: median 26 months)

Between group difference

Outcome	Evolocumab vs Placebo, 48 week, N2 = 13784, N1 = 13780	Evolocumab vs Placebo, 36 month, N2 = , N1 =
% change LDL-C least squares mean Mean (95% CI)	-59 (-60 to -58)	-
Absolute reduction LDL-C (mg/dl) Mean (95% CI)	-56 (-57 to -55)	-
MACE cardiovascular death, myocardial infarction, or stroke	-	0.8 (0.73 to 0.88)

Outcome	Evolocumab vs Placebo, 48 week, N2 = 13784, N1 = 13780	Evolocumab vs Placebo, 36 month, N2 = , N1 =
Hazard ratio/95% CI		
Baseline LDL-C: <80 mg/dl N= 6961; Event rate: 5.1 vs 6.6% Hazard ratio/95% CI	-	0.78 (0.64 to 0.95)
Baseline LDL-C: 80-<92 mg/dl N= 6886; Event rate: 5.4 vs 6.8% Hazard ratio/95% CI	-	0.79 (0.65 to 0.96)
Baseline LDL-C: 92-109 mg/dl N= 6887; Event rate: 6.3 vs 7.9% Hazard ratio/95% CI	-	0.79 (0.66 to 0.94)
Baseline LDL-C: >109 mg/dl N= 6829; Event rate: 6.9 vs 8.2% Hazard ratio/95% CI	-	0.83 (0.7 to 0.99)
Baseline statin intensity: 'high' N=19103; Event rate: 6.1 vs 7.4% Hazard ratio/95% CI	-	0.82 (0.74 to 0.92)
Baseline statin intensity: 'not high' N=8461; Event rate: 5.5 vs 7.2%	-	0.74 (0.63 to 0.88)

Outcome	Evolocumab vs Placebo, 48 week, N2 = 13784, N1 = 13780	Evolocumab vs Placebo, 36 month, N2 = , N1 =
Hazard ratio/95% CI		

% change LDL-C - Polarity - Higher values are better (greater reduction is better)

Absolute reduction LDL-C - Polarity - Higher values are better (greater reduction is better)

MACE - Polarity - Lower values are better

Dichotomous

Outcome	Evolocumab, 36 month, N = 13784	Placebo, 36 month, N = 13780
MACE cardiovascular death, myocardial infarction, or stroke No of events	n = 816 ; % = 5.9	n = 1013 ; % = 7.4
Rhabdomyolysis not defined No of events	n = 8 ; % = 0.1	n = 11 ; % = 0.1
New-onset diabetes N =8337 vs 8339 without prevalent diabetes No of events	n = 677 ; % = 8.1	n = 644 ; % = 7.7

Outcome	Evolocumab, 36 month, N = 13784	Placebo, 36 month, N = 13780
Increased liver transaminases Aminotransferase >3 times ULN (data available for 13543 vs 13523 pts) No of events	n = 240 ; % = 1.8	n = 242 ; % = 1.8
Injection site reaction No of events	n = 296 ; % = 2.1	n = 219 ; % = 1.6

MACE - Polarity - Lower values are better

Rhabdomyolysis - Polarity - Lower values are better

New-onset diabetes - Polarity - Lower values are better

Increased liver transaminases - Polarity - Lower values are better

Injection site reaction - Polarity - Lower values are better

Continuous

Outcome	Evolocumab, 48 week, N = 13784	Placebo, 48 week, N = 13780
% change non-HDL-C Results presented on graphs - no SD data to extract Mean (SD)	-51.2 (-)	0.4 (-)

% change non-HDL-C - Polarity - Higher values are better (greater reduction is better)

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

% change LDL-C 48 weeks

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Absolute reduction LDL-C 48 weeks

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

MACE-Hazard Ratio

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

MACE-Baseline LDL-C sensitivity analysis

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

MACE-Baseline statin intensity sensitivity analysis

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Indirectly applicable *(Statin intensity does not match protocol definition)*

MACE-Dichotomous

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Rhabdomyolysis

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Event rate less than number lost to follow up and outcome definition unclear)*
Overall bias and Directness	Overall Directness	Directly applicable

New-onset diabetes

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Injection-site reaction

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

% change non-HDL-C 48 weeks

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Schwartz, 2014

Bibliographic Reference	Schwartz, Gregory G; Bessac, Laurence; Berdan, Lisa G; Bhatt, Deepak L; Bittner, Vera; Diaz, Rafael; Goodman, Shaun G; Hanotin, Corinne; Harrington, Robert A; Jukema, J Wouter; Mahaffey, Kenneth W; Moryusef, Angele; Pordy, Robert; Roe, Matthew T; Rorick, Tyrus; Sasiela, William J; Shirodaria, Cheerag; Szarek, Michael; Tamby, Jean-Francois; Tricoci, Pierluigi; White, Harvey; Zeiher, Andreas; Steg, Philippe Gabriel; Effect of alirocumab, a monoclonal antibody to PCSK9, on long-term cardiovascular outcomes following acute coronary syndromes: rationale and design of the ODYSSEY outcomes trial.; American heart journal; 2014; vol. 168 (no. 5); 682-9

Study details

Secondary publication of another included study- see primary study for details	Rationale and design of the ODYSSEY outcomes trial. Full details available in main study entry (Schwartz 2018).

Schwartz, 2018

Bibliographic Reference	Schwartz, Gregory G; Steg, P Gabriel; Szarek, Michael; Bhatt, Deepak L; Bittner, Vera A; Diaz, Rafael; Edelberg, Jay M; Goodman, Shaun G; Hanotin, Corinne; Harrington, Robert A; Jukema, J Wouter; Lecorps, Guillaume; Mahaffey, Kenneth W; Moryusef, Angele; Pordy, Robert; Quintero, Kirby; Roe, Matthew T; Sasiela, William J; Tamby, Jean-Francois; Tricoci, Pierluigi; White, Harvey D; Zeiher, Andreas M; ODYSSEY OUTCOMES Committees and, Investigators; Alirocumab and Cardiovascular Outcomes after Acute Coronary Syndrome.; The New England journal of medicine; 2018; vol. 379 (no. 22); 2097-2107

Study details

Other publications associated with this study included in review	Schwartz 2014 - rationale and design NCT01663402
Trial name / registration number	ODYSSEY Outcomes NCT01663402
Study type	Randomised controlled trial (RCT)
Study location	Multicentre, international Argentina, Austria, Belgium, Bosnia and Herzegovina, Brazil, Bulgaria, Canada, Chile, China, Colombia, Croatia, Czech Republic, Denmark, Estonia, Finland, France, Georgia, Germany, Greece, Guatemala, Hong Kong, Hungary, India, Israel, Italy, Japan, Korea, Latvia, Lithuania, Macedonia, Malaysia, Mexico, Netherlands, New Zealand, Norway, Peru, Philippines, Poland, Portugal, Romania, Russian Federation, Serbia, Singapore, Slovakia, Slovenia, Republic of South Africa, Spain, Sri Lanka, Sweden, Switzerland, Taiwan, Thailand, Turkey, United Kingdom, United States,
Study setting	Enrolled after hospital admission

Study dates	Randomsation November 2012 to November 2015 (except in China, where 613 patients underwent randomisation from May 2016 to February 2017). Trial end date: 11 November 2017
Sources of funding	Sanofi-Aventis SA and Regeneron Pharmaceuticals.
Inclusion criteria	Hospitalisation for ACS (symptoms of myocardial ischemia with an unstable pattern, occurring at rest or with minimal exertion, within 72 h of an unscheduled hospital admission due to presumed or proven obstructive coronary disease) and at least one of the following: • Elevated cardiac biomarkers • Resting ECG changes consistent with ischemia or infarction, plus additional evidence of obstructive coronary disease from regional wall motion or perfusion abnormality, ≥70% epicardial coronary stenosis by angiography, or need for coronary revascularization procedure. Lipid levels inadequately controlled by atorvastatin 40-80 mg or rosuvastatin 20-40 mg daily or maximum tolerated dose of one of these agents, defined by at least one of the following: • LDL-C ≥ 70 mg/dl • Non–HDL-C ≥ 100 mg/dl • Apolipoprotein B ≥ 80 mg/dl
Exclusion criteria	• Age <40 years • Not on stable lipid-modifying therapy for ≥2 weeks before randomization • Uncontrolled hypertension • New York Heart Association class III or IV congestive heart failure persisting despite treatment or LVEF <25% if measured

	• History of haemorrhagic stroke • Fasting triglycerides >400 mg/dl • Recurrent ACS event within 2 weeks prior to randomisation • Coronary revascularization procedure performed within 2 weeks prior to randomisation visit or planned after randomisation • Liver transaminases >3 times upper limit of normal; laboratory evidence of current hepatitis B or C infection; creatine kinase >3 times upper limit of normal; eGFR <30 mL/(min 1.73 m2); positive urine or serum pregnancy test • Use of fibrates other than fenofibrate or fenofibric acid
Recruitment / selection of participants	Qualifying patients must have had a recent ACS event (1-12 months prior to randomisation) and have inadequate control of atherogenic lipoproteins despite optimal statin treatment. Run-in period of up to 16 weeks to optimise statin, practice self-injection with placebo and complete any planned revascularisation.
Intervention(s)	Alirocumab self-injection (SC), 75 mg every 2 weeks until month 2, and then 75 or 150 mg adjusted to achieve 15 ≤LDL-C<50 mg/dl
Comparator	Placebo
Background treatment	Atorvastatin 40 or 80 mg, rosuvastatin 20 or 40 mg, or maximal tolerated dose of one of these statins, with or without non-statin lipid treatments. NCEP-ATPIII therapeutic lifestyle changes or equivalent throughout study.
Number of participants	18,924
Duration of follow-up	Median 2.8 years (interquartile range, 2.3-3.4)

	Follow-up visits were at 1, 2, 4, 8, 12, 16, 20, and 24 months after randomisation and then at 6-month intervals.
Indirectness	Not serious
Additional comments	

Study arms

Alirocumab (N = 9462)

Alirocumab 75 mg subcutaneously every 2 weeks, increased to 150 mg if LDL-C remains ≥50 mg/dl after 1 month

Placebo (N = 9462)

Characteristics

Arm-level characteristics

Characteristic	Alirocumab (N = 9462)	Placebo (N = 9462)
% Female Sample size	n = 2390 ; % = 25.3	n = 2372 ; % = 25.1
Mean age (SD) Mean (SD)	58.5 (9.3)	58.6 (9.4)
Ethnicity		
White Sample size	n = 7500 ; % = 79.3	n = 7524 ; % = 79.5
Asian Sample size	n = 1251 ; % = 13.2	n = 1247 ; % = 13.2
Black Sample size	n = 235 ; % = 2.5	n = 238 ; % = 2.5
Other Sample size	n = 475 ; % = 5	n = 451 ; % = 4.8
Existing CVD diagnoses		
Myocardial infarction Sample size	n = 1790 ; % = 18.9	n = 1843 ; % = 19.5

Percutaneous coronary intervention Sample size	n = 1626 ; % = 17.2	n = 1615 ; % = 17.1
Coronary-artery bypass grafting Sample size	n = 521 ; % = 5.5	n = 526 ; % = 5.6
Stroke Sample size	n = 306 ; % = 3.2	n = 305 ; % = 3.2
Peripheral artery disease Sample size	n = 373 ; % = 3.9	n = 386 ; % = 4.1
Type 2 diabetes **'Diabetes'** Sample size	n = 2693 ; % = 28.5	n = 2751 ; % = 29.1
Chronic kidney disease Nominal	NR	NR
LDL cholesterol (mg/dl (to convert to millimoles per liter, multiply by 0.02586)) at randomisation (calculated with the Friedewald formula) Mean (SD)	92 (31)	92 (31)
Non-HDL cholesterol (mg/dl) Mean (SD)	122 (35)	123 (36)

Statins used		
Atorvastatin 80 mg or rosuvastatin 40 mg Sample size	n = 2611 ; % = 27.6	n = 2573 ; % = 27.2
Atorvastatin 40 mg or rosuvastatin 20 mg Sample size	n = 5771 ; % = 61	n = 5857 ; % = 61.9
Low or moderate-intensity atorvastatin/rosuvastatin Sample size	n = 833 ; % = 8.8	n = 776 ; % = 8.2
Ezetimibe Sample size	n = 265 ; % = 2.8	n = 284 ; % = 3
Index ACS event		
ST-segment elevation myocardial infarction Sample size	n = 3301 ; % = 34.9	n = 3235 ; % = 34.2
Non−ST-segment elevation myocardial infarction Sample size	n = 4574 ; % = 48.3	n = 4601 ; % = 48.6
Unstable angina Sample size	n = 1568 ; % = 16.6	n = 1614 ; % = 17.1

Outcomes

Study timepoints

- Baseline
- 12 month
- 4 year

Continuous

Outcome	Alirocumab, Baseline, N = 9462	Alirocumab, 12 month, N = 9462	Alirocumab, 4 year, N =	Placebo, Baseline, N = 9462	Placebo, 12 month, N = 9462	Placebo, 4 year, N =
LDL-C absolute value (mg/dl) variance not given for 12 month values Mean (SD)	92 (31)	48 (-)	-	92 (31)	96 (-)	-

LDL-C absolute value - Polarity - Lower values are better

Time-to-event

Outcome	Alirocumab vs Placebo, 4 year, N2 = 9462, N1 = 9462
MACE composite of death from coronary heart disease, nonfatal myocardial infarction, fatal or nonfatal ischemic stroke, or unstable angina requiring hospitalisation Hazard ratio/95% CI	0.85 (0.78 to 0.93)
MACE: statin dose sensitivity analysis	
High statin dose N = 8380 vs 8431 Hazard ratio/95% CI	0.88 (0.8 to 0.96)
Low or moderate statin dose N = 849 vs 804 Hazard ratio/95% CI	0.69 (0.5 to 0.95)
No statin N = 233 vs 227 Hazard ratio/95% CI	0.65 (0.43 to 0.96)
MACE: baseline LDL-C sensitivity analysis	
<80 mg/dl N=7164 Hazard ratio/95% CI	0.86 (0.74 to 1.01)

Outcome	Alirocumab vs Placebo, 4 year, N2 = 9462, N1 = 9462
80- <100 mg/dl N=6128 Hazard ratio/95% CI	0.96 (0.82 to 1.14)
≥100 mg/dl N=5629 Hazard ratio/95% CI	0.76 (0.65 to 0.87)
MACE: baseline non-HDL-C sensitivity analysis	
<110 mg/dl N=7927 Hazard ratio/95% CI	0.84 (0.72 to 0.98)
110-<130 mg/dl N=5006 Hazard ratio/95% CI	0.97 (0.82 to 1.16)
≥130 mg/dl N=5988 Hazard ratio/95% CI	0.78 (0.68 to 0.9)

Kaplan Meier estimates

Dichotomous

Outcome	Alirocumab, 4 year, N = 9462	Placebo, 4 year, N = 9462
MACE composite of death from coronary heart disease, nonfatal myocardial infarction, fatal or nonfatal ischemic stroke, or unstable angina requiring hospitalisation No of events	n = 903 ; % = 9.5	n = 1052 ; % = 11.1
Baseline LDL-C < 80 mg/dl N=7164 No of events	n = 296 ; % = 8.3	n = 341 ; % = 9.5
Baseline LDL-C 80 to <100 mg/dl N=6128 No of events	n = 283 ; % = 9.2	n = 291 ; % = 9.5
Baseline LDL-C ≥100 mg/dl N=5629 No of events	n = 324 ; % = 11.5	n = 420 ; % = 14.9
Myopathy/rhabdomyolysis Creatine kinase >10 times upper limit of normal range; N analysed = 9369 vs 9338 No of events	n = 46	n = 48
New-onset diabetes among patients without diabetes at baseline; n = 6763 vs 6696	n = 648 ; % = 9.6	n = 676 ; % = 10.1

Outcome	Alirocumab, 4 year, N = 9462	Placebo, 4 year, N = 9462
No of events		
Alanine aminotransferase >3 times ULN N= 9369 vs 9341 No of events	n = 212 ; % = 2.3	n = 228 ; % = 2.4
Aspartate aminotransferase >3 times ULN N= 9367 vs 9338 No of events	n = 160 ; % = 1.7	n = 166 ; % = 1.8
Injection-site reaction No of events	n = 360 ; % = 3.8	n = 203 ; % = 2.1

MACE - Polarity - Lower values are better

Myopathy/rhabdomyolysis - Polarity - Lower values are better

New-onset diabetes - Polarity - Lower values are better

Increased liver transaminases - Polarity - Lower values are better

Injection-site reaction - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

LDL-C absolute value-12 month

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Variance not reported)*
Overall bias and Directness	Overall Directness	Directly applicable

Time-to-event-MACE

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Time-to-event-MACE: statin dose sensitivity analysis

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Time-to-event-MACE: baseline LDL-C sensitivity analysis

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Time-to-event-MACE: baseline non-HDL-C sensitivity analysis

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Dichotomous-MACE

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Dichotomous-MACE-Baseline LDL-C

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Myopathy/rhabdomyolysis

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Event rate similar to number lost to follow-up)*
Overall bias and Directness	Overall Directness	Directly applicable

New-onset diabetes

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Increased liver transaminases

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Injection-site reaction

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Tsujita, 2015

Bibliographic Reference	Tsujita, Kenichi; Sugiyama, Seigo; Sumida, Hitoshi; Shimomura, Hideki; Yamashita, Takuro; Yamanaga, Kenshi; Komura, Naohiro; Sakamoto, Kenji; Ono, Takamichi; Oka, Hideki; Nakao, Koichi; Nakamura, Sunao; Ishihara, Masaharu; Matsui, Kunihiko; Sakaino, Naritsugu; Nakamura, Natsuki; Yamamoto, Nobuyasu; Koide, Shunichi; Matsumura, Toshiyuki; Fujimoto, Kazuteru; Tsunoda, Ryusuke; Morikami, Yasuhiro; Matsuyama, Koushi; Oshima, Shuichi; Kaikita, Koichi; Hokimoto, Seiji; Ogawa, Hisao; PRECISE-IVUS study, investigators; Plaque REgression with Cholesterol absorption Inhibitor or Synthesis inhibitor Evaluated by IntraVascular UltraSound (PRECISE-IVUS Trial): Study protocol for a randomized controlled trial.; Journal of cardiology; 2015; vol. 66 (no. 4); 353-8

Study details

Secondary publication of another included study- see primary study for details	Study protocol for PRECISE-IVUS Trial. Full details available in main trial entry: Impact of Dual Lipid-Lowering Strategy With **Ezetimibe** and Atorva**statin** on Coronary Plaque Regression in Patients With Percutaneous Coronary Intervention: The Multicenter **Randomized** Controlled PRECISE-IVUS Trial. (Tsujita 2015)

Tsujita, 2015

Bibliographic Reference	Tsujita, Kenichi; Sugiyama, Seigo; Sumida, Hitoshi; Shimomura, Hideki; Yamashita, Takuro; Yamanaga, Kenshi; Komura, Naohiro; Sakamoto, Kenji; Oka, Hideki; Nakao, Koichi; Nakamura, Sunao; Ishihara, Masaharu; Matsui, Kunihiko; Sakaino, Naritsugu; Nakamura, Natsuki; Yamamoto, Nobuyasu; Koide, Shunichi; Matsumura, Toshiyuki; Fujimoto, Kazuteru; Tsunoda, Ryusuke; Morikami, Yasuhiro; Matsuyama, Koushi; Oshima, Shuichi; Kaikita, Koichi; Hokimoto, Seiji; Ogawa, Hisao; PRECISE-IVUS, Investigators; Impact of Dual Lipid-Lowering Strategy With Ezetimibe and Atorvastatin on Coronary Plaque Regression in Patients With Percutaneous Coronary Intervention: The Multicenter Randomized Controlled PRECISE-IVUS Trial.; Journal of the American College of Cardiology; 2015; vol. 66 (no. 5); 495-507

Study details

Other publications associated with this study included in review	Study protocol: Plaque REgression with Cholesterol absorption Inhibitor or Synthesis inhibitor Evaluated by IntraVascular UltraSound (PRECISE-IVUS Trial): Study protocol for a randomized controlled trial
Trial name / registration number	**P**laque **RE**gression with **C**holesterol absorption **I**nhibitor or **S**ynthesis inhibitor **E**valuated by **I**ntra**V**ascular **U**ltra**S**ound (PRECISE-IVUS)
Study type	Randomised controlled trial (RCT)

Study location	Japan
Study setting	Secondary care
Study dates	June 2010 - April 2013
Sources of funding	Supported in part by a Grants from the Ministry of Education, Science, and Culture, Japan
Inclusion criteria	Aged 30-85 years at enrollment, diagnosed with acute coronary syndrome or stable coronary heart disease, undergoing coronary angiography or percutaneous coronary intervention under intravascular ultrasound guidance, with LDL-C ≥100 mg/dl
Exclusion criteria	Patients with familial hypercholesterolemia, already treated with ezetimibe or fibrates, renal insufficiency (serum creatinine ≥2.0 mg/dl), altered hepatic function (serum AST or ALT ≥3-fold standard value at each institute), undergoing haemodialysis or peritoneal dialysis, any allergy to treatments, severe underlying disease, lack of decision-making capacity, recognized as inadequate by the attending physician
Recruitment / selection of participants	Method not reported
Population subgroups	No additional information
Intervention(s)	Atorvastatin monotherapy titrated to achieve an LDL-C <70 mg/dl at consecutive follow-up visits. Dose could be decreased if excessive LDL-C lowering was observed or if adverse events occurred.
Comparator	Atorvastatin plus ezetimibe (10 mg/day). Atorvastatin titrated to achieve an LDL-C <70 mg/dl at consecutive follow-up visits. Dose could be decreased if excessive LDL-C lowering was observed or if adverse events occurred.

Background treatment	**Atorvastatin + ezetimibe** Aspirin= 100% Thienopyridines= 100% Cilostazol= 1% Sarpogrelate hydrochlorine= 2% Warfarin= 5% Nitrates= 6% Beta-blockers= 41% Calcium blockers= 44% ACE inhibitors= 25% Angiotensin II receptor blocker= 48% Stomach medicines= 89% Hypoglycemic agents= 25% **Atorvastatin monotherapy** Aspirin= 100% Thienopyridines= 99% Cilostazol= 0% Sarpogrelate hydrochlorine= 2% Warfarin= 1%

	Nitrates= 14% Beta-blockers= 50% Calcium blockers= 34% ACE inhibitors= 27% Angiotensin II receptor blocker= 36% Stomach medicines= 87% Hypoglycaemic agents= 25%
Number of participants	246 randomised 122 assigned to Atorvastatin + ezetimibe, 100 ACA, 89 per protocol 124 assigned to Atorvastatin monotherapy, 102 ACA, 89 per protocol
Duration of follow-up	9-12 months
Indirectness	Downgraded by one increment due to intervention indirectness (unlikely that dose titration was matched between study arms)
Additional comments	Available case analysis

Study arms

Atorvastatin & Ezetimibe (N = 100)

Atorvastatin dose titration with a treatment goal of LDL-C <70 mg/dl. Ezetimibe 10 mg/day (122 assigned to study arm)

Atorvastatin (N = 102)

Dose titration with a treatment goal of LDL-C <70 mg/dl (124 assigned to study arm)

Characteristics

Arm-level characteristics

Characteristic	Atorvastatin & Ezetimibe (N = 100)	Atorvastatin (N = 102)
% Female Sample size	n = 22 ; % = 22	n = 20 ; % = 22
Mean age (SD) Mean (SD)	66 (10)	67 (10)
Ethnicity Nominal	NR	NR
Existing CVD diagnoses		
History of percutaneous coronary intervention Sample size	n = 19 ; % = 19	n = 15 ; % = 15
History of coronary artery bypass grafting	n = 0 ; % = 0	n = 0 ; % = 0

Characteristic	Atorvastatin & Ezetimibe (N = 100)	Atorvastatin (N = 102)
Sample size		
History of myocardial infarction Sample size	n = 15 ; % = 15	n = 13 ; % = 13
History of stroke Sample size	n = 10 ; % = 10	n = 1 ; % = 1
History of peripheral artery disease % Sample size	n = 3 ; % = 3	n = 4 ; % = 4
Diabetes Sample size	n = 29 ; % = 29	n = 31 ; % = 31
Insulin Sample size	n = 4 ; % = 4	n = 4 ; % = 4
Non-insulin Sample size	n = 25 ; % = 25	n = 27 ; % = 27
Chronic kidney disease Nominal	NR	NR
LDL cholesterol	109.8 (25.4)	108.3 (26.3)

Characteristic	Atorvastatin & Ezetimibe (N = 100)	Atorvastatin (N = 102)
Mean (SD)		
Statins used Sample size	n = 46 ; % = 46	n = 49 ; % = 48
Other lipid-lowering medication used Nominal	NR	NR

Outcomes

Study timepoints

- Baseline
- 10 month (Follow-up between 9-12 months, average follow-up in combination therapy group= 10.1 months, monotherapy group= 9.7 months)

Continuous Outcomes

Outcome	Atorvastatin & Ezetimibe , Baseline, N = 100	Atorvastatin & Ezetimibe , 10 month, N = 100	Atorvastatin , Baseline, N = 102	Atorvastatin , 10 month, N = 102
LDL-c (mg/dl) Final values Mean (SD)	109.8 (25.4)	63.2 (16.3)	108.3 (26.3)	73.3 (20.3)

Outcome	Atorvastatin & Ezetimibe , Baseline, N = 100	Atorvastatin & Ezetimibe , 10 month, N = 100	Atorvastatin , Baseline, N = 102	Atorvastatin , 10 month, N = 102
LDL-c (%) Percentage change from baseline Mean (SD)	NA (NA)	-40 (18)	NA (NA)	-29 (24)

LDL-c - Polarity - Lower values are better

LDL-c % change - Polarity - higher values are better (greater reduction is better)

Dichotomous Outcomes

Outcome	Atorvastatin & Ezetimibe , Baseline, N = 121	Atorvastatin & Ezetimibe , 10 month, N = 121	Atorvastatin , Baseline, N = 122	Atorvastatin , 10 month, N = 122
Increased liver transaminases Abnormal AST/ALT values No of events	n = NA ; % = NA	n = 1 ; % = 1	n = NA ; % = NA	n = 2 ; % = 2
Cardiovascular events No of events	n = NR ; % = NR	n = 24 ; % = 20	n = NR ; % = NR	n = 24 ; % = 20

Increased liver transaminases - Polarity - Lower values are better

Cardiovascular events - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

LDL-c

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

LDL-c % change

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Increased liver transaminases

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Indirectly applicable *(Lack of clarity for definition of abnormal lab value)*

Cardiovascular events-No Of Events

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Indirectly applicable *(Follow-up <12 months)*

Ueda, 2017

Bibliographic Reference	Ueda, Yasunori; Hiro, Takafumi; Hirayama, Atsushi; Komatsu, Sei; Matsuoka, Hiroshi; Takayama, Tadateru; Ishihara, Masaharu; Hayashi, Takatoshi; Saito, Satoshi; Kodama, Kazuhisa; ZIPANGU, Investigators; Effect of Ezetimibe on Stabilization and Regression of Intracoronary Plaque - The ZIPANGU Study.; Circulation journal : official journal of the Japanese Circulation Society; 2017; vol. 81 (no. 11); 1611-1619

Study details

Other publications associated with this study included in review	Hiro T, Hirayama A, Ueda Y, Komatsu S, Matsuoka H, Takayama T, Ishihara M, Hayashi T, Saito S, Kodama K; ZIPANGU investigators. Rationale and design of a randomized clinical study to investigate the effect of ezetimibe, a cholesterol absorption inhibitor, on the regression of intracoronary plaque evaluated by non-obstructive angioscopy and ultrasound: The ZIPANGU study. J Cardiol. 2014 Dec;64(6):501-7. doi: 10.1016/j.jjcc.2014.02.026. Epub 2014 Apr 13. PMID: 24725763.
Trial name / registration number	The ZIPANGU study. Registered in the UMIN Clinical Trial Registry (UMIN000006971).
Study location	Japan.

Study setting	Multi-centre- 14 sites.
Study dates	Recruitment began November 2011.
Sources of funding	Funding form Bayer Yakuhin, Ltd.
Inclusion criteria	People aged 20-80 years with elective percutaneous coronary intervention (PCI) who had at least 1 yellow plaque of grade ≥ 2 in the non-PCI target coronary artery segments and hypercholesterolemia (LDL-C > 100mg/dl) with or with out statin treatment.
Exclusion criteria	Pat history of hypersensitivity to the study drugs, triglycerides ≥ 400 mg/dl, AST or ALT > 3 times the upper limit of the normal range, serum creatinine ≥2.0 mg/dl, HbA1c ≥ 8% or ≥ 8.4%, insulin use, acute coronary syndrome in the past 3 months, secondary hypercholesterolemia, malignant tumour, familial hypercholesterolemia, pregnancy or cyclosporine use.
Recruitment / selection of participants	Patients enrolled at participating centres.
Intervention(s)	Ezetimibe 10 mg/day and atorvastatin was initially 10 mg/day (medium intensity intensity). Treatment started within 72 hours of PCI. Target LDL-C was < 70 mg/dl. If the LDL-C levels within 3 moths were ≥ 70 mg/dl the dosage of atorvastatin was increased to the maximum of 20 mg (high intensity statin) which is the maximum allowed dosage in Japan.
Comparator	Atorvastatin was initially 10 mg/day (medium intensity statin). Treatment started within 72 hours of PCI. Target LDL-C was < 100 mg/dl. If the LDL-C levels within 3 moths were ≥ 100 mg/dl the dosage of atorvastatin was increased to the maximum of 20 mg (high intensity statin), which is the maximum allowed dosage in Japan.
Background treatment	During follow up period, the medication compliance for the investigational drugs was checked regularly. Participants had counselling on lifestyle improvement. Diet and medical treatments for their complications or atherosclerosis prevention other than lipid management were administered comprehensively for all enrolled patients based on the individualised strategies of their doctors.

	The examinations by nonobstructive coronary angioscopy and intravascular ultrasound were serially performed at baseline and 9 months follow-up to evaluate the changes in plaque colour and volume. **Baseline characteristics** **Ezetimibe and atorvastatin:** Aspirin: 52 (96%) Clopidogrel: 53 (98%) Ticlopidine: 0 (0%) Current smoking: 18 (33%) Hypertension: 46 (85%) **Atorvastatin** Aspirin: 53 (98%) Clopidogrel: 50 (93%) Ticlopidine: 3 (6%) Current smoking: 22 (41%) Hypertension: 43 (80%)
Number of participants	131
Duration of follow-up	9 ± 2 months.

Indirectness	Intervention indirectness as dose titration unlikely to be matched between arms.
Additional comments	Available case analysis (following drops outs due to violation of inclusion/exclusion criteria and lack of follow-up examination).

Study arms

Ezetimibe and atorvastatin (N = 65)

Intervention(s)	Ezetimibe 10 mg/day and atorvastatin was initially 10 mg/day. Treatment started within 72 hours of PCI. Target LDL-C was < 70 mg/dl. If the LDL-C levels within 3 moths were ≥ 70 mg/dl the dosage of atorvastatin was increased to the maximum of 20 mg (maximum allowed dosage in Japan).
Comparator	Atorvastatin was initially 10 mg/day. Treatment started within 72 hours of PCI. Target LDL-C was < 100 mg/dl. If the LDL-C levels within 3 moths were ≥ 100 mg/dl the dosage of atorvastatin was increased to the maximum of 20 mg (maximum allowed dosage in Japan).
Background treatment	During follow up period, the medication compliance for the investigational drugs was checked regularly. Participants had counselling on lifestyle improvement. Diet and medical treatments for their complications or atherosclerosis prevention other than lipid management were administered comprehensively for all enrolled patients based on the individualised strategies of their doctors. The examinations by nonobstructive coronary angioscopy and intravascular ultrasound were serially performed at baseline and 9 months follow-up to evaluate the changes in plaque colour and volume.

Ezetimibe 10 mg/day and atorvastatin was initially 10 mg/day (medium intensity statin). Target LDL-C was < 70 mg/dl. If the LDL-C levels within 3 months were ≥ 70 mg/dl the dosage of atorvastatin was increased to the maximum of 20 mg (high intensity).

Atorvastatin (N = 66)

Atorvastatin was initially 10 mg/day (medium intensity statin). Target LDL-C was < 100 mg/dl. If the LDL-C levels within 3 months were ≥ 100 mg/dl the dosage of atorvastatin was increased to the maximum of 20 mg (high intensity statin).

Characteristics

Arm-level characteristics

Characteristic	Ezetimibe and atorvastatin (N = 65)	Atorvastatin (N = 66)
% Female Sample size	n = 13 ; % = 24	n = 10 ; % = 19
Mean age (SD) Mean (SD)	71 (8)	68 (11)
Ethnicity Nominal	NR	NR
Existing CVD diagnosis		
Myocardial infarction Sample size	n = 7 ; % = 13	n = 16 ; % = 30
Angina Pectoris Sample size	n = 30 ; % = 56	n = 22 ; % = 41
Stroke	n = 7 ; % = 13	n = 6 ; % = 11

Characteristic	Ezetimibe and atorvastatin (N = 65)	Atorvastatin (N = 66)
Sample size		
Peripheral artery disease Sample size	n = 4 ; % = 7	n = 3 ; % = 6
Chronic kidney disease Sample size	n = 20 ; % = 37	n = 15 ; % = 28
LDL-cholesterol (mg/dl) Mean (SD)	101 (27)	100 (27)
Non-HDL cholesterol Nominal	NR	NR
Statins used Sample size	n = 3 ; % = 6	n = 4 ; % = 7
Other lipid lowering medications Nominal	NR	NR
Type 2 diabetes Diabetes (type not reported) Sample size	n = 20 ; % = 37	n = 17 ; % = 31

Outcomes

Study timepoints

- Baseline
- 9 month (Months ± 2)

Continuous outcomes - lipids at 9 months

Outcome	Ezetimibe and atorvastatin, Baseline, N = 65	Ezetimibe and atorvastatin, 9 month, N = 54	Atorvastatin, Baseline, N = 66	Atorvastatin, 9 month, N = 54
LDL cholesterol (mg/dl) Mean (SD)	101 (27)	61 (17)	101 (27)	75 (16)

LDL cholesterol - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

LDL cholesterol

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Bias due to missing outcome data)*

Section	Question	Answer
Overall bias and Directness	Overall Directness	Indirectly applicable *(Intervention indirectness - dose titration unlikely to be matched between groups.)*

Wang, 2017

Bibliographic Reference	Wang, Jing; Ai, Xiao-Bo; Wang, Fei; Zou, Yao-Wu; Li, Li; Yi, Xiao-Lei; Efficacy of ezetimibe combined with atorvastatin in the treatment of carotid artery plaque in patients with type 2 diabetes mellitus complicated with coronary heart disease.; International angiology : a journal of the International Union of Angiology; 2017; vol. 36 (no. 5); 467-473

Study details

Secondary publication of another included study- see primary study for details	No additional information
Other publications associated with this study included in review	No additional information
Trial name / registration number	No additional information

Study type	Randomised controlled trial (RCT)
Study location	China
Study setting	Secondary care
Study dates	June 2015 - June 2016
Sources of funding	None reported
Inclusion criteria	Patients with all three of: carotid atherosclerosis, type 2 diabetes and coronary heart disease, who had an LDL-C ≥2.6 mmol/l after 3 months of statin treatment
Exclusion criteria	Type 1 diabetes, malignant tumours, secondary hypertension, diabetic ketoacidosis, hyperglycaemic hyperosmolar status, heart failure, liver and kidney disease and other serious organic disease, suffering from infectious diseases within 2 weeks, trauma, surgery, mental stimulation within 6 months.
Recruitment / selection of participants	Method not reported
Population subgroups	No additional information
Intervention(s)	Atorvastatin (20 mg/day)
Comparator	Ezetimibe (10 mg/d) and Atorvastatin (20 mg/day)
Background treatment	Other drugs for hypertension and arterial sclerosis such as aspirin, β-blockers, angiotensin converting enzyme inhibitors, angiotensin II receptor antagonist and hypoglycaemic drugs in both groups of patients were routinely used

Number of participants	100 randomised 49 assigned to atorvastatin group 51 assigned to atorvastatin + ezetimibe group
Duration of follow-up	12 months
Indirectness	None
Additional comments	No additional information

Study arms

Ezetimibe plus atorvastatin (N = 51)

Ezetimibe (10 mg/day) and atorvastatin (20 mg/day)

Atorvastatin (N = 49)

Atorvastatin (20 mg/day)

Characteristics

Arm-level characteristics

Characteristic	Ezetimibe plus atorvastatin (N = 51)	Atorvastatin (N = 49)
% Female Sample size	n = 20 ; % = 40	n = 19 ; % = 38
Mean age (SD) Mean (SD)	58 (10)	58 (9)
Ethnicity Nominal	NR	NR
Existing CVD diagnoses Nominal	NR	NR
Type 2 diabetes (years) Duration of diabetes (inclusion criteria was type 2 diabetes) Mean (SD)	5 (4)	5 (3.5)
Chronic kidney disease Nominal	NR	NR
LDL cholesterol Mean (SD)	3.53 (0.87)	3.45 (0.75)
Non-HDL cholesterol	NR	NR

Characteristic	Ezetimibe plus atorvastatin (N = 51)	Atorvastatin (N = 49)
Nominal		
Statins used Sample size	n = 51 ; % = 100	n = 49 ; % = 100
Other lipid-lowering medication used Nominal	NR	NR

Outcomes

Study timepoints

- Baseline
- 12 month

Continuous Outcomes

Outcome	Ezetimibe plus atorvastatin , Baseline, N = 49	Ezetimibe plus atorvastatin , 12 month, N = 49	Atorvastatin , Baseline, N = 51	Atorvastatin , 12 month, N = 51
LDL-c (mmol/l) final values Mean (SD)	3.53 (0.87)	1.67 (0.43)	3.45 (0.75)	2.04 (0.54)

LDL-c - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

LDL-c

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(no details about randomisation, allocation concealment or treatment adherence)*
Overall bias and Directness	Overall Directness	Directly applicable

Wang, 2016

Bibliographic Reference	Wang, Xiaofang; Zhao, Xiaoyan; Li, Ling; Yao, Haimu; Jiang, Yan; Zhang, Jinying; Effects of Combination of Ezetimibe and Rosuvastatin on Coronary Artery Plaque in Patients with Coronary Heart Disease.; Heart, lung & circulation; 2016; vol. 25 (no. 5); 459-65

Study details

Study type	Randomised controlled trial (RCT)
Study location	China
Study setting	Secondary care
Study dates	January 2011 - January 2014

Sources of funding	Supported by the Medical Science and Technology Research Projects of Henan Province
Inclusion criteria	One or more atherosclerotic lesions near the middle of the coronary arteries, total cholesterol ≥5.2 mmol/l and/or LDL-C ≥3.6 mmol/l
Exclusion criteria	Contraindications to the intervention, statin use, high transaminase levels (>2-fold normal)
Recruitment / selection of participants	Method not reported
Population subgroups	No additional information
Intervention(s)	Ezetimibe (10 mg, once a night) plus rosuvastatin (10 mg, once a night)
Comparator	Rosuvastatin alone (10 mg, once a night)
Background treatment	**Ezetimibe + rosuvastatin group** Nitrate ester= 84% Antiplatelet= 100% Beta-receptor blocker= 78% Calcium channel blocker= 30% Low weight molecular heparin= 80% Angiotensin-converting enzyme inhibitor/angiotensin receptor blocker= 36% **Rosuvastatin group**

	Nitrate ester= 81% Antiplatelet= 100% Beta-receptor blocker= 73% Calcium channel blocker= 27% Low weight molecular heparin= 81% Angiotensin-converting enzyme inhibitor/angiotensin receptor blocker= 33%
Number of participants	106 participants randomised 55 assigned to ezetimibe + rosuvastatin group, 50 completed 51 assigned to rosuvastatin group, 48 completed
Duration of follow-up	12 months
Indirectness	None
Additional comments	Per protocol

Study arms

Ezetimibe & Rosuvastatin (N = 50)

Both 10 mg/night (55 patients assigned to study arm)

Rosuvastatin (N = 48)

10 mg/night (51 patients assigned to study arm)

Characteristics

Arm-level characteristics

Characteristic	Ezetimibe & Rosuvastatin (N = 50)	Rosuvastatin (N = 48)
% Female Sample size	n = 14 ; % = 28	n = 13 ; % = 27
Mean age (SD) Mean (SD)	63 (10)	65 (12)
Ethnicity Nominal	NR	NR
Existing CVD diagnoses Nominal	NR	NR
Type 2 diabetes Sample size	n = 18 ; % = 36	n = 17 ; % = 35
Chronic kidney disease Nominal	NR	NR

Characteristic	Ezetimibe & Rosuvastatin (N = 50)	Rosuvastatin (N = 48)
LDL cholesterol Mean (SD)	3.62 (1.18)	3.48 (1.26)
Non-HDL cholesterol Nominal	NR	NR
Statins used Sample size	n = 0 ; % = 0	n = 0 ; % = 0
Other lipid-lowering medication used Nominal	NR	NR

Outcomes

Study timepoints

- Baseline
- 12 month

Continuous Outcomes

Outcome	Ezetimibe & Rosuvastatin, Baseline, N = 50	Ezetimibe & Rosuvastatin, 12 month, N = 50	Rosuvastatin , Baseline, N = 48	Rosuvastatin , 12 month, N = 48
LDL-c (mmol/l) Final values Mean (SD)	3.62 (1.18)	1.37 (0.83)	3.48 (1.26)	1.85 (0.79)

LDL-c - Polarity - Lower values are better

Dichotomous Outcomes

Outcome	Ezetimibe & Rosuvastatin, Baseline, N = 50	Ezetimibe & Rosuvastatin, 12 month, N = 50	Rosuvastatin , Baseline, N = 48	Rosuvastatin , 12 month, N = 48
Rhabdomyolysis Final values No of events	n = NA ; % = NA	n = 0 ; % = 0	n = NA ; % = NA	n = 0 ; % = 0
Increased liver transaminases (AST or ALT >3x ULN) Final values No of events	n = NA ; % = NA	n = 2 ; % = 4	n = NA ; % = NA	n = 1 ; % = 2.1
Major adverse cardiac events (MI, cardiac death or stroke) Final values No of events	n = NA ; % = NA	n = 0 ; % = 0	n = NA ; % = NA	n = 1 ; % = 2.1

Rhabdomyolysis - Polarity - Lower values are better

Increased liver transaminases (AST or ALT >3x ULN) - Polarity - Lower values are better

Major adverse cardiac events - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

LDL-c

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(no details about randomisation, or allocation concealment)*
Overall bias and Directness	Overall Directness	Directly applicable

Rhabdomyolysis

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(no details about randomisation, or allocation concealment)*
Overall bias and Directness	Overall Directness	Directly applicable

Increased liver transaminases (ASTorALT>3xULN)

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(no details about randomisation, or allocation concealment)*
Overall bias and Directness	Overall Directness	Directly applicable

MACE

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(no details about randomisation, or allocation concealment)*
Overall bias and Directness	Overall Directness	Directly applicable

West, 2011

Bibliographic Reference	West, AM; Anderson, JD; Epstein, FH; Meyer, CH; Wang, H; Hagspiel, KD; Berr, SS; Harthun, NL; Weltman, AL; Dimaria, JM; et, al.; Low-density lipoprotein lowering does not improve calf muscle perfusion, energetics, or exercise performance in peripheral arterial disease; Journal of the American College of Cardiology; 2011; vol. 58 (no. 10); 1068-1076

Study details

Secondary publication of another included	West 2011, The Effect of Ezetimibe on Peripheral Arterial Atherosclerosis Depends Upon Statin Use at Baseline. See primary study for details.

study- see primary study for details	

West, 2011

Bibliographic Reference	West, Amy M; Anderson, Justin D; Meyer, Craig H; Epstein, Frederick H; Wang, Hongkun; Hagspiel, Klaus D; Berr, Stuart S; Harthun, Nancy L; DiMaria, Joseph M; Hunter, Jennifer R; Christopher, John M; Chew, Joshua D; Winberry, Gabriel B; Kramer, Christopher M; The effect of ezetimibe on peripheral arterial atherosclerosis depends upon statin use at baseline.; Atherosclerosis; 2011; vol. 218 (no. 1); 156-62

Study details

Other publications associated with this study included in review	West, 2011; Low-density lipoprotein lowering does not improve calf muscle perfusion, energetics, or exercise performance in peripheral arterial disease (additional report of the same trial)
Trial name / registration number	NCT00587678
Study type	Randomised controlled trial (RCT)
Study location	not specified
Study setting	Primary care

Study dates	not specified
Sources of funding	National Heart Lung and Blood Institute at the National Institutes of Health, grant number: R01 HL075792 (CMK) and the National Center for Research Resources, grant number: M01RR000847 and the National Institute of Biomedical Imaging and Bioengineering, grant number: T32 EB003841 (JDA, AMW).
Inclusion criteria	Peripheral artery disease patients between the ages of 30 and 85 years with symptoms of intermittent claudication and an ankle-brachial index (ABI) between 0.4 and 0.9, based on vascular lab testing done during the screening period; statin-naïve patients (no statin therapy for at least the prior 6 months) regardless of baseline LDL-C cholesterol
Exclusion criteria	rest pain, critical limb ischemia, contraindication to MRI, and pregnancy.
Recruitment / selection of participants	15 months recruitment period; people meeting inclusion criteria
Population subgroups	none reported; study fall under medium intensity statin strata
Intervention(s)	Combination of simvastatin 40mg plus ezetimibe 10mg daily
Comparator	Simvastatin 40mg daily
Background treatment	No information
Number of participants	67 analysed but 33 patients included in the present analysis as paper included a randomised population (n=33) and a non-randomised ezetimibe group in a parallel observational study not eligible for the present review due to study design.
Duration of follow-up	2 years but 1-year time point relevant and extracted in the present review; mean (SD) time to year 1 visit: 383 (64) days

Indirectness	none
Additional comments	Lipids were quantified at study entry and annually for two years. Patients were screened at 8 weeks via study coordinator verbal questioning and annually thereafter for symptoms of muscle pain, weakness, or tenderness, and blood was drawn for liver function tests at the same time points. Over the two year study period, patients were also followed for major adverse cardiovascular events (MACE = death, myocardial infarction, stroke, and transient ischemic attack). All lipid and plaque parameters are reported from the repeated measures model. The results were adjusted for pairwise comparison using Bonferroni correction. Subjects with incomplete data were assumed to be missing at random. Given the relatively small sample size for each group, imputation analysis was not performed as it may distort the distribution of variables and introduce bias. Bivariate relationships between changes in lipid parameters and changes in vessel wall parameters were examined using either Pearson's correlation coefficient or Spearman's rank correlation coefficient.

Study arms

Simvastatin 40 mg + Ezetimibe 10mg (N = 22)

Combination of simvastatin 40mg plus ezetimibe 10mg daily

Simvastatin 40mg (N = 22)

Simvastatin 40mg daily

Characteristics

Arm-level characteristics

Characteristic	Simvastatin 40 mg + Ezetimibe 10mg (N = 22)	Simvastatin 40mg (N = 22)
% Female Sample size	n = 8 ; % = 44	n = 5 ; % = 31
Mean age (SD) Mean (SD)	62 (8)	59 (10)
Ethnicity White Sample size	n = 14 ; % = 78	n = 13 ; % = 81
Black Sample size	n = 3 ; % = 17	n = 2 ; % = 13
American Indian Sample size	n = 1 ; % = 5	n = 1 ; % = 6
Existing CVD diagnoses History of coronary artery disease (CAD) Sample size	n = 10 ; % = 56	n = 8 ; % = 50
LDL cholesterol (mg/dl) Mean (SD)	118 (41)	118 (34)
Aspirin/clopidogrel	n = 13 ; % = 72	n = 11 ; % = 69

Characteristic	Simvastatin 40 mg + Ezetimibe 10mg (N = 22)	Simvastatin 40mg (N = 22)
Sample size		
ACE inhibitor Sample size	n = 5 ; % = 28	n = 8 ; % = 50
ARB Sample size	n = 4 ; % = 22	n = 2 ; % = 13
β-Blockers Sample size	n = 6 ; % = 33	n = 6 ; % = 38
Cilastazol Sample size	n = 2 ; % = 11	n = 2 ; % = 13
Niacin Sample size	n = 0 ; % = 0	n = 1 ; % = 6.25
Fibrate Sample size	n = 0 ; % = 0	n = 2 ; % = 13
Fish oils Sample size	n = 1 ; % = 5.55	n = 1 ; % = 6.25
Diabetes mellitus	n = 5 ; % = 28	n = 5 ; % = 31

Characteristic	Simvastatin 40 mg + Ezetimibe 10mg (N = 22)	Simvastatin 40mg (N = 22)
Sample size		

Outcomes

Study timepoints

- 1 year (mean (SD) = 383 (64) days to 1 year time-point)
- 2 year

LDL-C

Outcome	Simvastatin 40 mg + Ezetimibe 10mg, 1 year, N = 18	Simvastatin 40 mg + Ezetimibe 10mg, 2 year, N =	Simvastatin 40mg, 1 year, N = 16	Simvastatin 40mg, 2 year, N =
LDL-C mean (SD) at 1 year (mg/dl) Mean (SD)	67 (31)	-	91 (32)	-

LDL-C mean (SD) at 1 year - Polarity - Lower values are better

MACE at 2 year follow-up

Outcome	Simvastatin 40 mg + Ezetimibe 10mg, 1 year, N =	Simvastatin 40 mg + Ezetimibe 10mg, 2 year, N = 22	Simvastatin 40mg, 1 year, N =	Simvastatin 40mg, 2 year, N = 22
MACE (n (%)) death, myocardial infarction, stroke, and transient ischemic attack No of events	-	n = 4 ; % = 23.5	-	n = 2 ; % = 14.3

MACE - Polarity - Lower values are better

Major adverse cardiovascular events (MACE) = death, myocardial infarction, stroke, and transient ischemic attack

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

LDL-C-at 1 year

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

MACE at 2 years

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Zanchin, 2021

Bibliographic Reference	Zanchin, Christian; Koskinas, Konstantinos C; Ueki, Yasushi; Losdat, Sylvain; Haner, Jonas D; Bar, Sarah; Otsuka, Tatsuhiko; Inderkum, Andrea; Jensen, Maria Radu Juul; Lonborg, Jacob; Fahrni, Gregor; Ondracek, Anna S; Daemen, Joost; van Geuns, Robert-Jan; Iglesias, Juan F; Matter, Christian M; Spirk, David; Juni, Peter; Mach, Francois; Heg, Dik; Engstrom, Thomas; Lang, Irene; Windecker, Stephan; Raber, Lorenz; Effects of the PCSK9 antibody alirocumab on coronary atherosclerosis in patients with acute myocardial infarction: a serial, multivessel, intravascular ultrasound, near-infrared spectroscopy and optical coherence tomography imaging study-Rationale and design of the PACMAN-AMI trial.; American heart journal; 2021; vol. 238; 33-44

Study details

Secondary publication of another included study- see primary study for details	Rationale and design of PACMAN-AMI trial. See main study entry for full details (Räber 2022).
Trial name / registration number	PACMAN-AMI NCT03067844

Appendix E Forest plots: primary analyses

For all outcomes lower values are better, as this would represent either a greater reduction in cholesterol, a lower level of cholesterol at the study endpoint or fewer adverse events occurring.

E.1 Ezetimibe plus high or moderate intensity statin versus high or moderate statin in CVD secondary prevention

Figure 2: % change from baseline in LDL-C

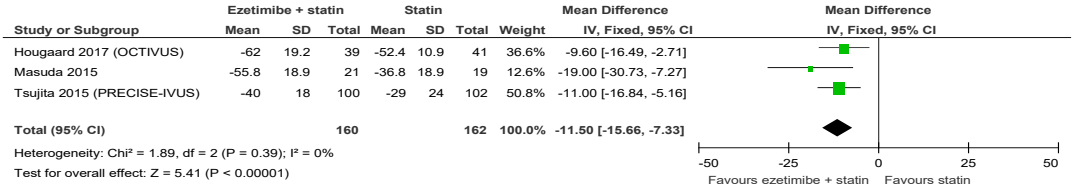
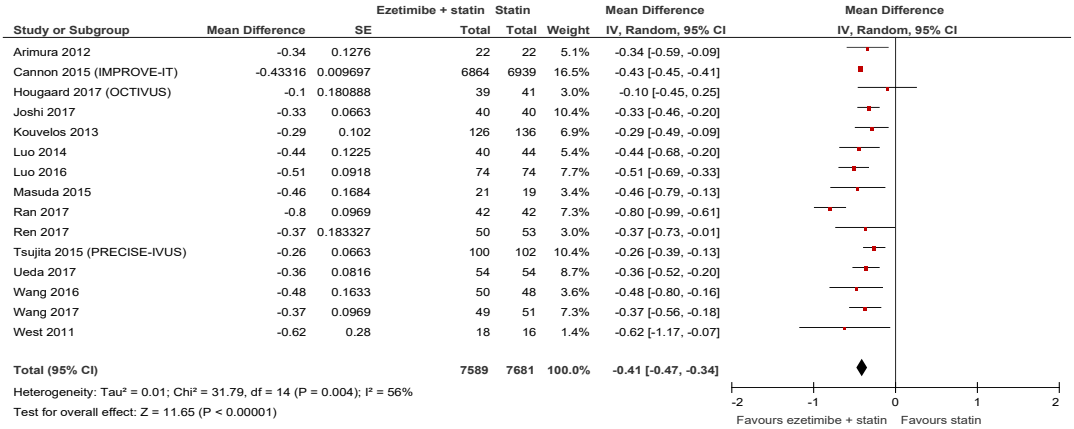


Figure 3: Absolute change from baseline or final LDL-C value (mmol/l)



A random effects model was used for the analysis due to heterogeneity unexplained by subgroup analysis.

Figure 4: % change from baseline in non-HDL-C

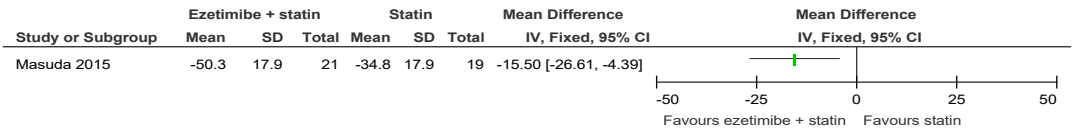
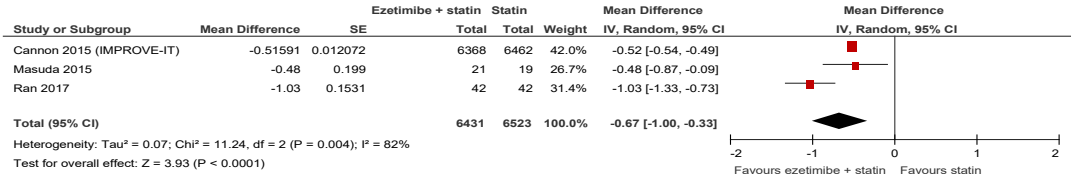


Figure 5: Absolute change from baseline or final non-HDL-C value (mmol/l)



A random effects model was used for the analysis due to heterogeneity unexplained by subgroup analysis.

Figure 6: Major adverse cardiovascular events (dichotomous)

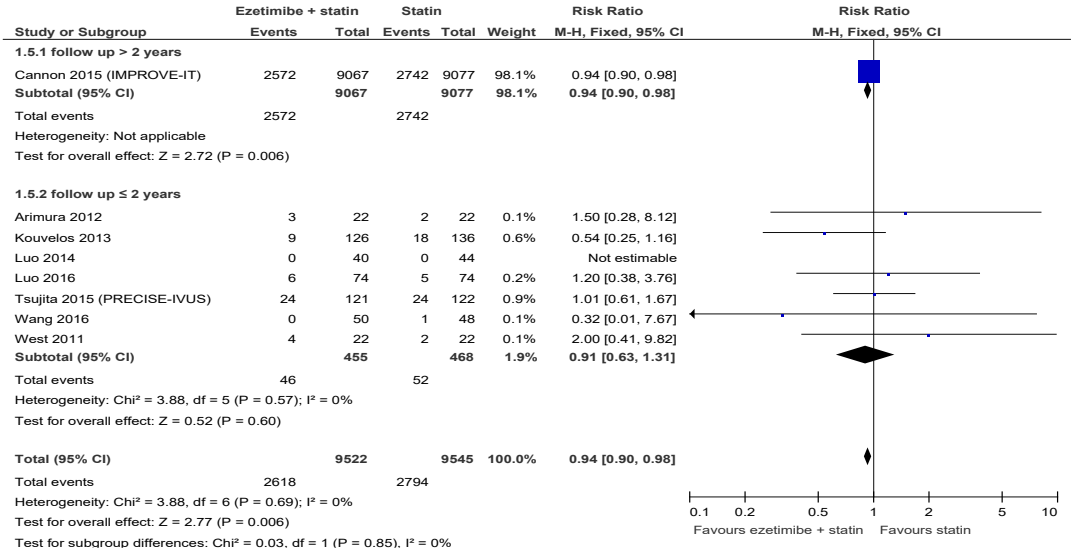


Figure 7: Major adverse cardiovascular events (time-to-event)

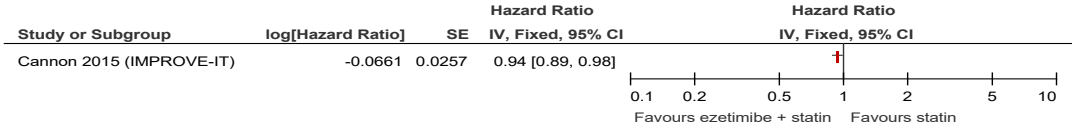


Figure 8: Myopathy or rhabdomyolysis

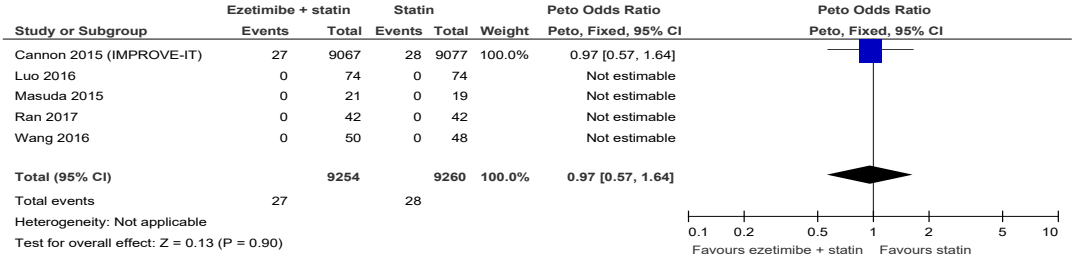


Figure 9: Raised liver transaminases

Scale larger than other dichotomous outcomes to accommodate 95% CI width.

Figure 10: Cancer

Study or Subgroup	Ezetimibe + statin Events	Total	Statin Events	Total	Risk Ratio M-H, Fixed, 95% CI
Cannon 2015 (IMPROVE-IT)	748	9067	732	9077	1.02 [0.93, 1.13]

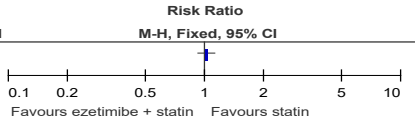
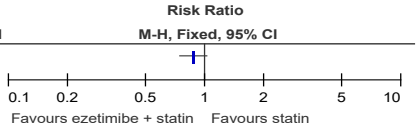


Figure 11: Gall-bladder-related adverse events

Study or Subgroup	Ezetimibe + statin Events	Total	Statin Events	Total	Risk Ratio M-H, Fixed, 95% CI
Cannon 2015 (IMPROVE-IT)	281	9067	321	9077	0.88 [0.75, 1.03]



E.2 PCSK9 monoclonal antibodies versus placebo or usual care in CVD secondary prevention

Figure 12: % change from baseline in LDL-C

Study or Subgroup	Mean Difference	SE	PCSK9i Total	Placebo or UC Total	Weight	Mean Difference IV, Random, 95% CI
Ako 2019	-50.5	2.758623	93	89	11.5%	-50.50 [-55.91, -45.09]
Giugliano 2012 (LAPLACE-TIMI 57: 140mg)	-66.1	2.758812	78	78	11.5%	-66.10 [-71.51, -60.69]
Giugliano 2012 (LAPLACE-TIMI 57: 420 mg)	-50.3	0.059013	80	79	13.7%	-50.30 [-50.42, -50.18]
Kereiakes 2015 (ODYSSEY COMBO I)	-41	3.677698	167	79	10.3%	-41.00 [-48.21, -33.79]
Koh 2018 (ODYSSEY KT)	-63.4	4.172529	97	102	9.6%	-63.40 [-71.58, -55.22]
McCullough 2018 (ODYSSEY Long Term)	-61.8	1.442221	1201	626	13.0%	-61.80 [-64.63, -58.97]
Ray 2019 (ODYSSEY DM-DYSLIPIDEMIA)	-45.9	5.8	94	47	7.5%	-45.90 [-57.27, -34.53]
Ray 2019 (ODYSSEY DM-INSULIN)	-48.5	4.4	115	55	9.3%	-48.50 [-57.12, -39.88]
Sabatine 2017 (FOURIER)	-59	0.5102	13784	13780	13.6%	-59.00 [-60.00, -58.00]
Total (95% CI)			**15709**	**14935**	**100.0%**	**-54.62 [-59.28, -49.97]**

Heterogeneity: Tau² = 41.25; Chi² = 398.43, df = 8 (P < 0.00001); I² = 98%
Test for overall effect: Z = 23.01 (P < 0.00001)

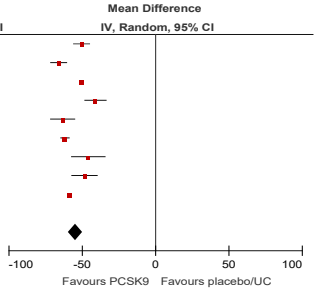
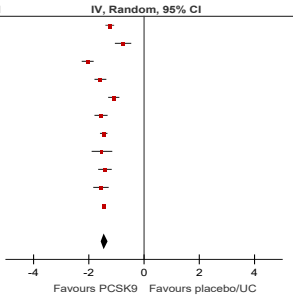


Figure 13: Absolute change from baseline or final LDL-C value (mmol/l)

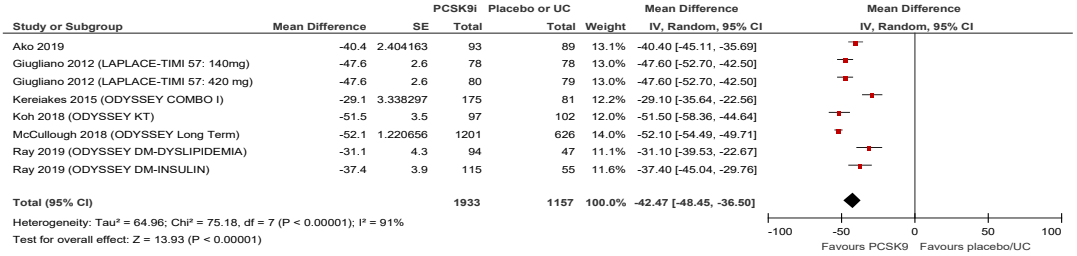
Study or Subgroup	Mean Difference	SE	Favours PCSK9 Total	Placebo or UC Total	Weight	Mean Difference IV, Random, 95% CI
Ako 2019	-1.24	0.070711	93	89	10.3%	-1.24 [-1.38, -1.10]
Gao 2021	-0.76	0.141064	30	31	7.7%	-0.76 [-1.04, -0.48]
Giugliano 2012 (LAPLACE-TIMI 57: 140mg)	-2.04	0.1	78	78	9.2%	-2.04 [-2.24, -1.84]
Giugliano 2012 (LAPLACE-TIMI 57: 420 mg)	-1.58	0.1	80	79	9.2%	-1.58 [-1.78, -1.38]
Kereiakes 2015 (ODYSSEY COMBO I)	-1.09646	0.093477	167	79	9.5%	-1.10 [-1.28, -0.91]
Koh 2018 (ODYSSEY KT)	-1.55677	0.111558	97	102	8.8%	-1.56 [-1.78, -1.34]
Nicholls 2016 (GLAGOV)	-1.46109	0.059013	484	484	10.7%	-1.46 [-1.58, -1.35]
Nicholls 2022 (HUYGENS)	-1.52315	0.181249	80	81	6.3%	-1.52 [-1.88, -1.17]
Raber 2022 (PACMAN AMI)	-1.41454	0.11582	126	132	8.6%	-1.41 [-1.64, -1.19]
Rehberger 2022	-1.56	0.1327	69	31	8.0%	-1.56 [-1.82, -1.30]
Sabatine 2017 (FOURIER)	-1.44816	0.013194	13784	13780	11.6%	-1.45 [-1.47, -1.42]
Total (95% CI)			**15088**	**14966**	**100.0%**	**-1.43 [-1.56, -1.30]**

Heterogeneity: Tau² = 0.04; Chi² = 85.25, df = 10 (P < 0.00001); I² = 88%
Test for overall effect: Z = 21.48 (P < 0.00001)



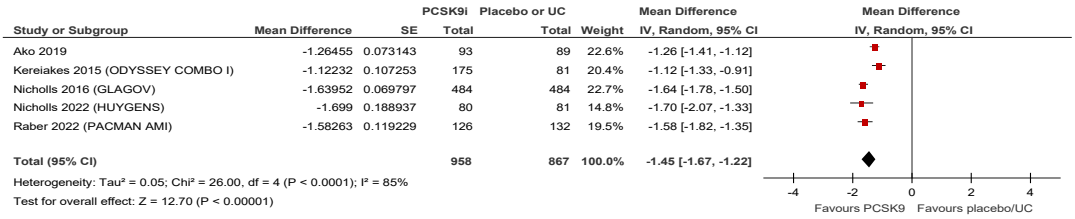
Random effects model was used for the analysis due to heterogeneity unexplained by subgroup analysis.

Figure 14: % change from baseline in non-HDL-C



Random effects model was used for the analysis due to heterogeneity unexplained by subgroup analysis.

Figure 15: Absolute change from baseline or final non-HDL-C value (mmol/l)



Random effects model was used for the analysis due to heterogeneity unexplained by subgroup analysis.

Figure 16: Major adverse cardiovascular events (dichotomous)

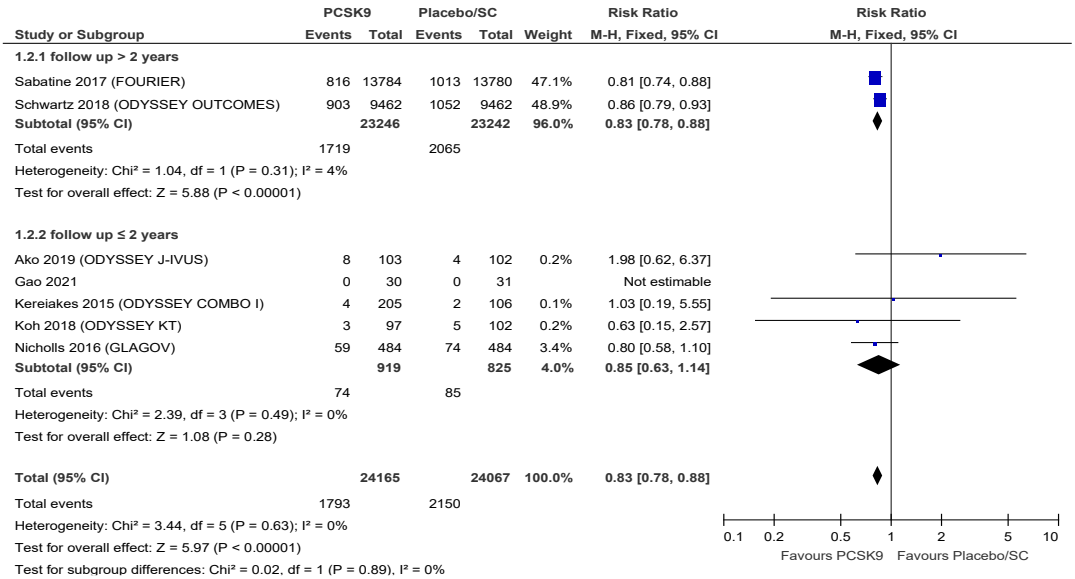


Figure 17: Major adverse cardiovascular events (time-to-event)

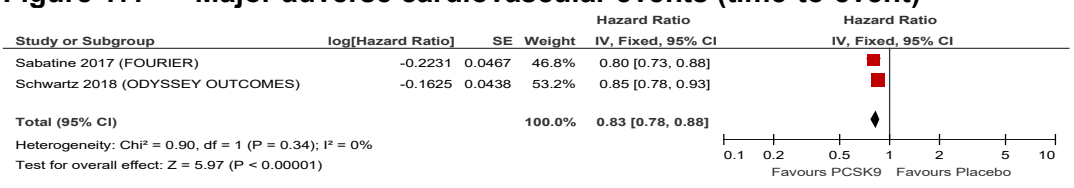


Figure 18: Myopathy/rhabdomyolysis

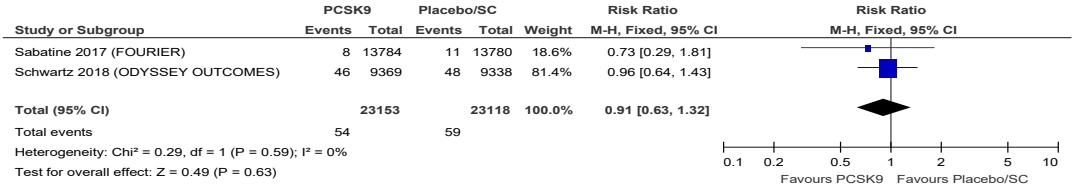


Figure 19: New-onset diabetes

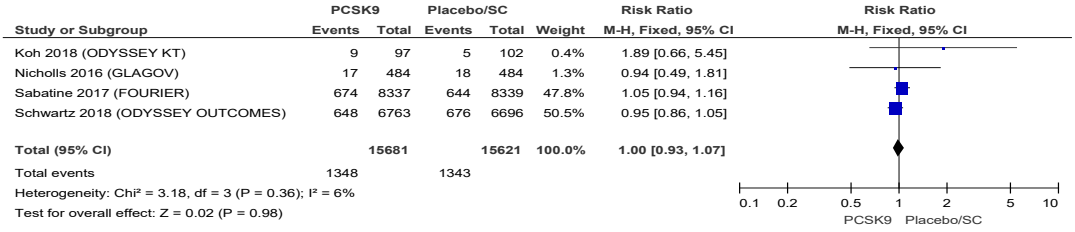
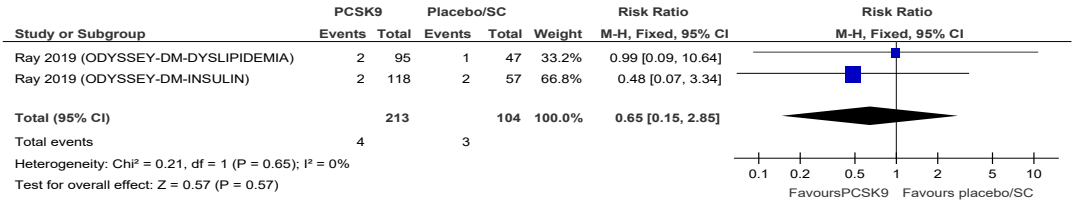


Figure 20: Increased liver transaminases

Figure 21: Injection-site reactions

Scale larger than other dichotomous outcomes to accommodate 95% CI width.

Figure 22: Nausea



E.3 PCSK9 monoclonal antibodies versus ezetimibe in CVD secondary prevention

Figure 23: % change from baseline in LDL-C

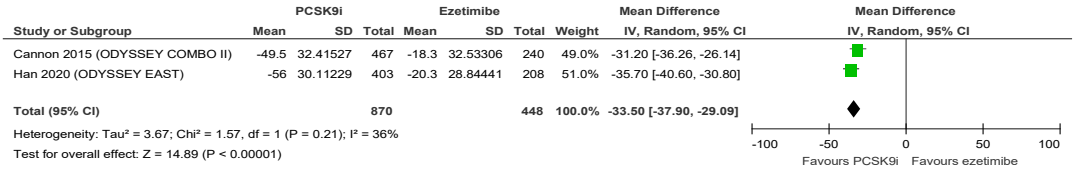


Figure 24: Final LDL-C value (mmol/l)

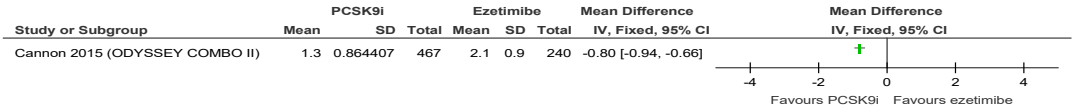


Figure 25: % change from baseline in non-HDL-C

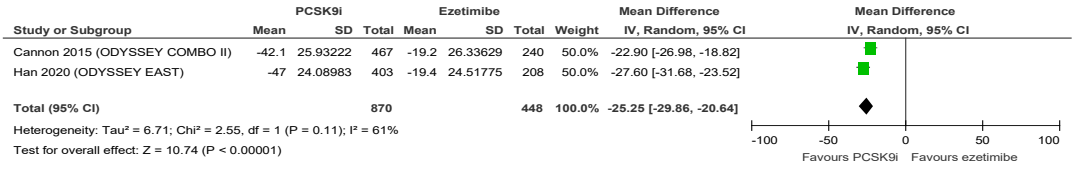


Figure 26: Major adverse cardiovascular events

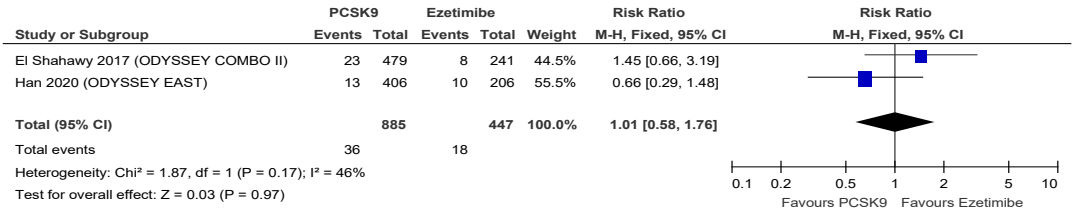


Figure 27: New-onset diabetes

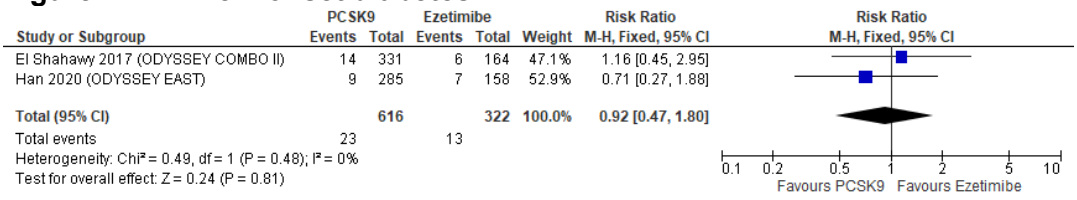
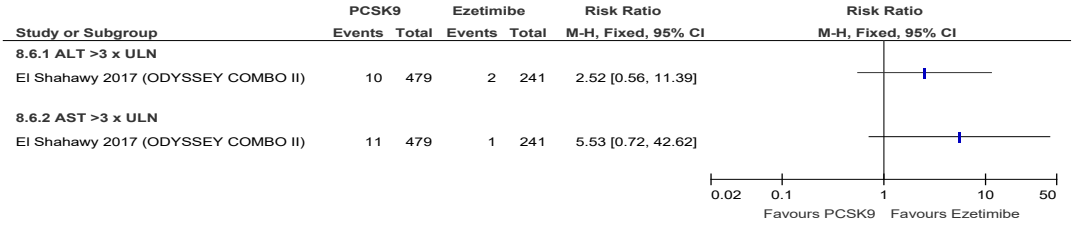


Figure 28: Increased liver transaminases



Scale larger than other dichotomous outcomes to accommodate 95% CI width.

Figure 29: Injection-site reactions

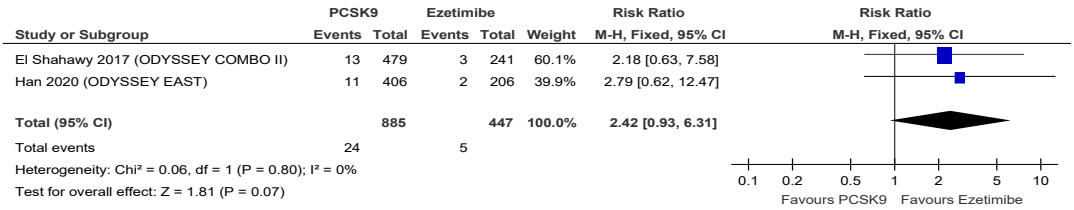
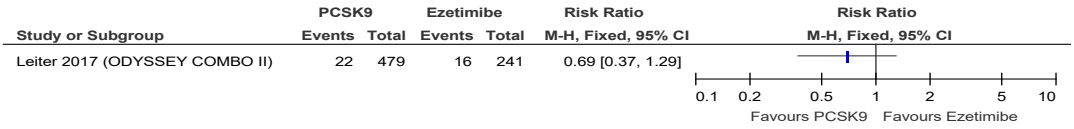
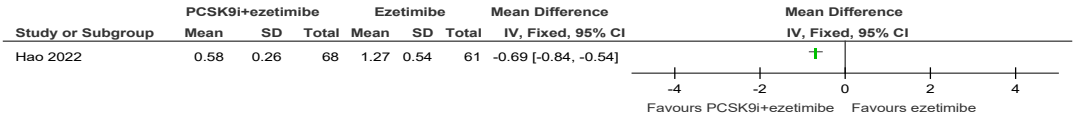


Figure 30: Influenza



E.4 PCSK9 monoclonal antibodies plus ezetimibe versus ezetimibe in CVD secondary prevention

Figure 31: Final LDL-C value (mmol/l)



E.5 Inclisiran versus placebo in CVD secondary prevention

Figure 32: % change from baseline in LDL-C

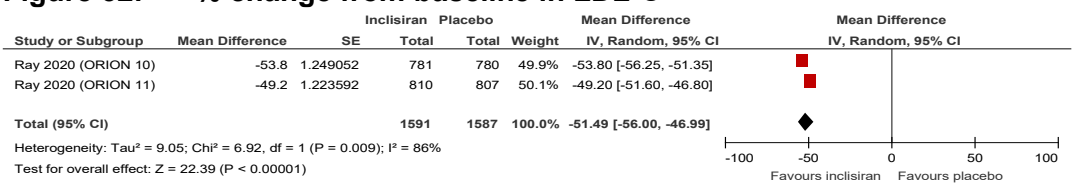


Figure 33: Absolute change from baseline in LDL-C (mmol/l)

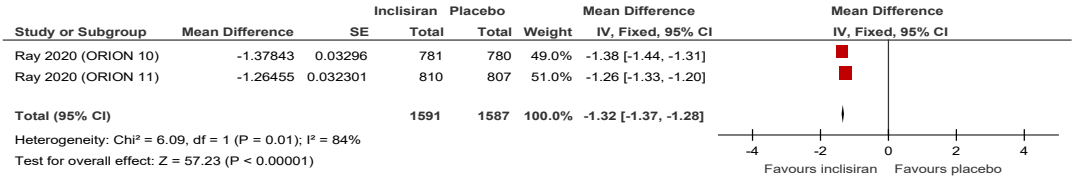


Figure 34: Major adverse cardiovascular events

Figure 35: Increased liver transaminases

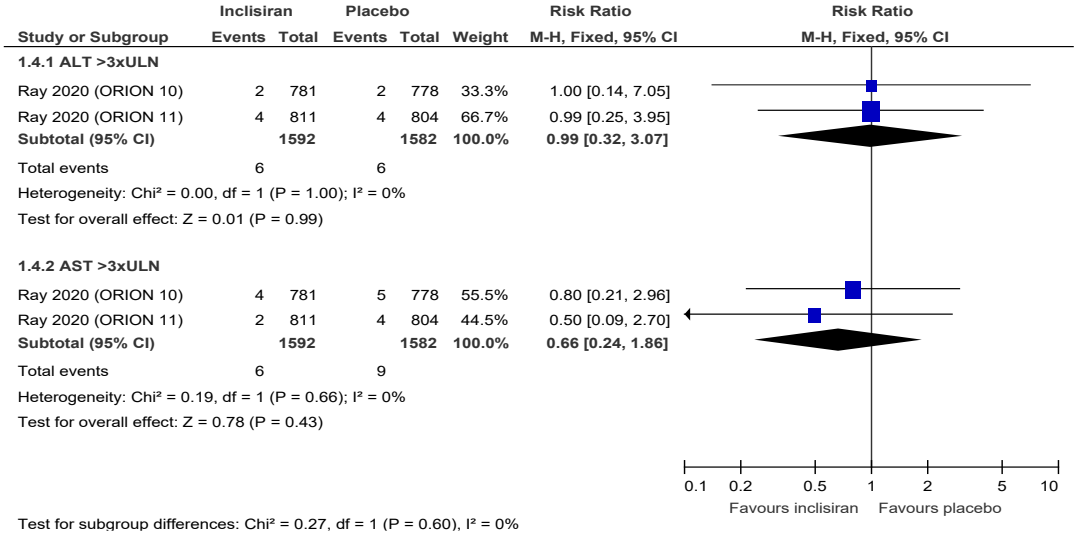
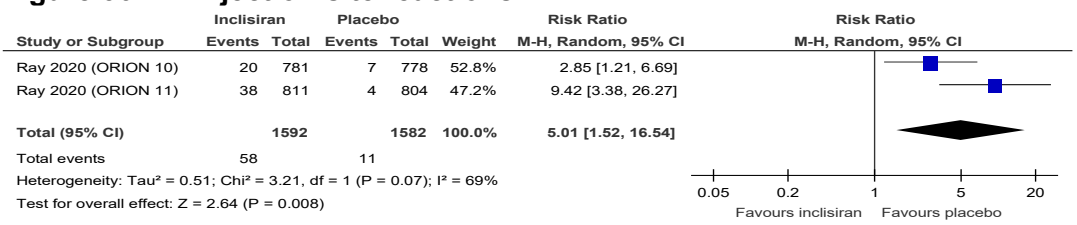


Figure 36: Injection-site reactions



Scale larger than other dichotomous outcomes to accommodate 95% CI width.

Appendix F Forest plots: sensitivity analyses

F.1 Ezetimibe plus high or moderate intensity statin versus high or moderate statin in CVD secondary prevention

F.1.1 Baseline lipid levels

Figure 37: Absolute change from baseline in LDL-C (mmol/l): between-trial subgroup analysis stratified by baseline LDL-C

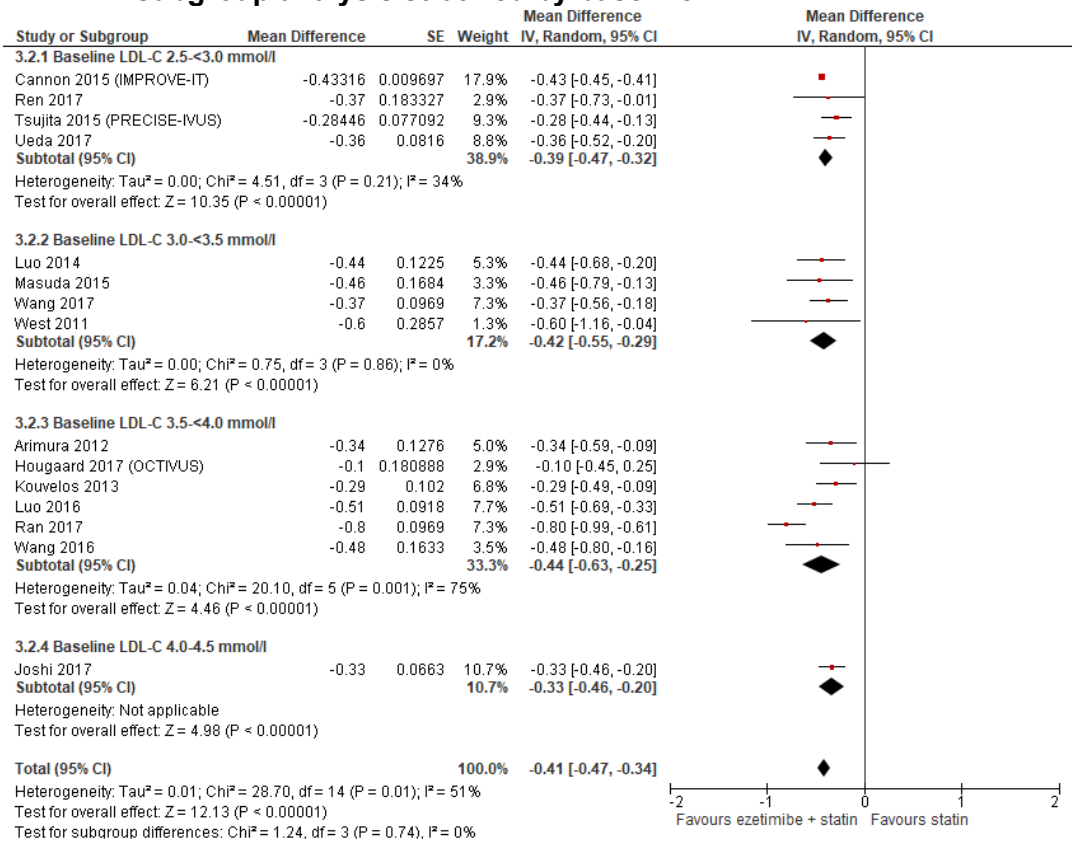


Figure 38: Absolute change from baseline in non-HDL-C (mmol/l): between-trial subgroup analysis stratified by baseline non-HDL-C

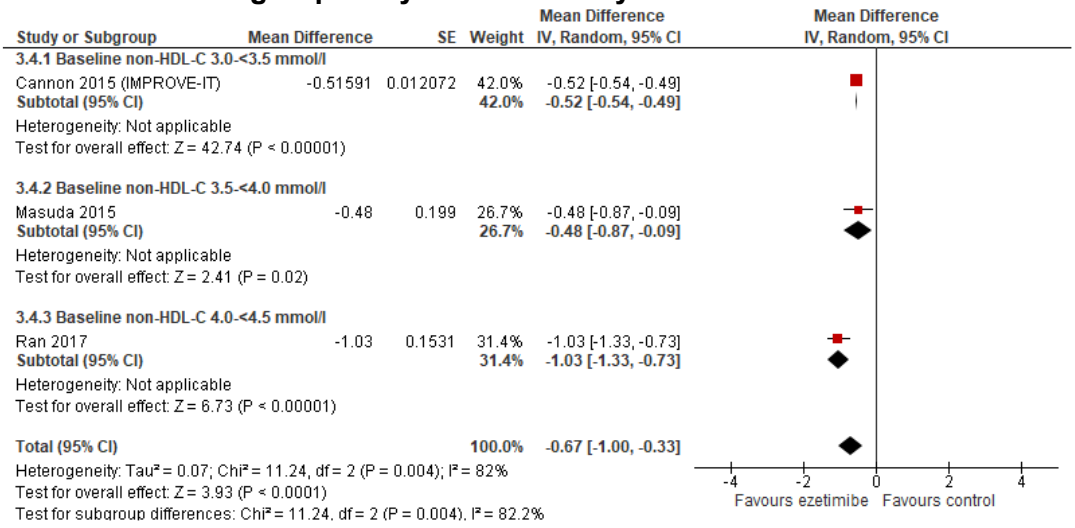


Figure 39: Major adverse cardiovascular events: within-trial subgroup analysis stratified by baseline LDL-C (mg/dl)

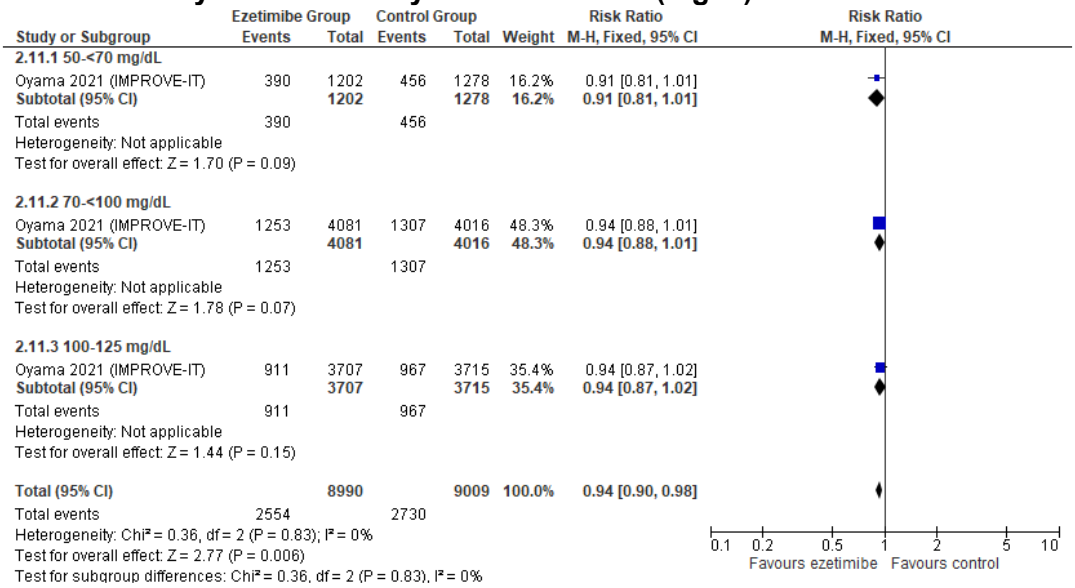
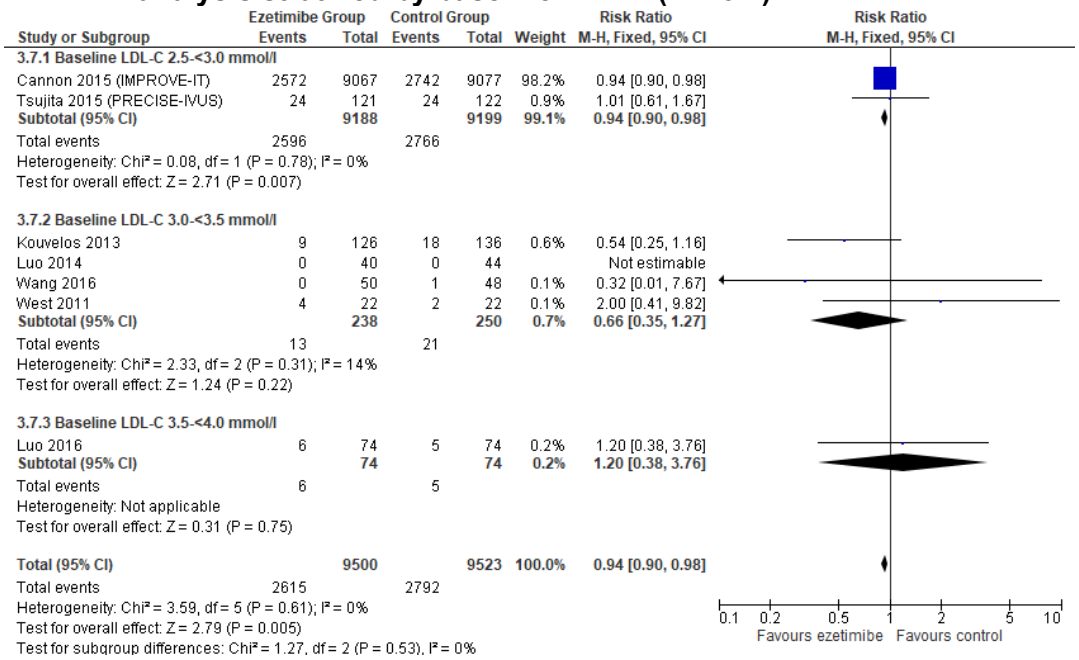


Figure 40: Major adverse cardiovascular events: between-trial subgroup analysis stratified by baseline LDL-C (mmol/l)



F.1.2 Statin experience or intensity

Figure 41: Absolute change from baseline in LDL-C (mmol/l): between-trial subgroup analysis stratified by statin experience

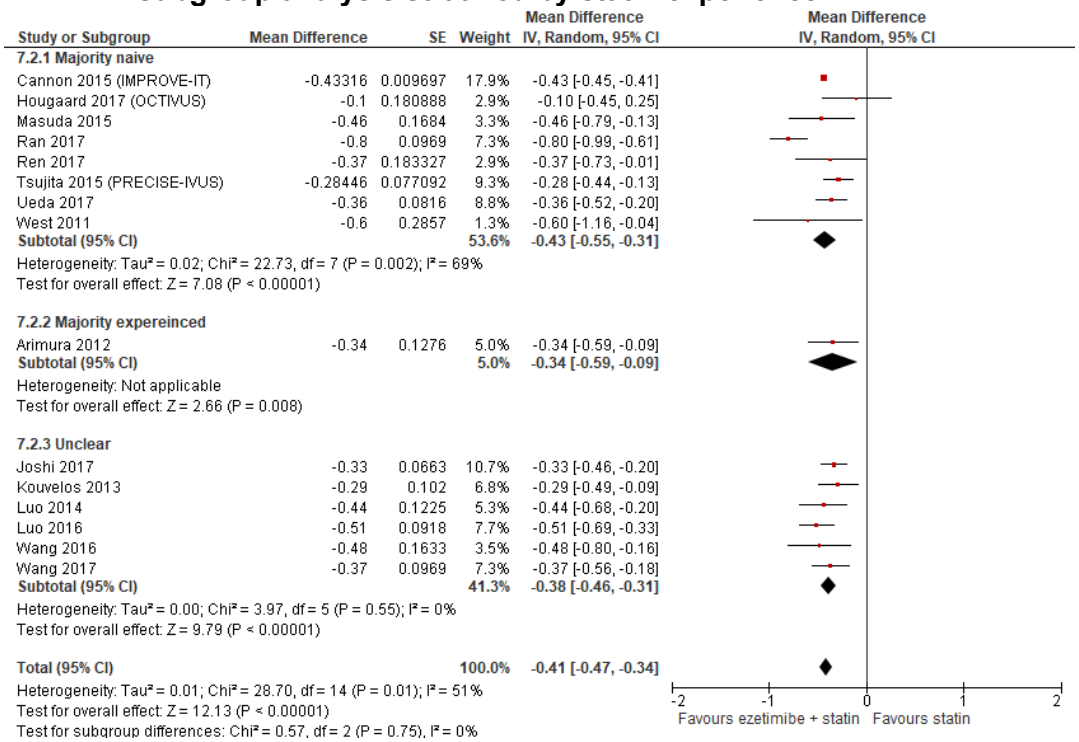
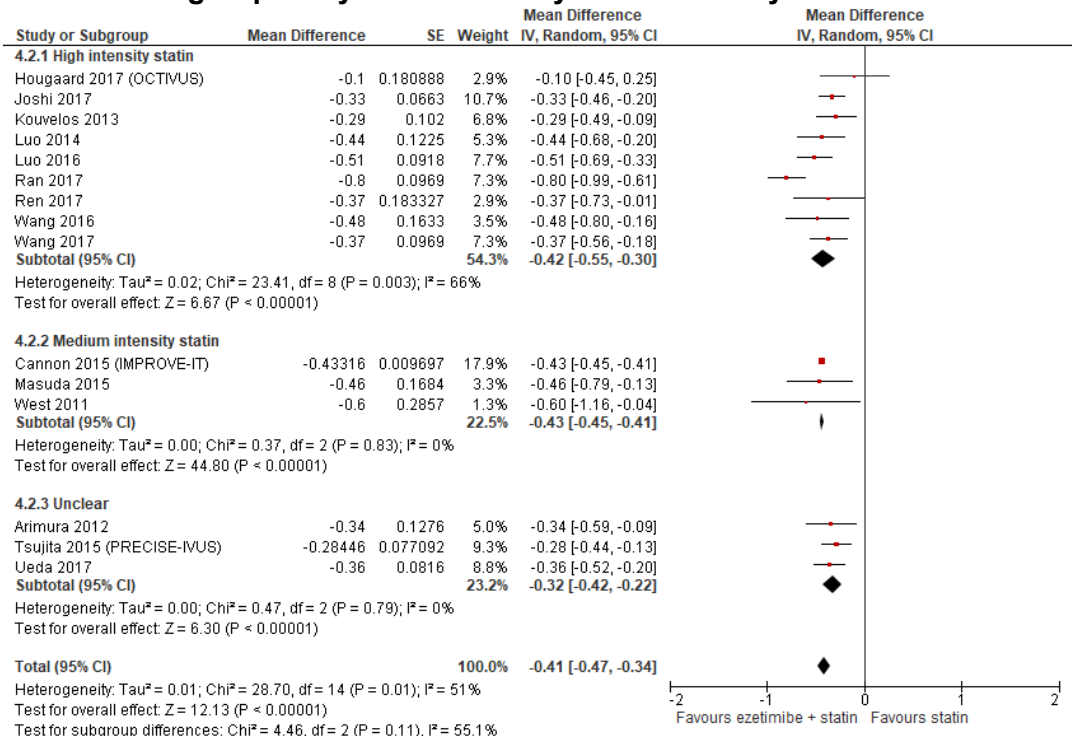
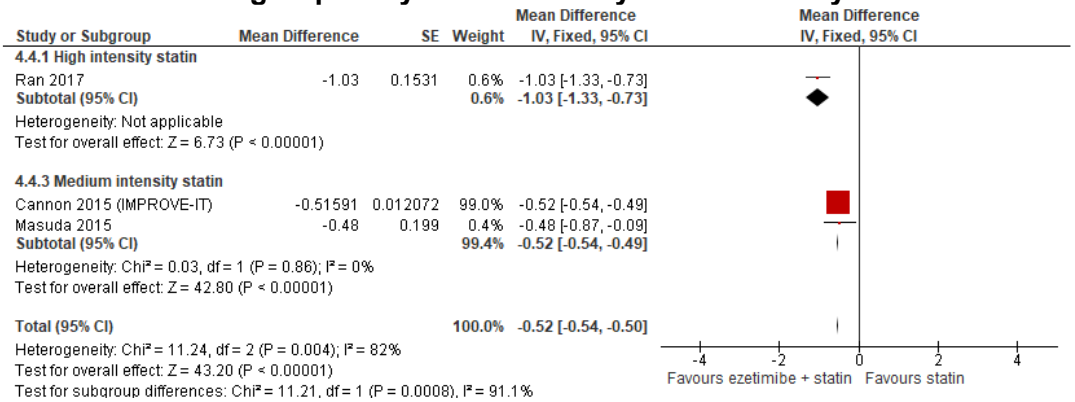


Figure 42: Absolute change from baseline in LDL-C (mmol/l): between-trial subgroup analysis stratified by statin intensity



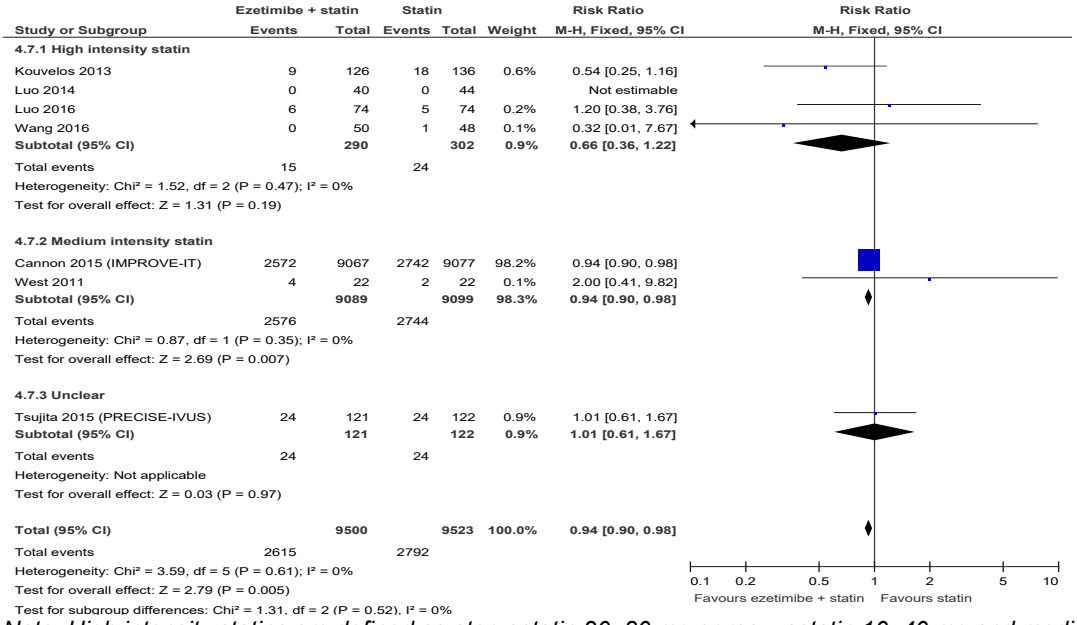
Note: High intensity statins are defined as atorvastatin 20–80 mg or rosuvastatin 10–40 mg and medium intensity statins as atorvastatin 10 mg, fluvastatin 80 mg, rosuvastatin 5 mg or simvastatin 20–40 mg.

Figure 43: Absolute change from baseline in non-HDL-C (mmol/l): between-trial subgroup analysis stratified by statin intensity



Note: High intensity statins are defined as atorvastatin 20–80 mg or rosuvastatin 10–40 mg and medium intensity statins as atorvastatin 10 mg, fluvastatin 80 mg, rosuvastatin 5 mg or simvastatin 20–40 mg.

Figure 44: Major adverse cardiovascular events: between-trial subgroup analysis stratified by statin intensity



Note: High intensity statins are defined as atorvastatin 20–80 mg or rosuvastatin 10–40 mg and medium intensity statins as atorvastatin 10 mg, fluvastatin 80 mg, rosuvastatin 5 mg or simvastatin 20–40 mg.

F.2 PCSK9i versus placebo or usual care in CVD secondary prevention

F.2.1 Baseline lipid levels

Figure 45: % change from baseline in LDL-C: between-trial subgroup analysis stratified by baseline LDL-C (mmol/l)

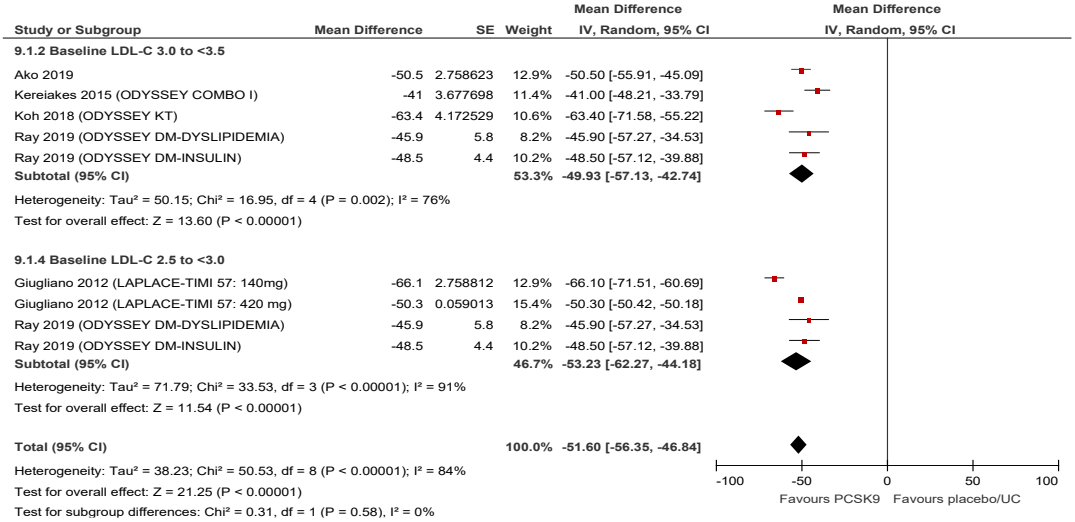


Figure 46: Absolute change from baseline in LDL-C (mmol/l): between-trial subgroup analysis stratified by baseline LDL-C (mmol/l)

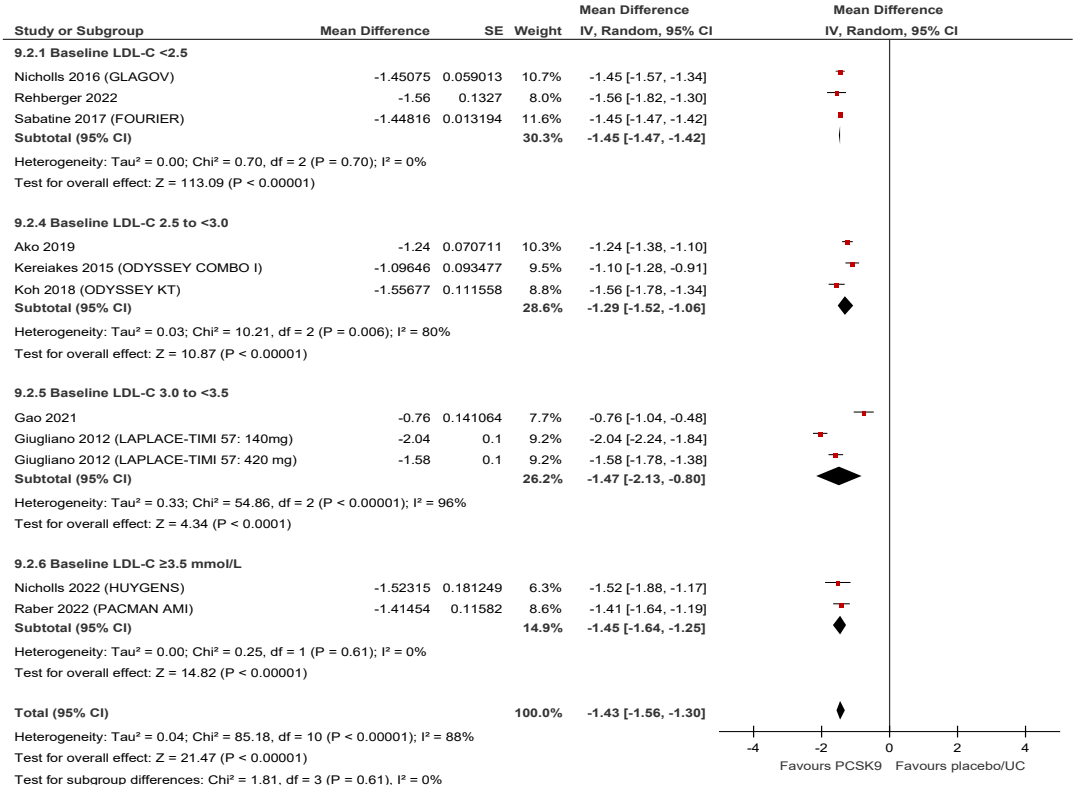


Figure 47: % change from baseline in non-HDL-C: between-trial subgroup analysis stratified by baseline non-HDL-C (mmol/l)

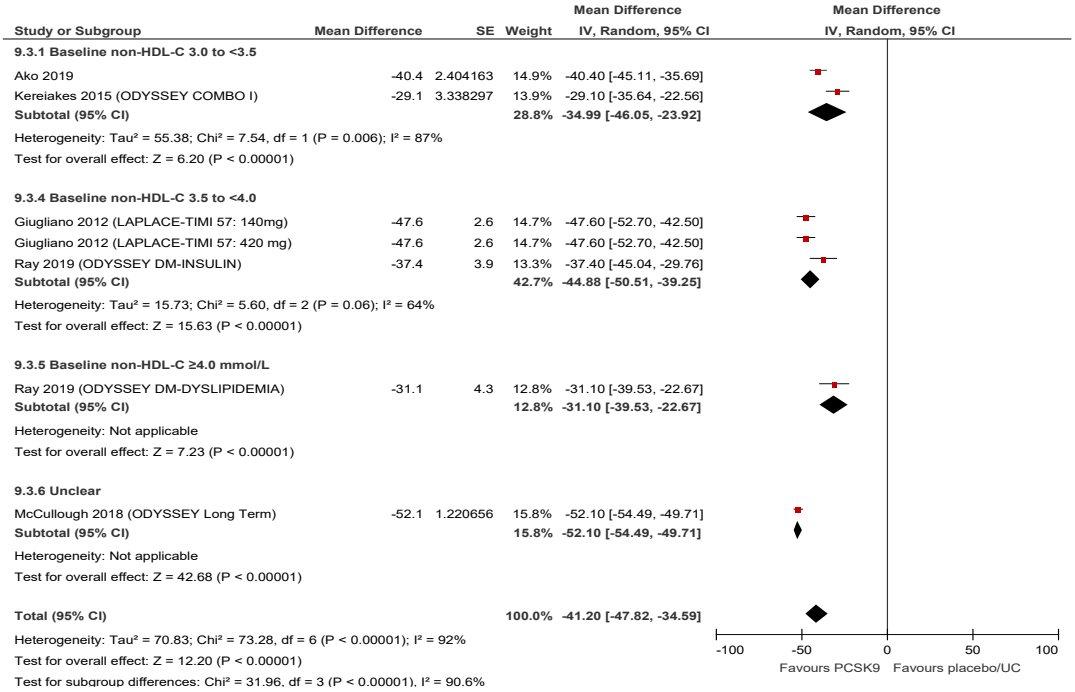


Figure 48: Absolute change from baseline in non-HDL-C (mmol/l): between-trial subgroup analysis stratified by baseline non-HDL-C (mmol/l)

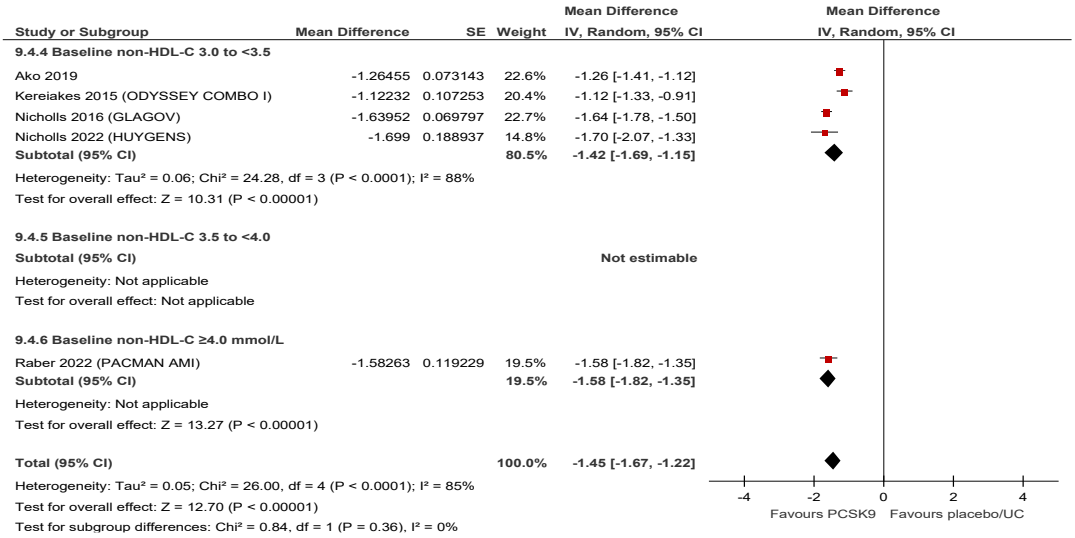


Figure 49: Major adverse cardiovascular events: between-trial subgroup analysis stratified by baseline LDL-C (mmol/l)

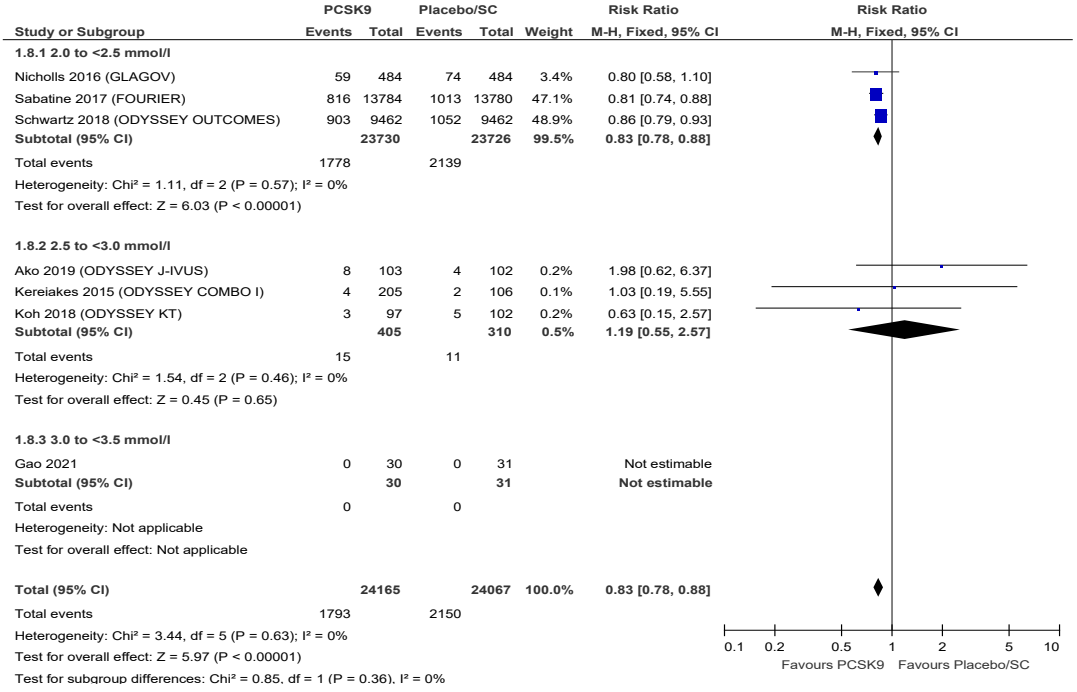


Figure 50: Major adverse cardiovascular events: within-trial subgroup analysis from the ODYSSEY OUTCOMES trial stratified by baseline LDL-C (mg/dl)

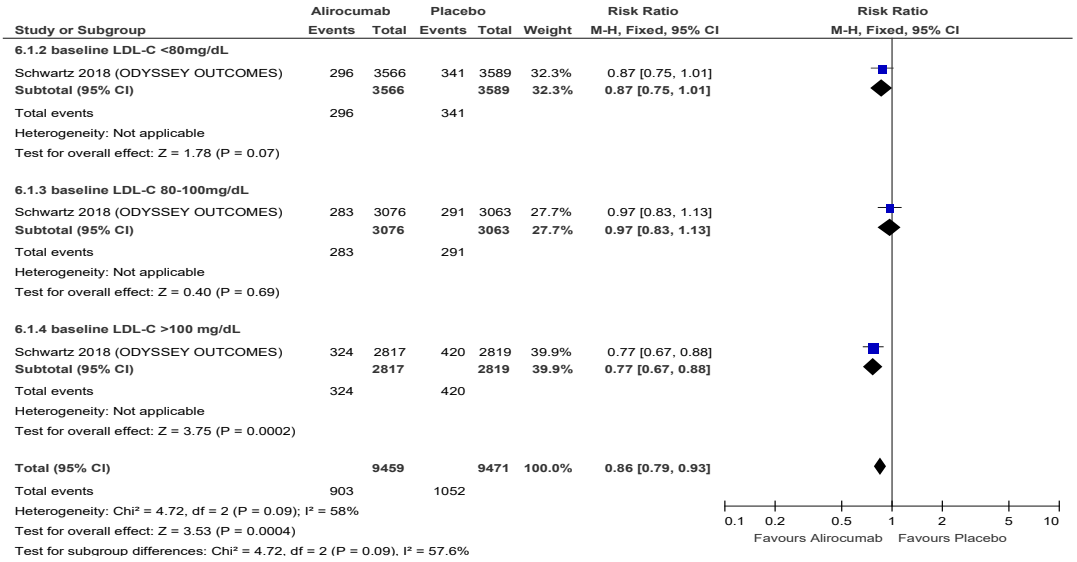


Figure 51: Major adverse cardiovascular events: within-trial subgroup analysis from the FOURIER trial stratified by baseline LDL-C (mg/dl)

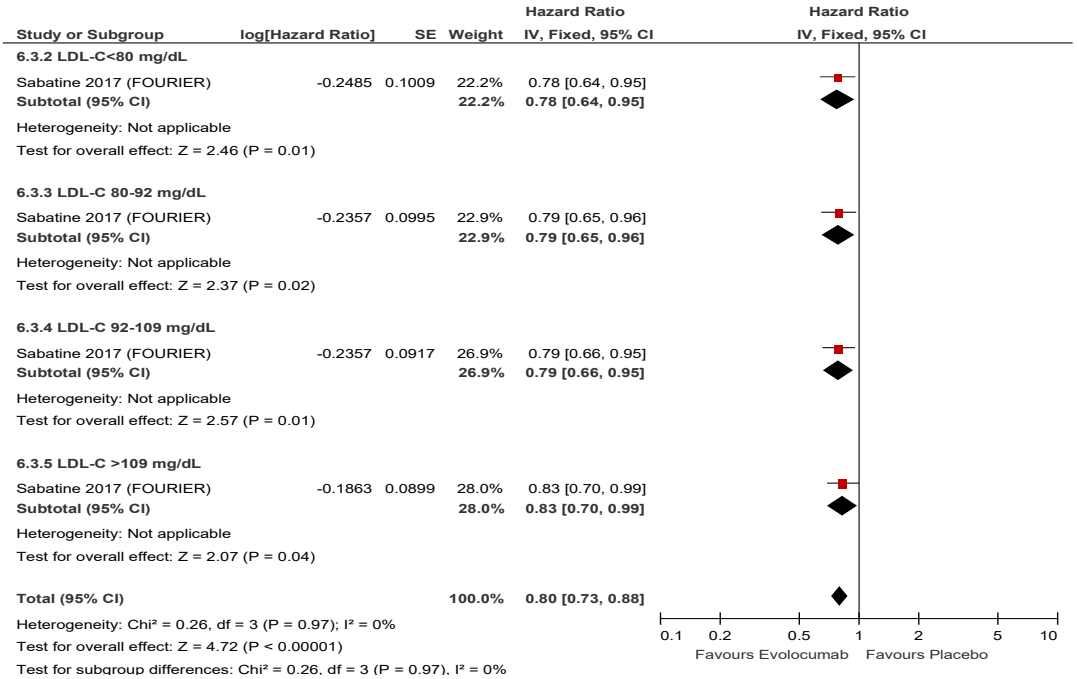
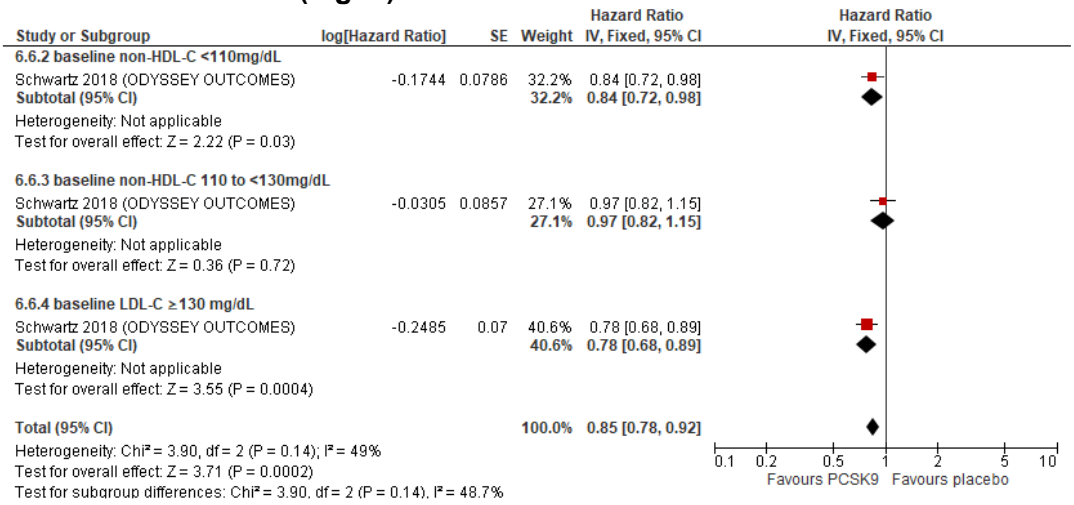
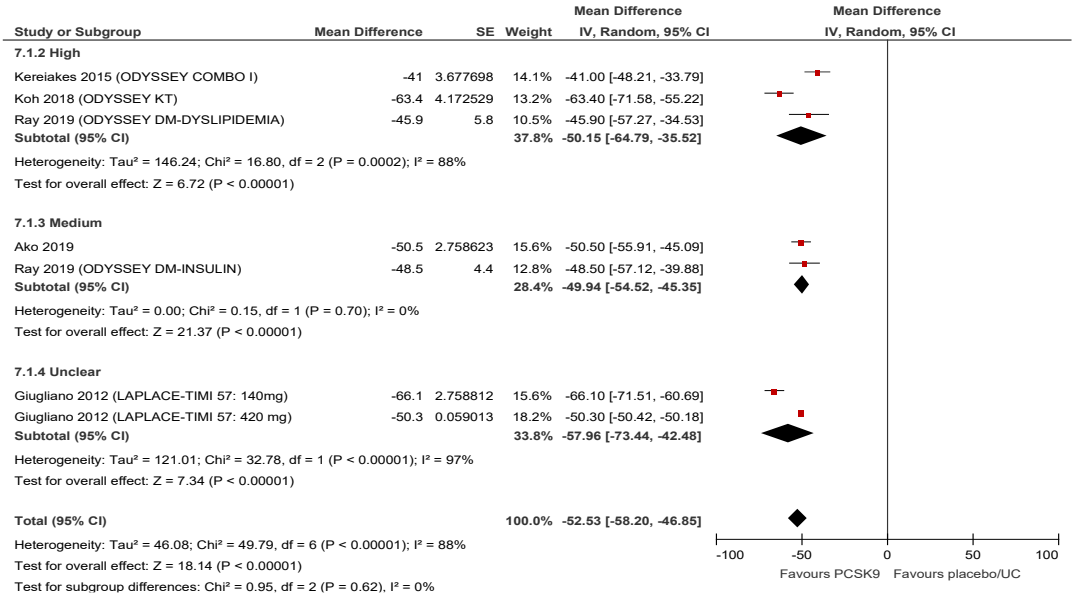


Figure 52: Major adverse cardiovascular events: within-trial subgroup analysis from the ODYSSEY OUTCOMES trial stratified by baseline non-HDL-C (mg/dl)



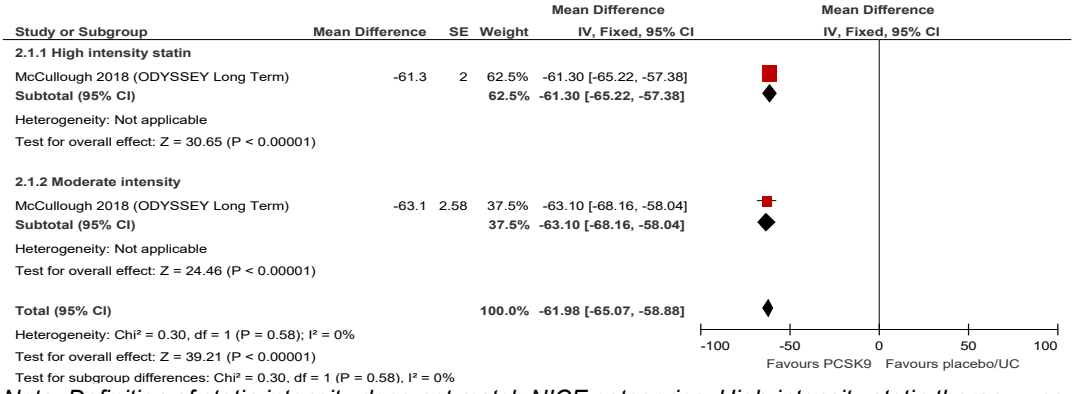
F.2.2 Statin intensity

Figure 53: % change from baseline in LDL-C: between-trial subgroup analysis stratified by statin intensity



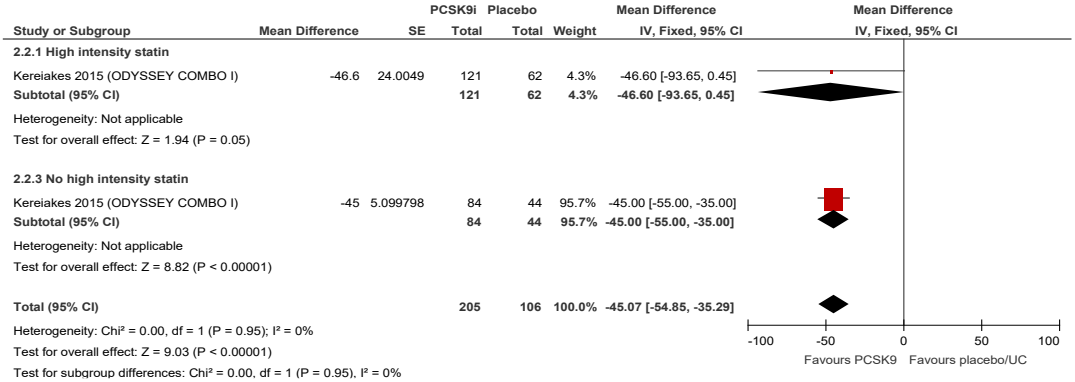
Note: High intensity statins are defined as atorvastatin 20–80 mg or rosuvastatin 10–40 mg and medium intensity statins as atorvastatin 10 mg, fluvastatin 80 mg, rosuvastatin 5 mg or simvastatin 20–40 mg.

Figure 54: % change from baseline in LDL-C: within-trial subgroup analysis from ODYSSEY LONG TERM stratified by statin intensity



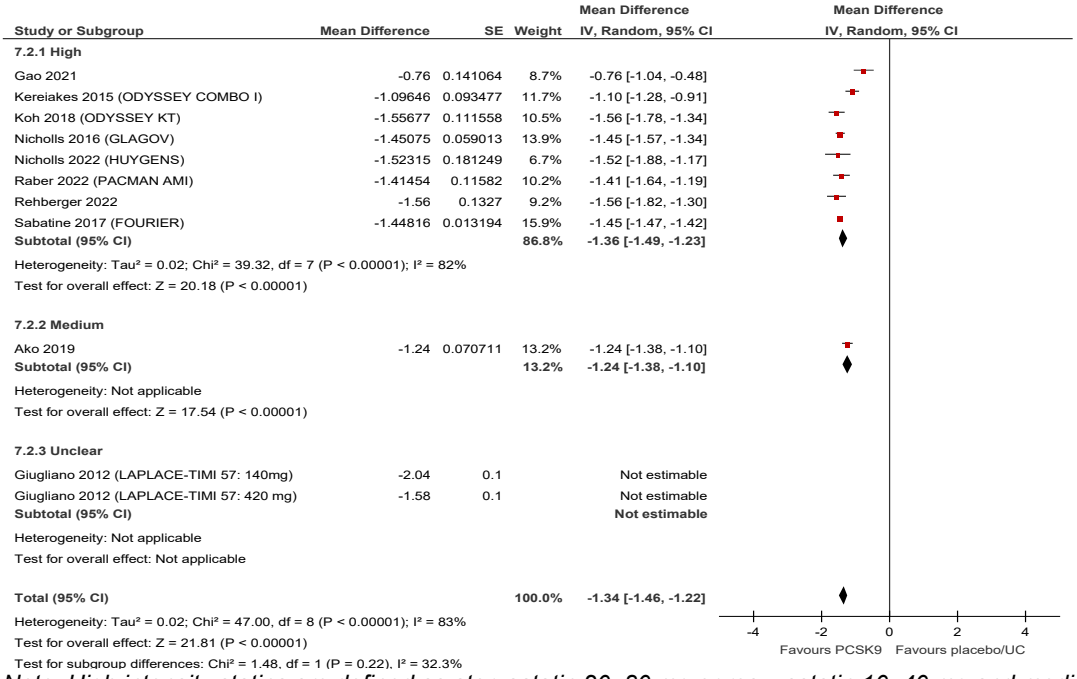
Note: Definition of statin intensity does not match NICE categories. High-intensity statin therapy was defined as taking atorvastatin 40–80 mg, rosuvastatin 20–40 mg, or simvastatin 80 mg. Moderate-intensity statin therapy was defined as taking atorvastatin 20–<40 mg, rosuvastatin 10–<20 mg, or simvastatin 40–<80 mg.

Figure 55: % change from baseline in LDL-C: within-trial subgroup analysis from ODYSSEY COMBO I stratified by statin intensity



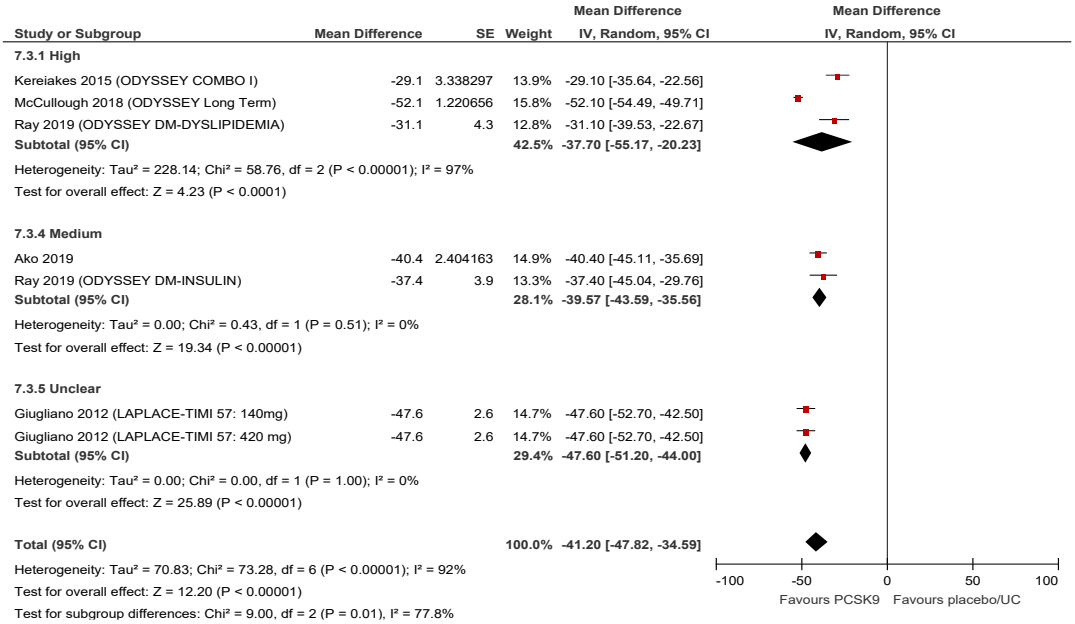
Note: Definition of statin intensity does not match NICE categories. High-intensity statin therapy was defined as taking atorvastatin 40–80 mg, rosuvastatin 20–40 mg.

Figure 56: Absolute change from baseline in LDL-C (mmol/l): between-trial subgroup analysis stratified by statin intensity



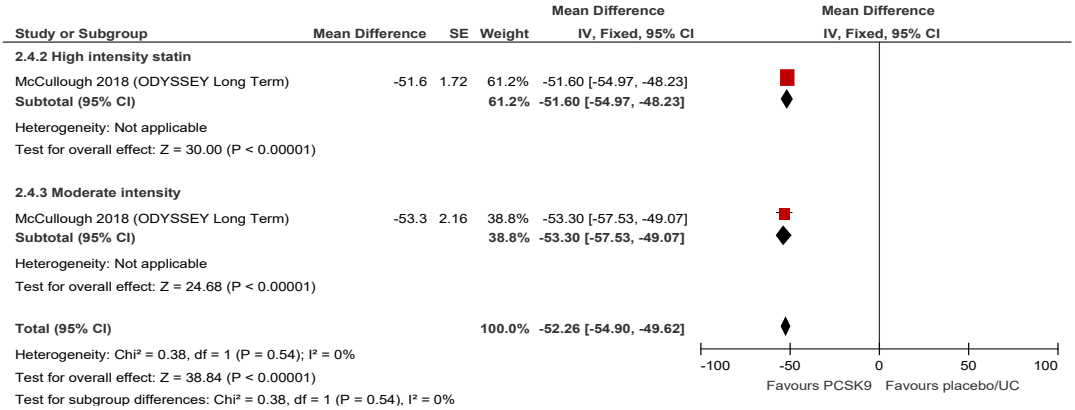
Note: High intensity statins are defined as atorvastatin 20–80 mg or rosuvastatin 10–40 mg and medium intensity statins as atorvastatin 10 mg, fluvastatin 80 mg, rosuvastatin 5 mg or simvastatin 20–40 mg.

Figure 57: % change from baseline in non-HDL-C: between-trial subgroup analysis stratified by statin intensity



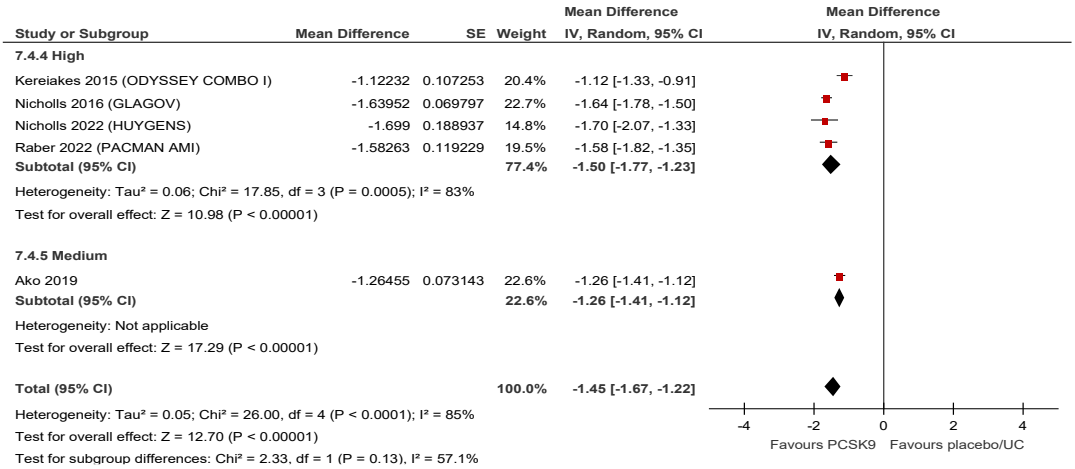
Note: High intensity statins are defined as atorvastatin 20–80 mg or rosuvastatin 10–40 mg and medium intensity statins as atorvastatin 10 mg, fluvastatin 80 mg, rosuvastatin 5 mg or simvastatin 20–40 mg.

Figure 58: % change from baseline in LDL-C: within-trial subgroup analysis from ODYSSEY LONG TERM stratified by statin intensity



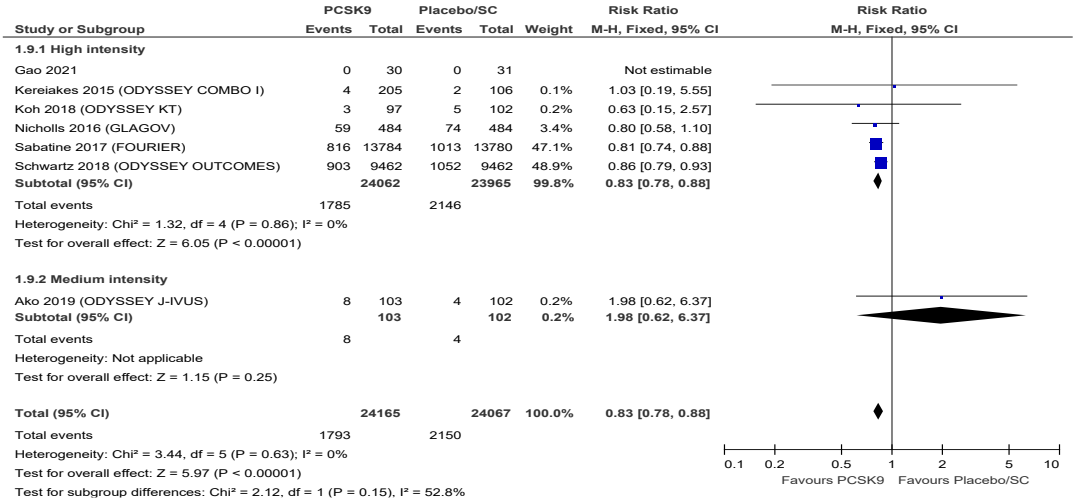
Note: Definition of statin intensity does not match NICE categories. High-intensity statin therapy was defined as taking atorvastatin 40–80 mg, rosuvastatin 20–40 mg, or simvastatin 80 mg. Moderate-intensity statin therapy was defined as taking atorvastatin 20–<40 mg, rosuvastatin 10–<20 mg, or simvastatin 40–<80 mg.

Figure 59: Absolute change from baseline in non-HDL-C (mmol/l): between-trial subgroup analysis stratified by statin intensity



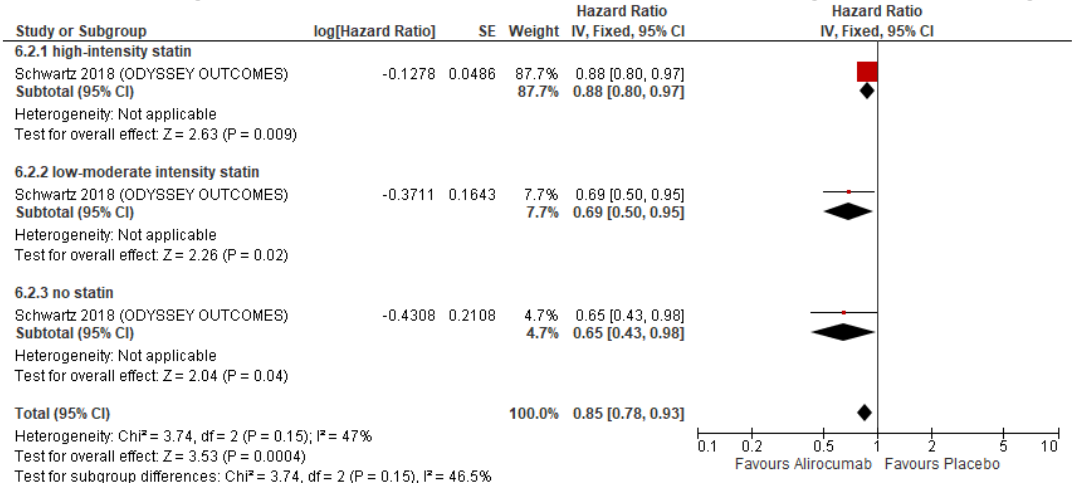
Note: High intensity statins are defined as atorvastatin 20–80 mg or rosuvastatin 10–40 mg and medium intensity statins as atorvastatin 10 mg, fluvastatin 80 mg, rosuvastatin 5 mg or simvastatin 20–40 mg.

Figure 60: Major adverse cardiovascular events: between-trial subgroup analysis stratified by statin intensity



Note: High intensity statins are defined as atorvastatin 20–80 mg or rosuvastatin 10–40 mg and medium intensity statins as atorvastatin 10 mg, fluvastatin 80 mg, rosuvastatin 5 mg or simvastatin 20–40 mg.

Figure 61: Major adverse cardiovascular events: within-trial subgroup analysis from ODYSSEY OUTCOMES stratified by statin intensity

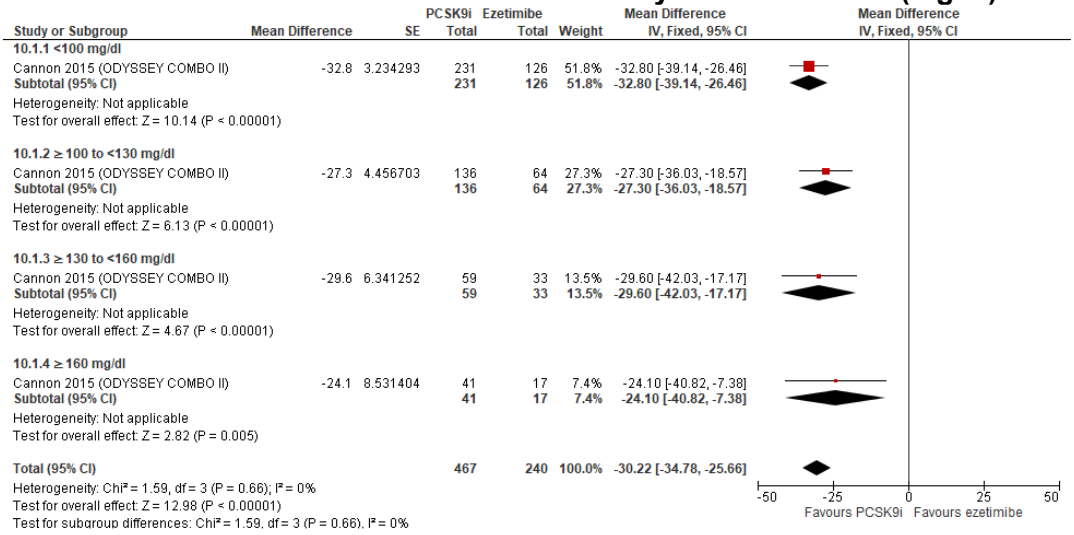


Note: Definition of statin intensity does not match NICE categories. High-intensity statin therapy was defined as taking atorvastatin 40–80 mg, or rosuvastatin 20–40 mg. Low/moderate-intensity statin therapy was defined as taking atorvastatin <40 mg, or rosuvastatin <20 mg.

F.3 PCSK9i versus ezetimibe in CVD secondary prevention

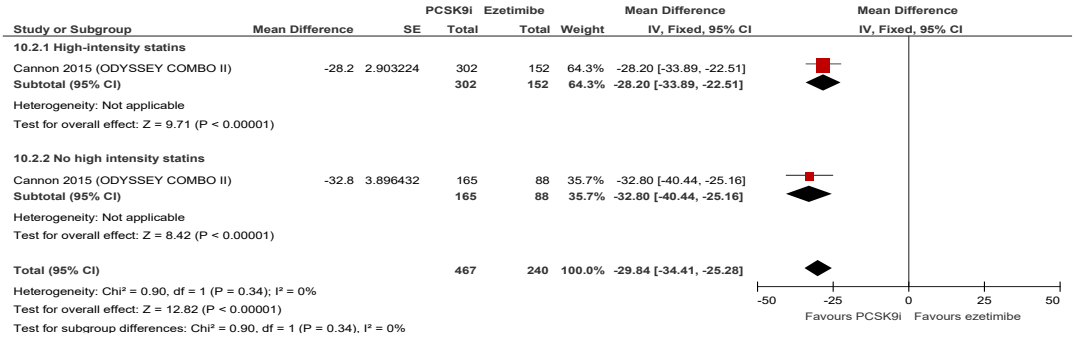
F.3.1 Baseline lipid levels

Figure 62: % change from baseline in LDL-C: within-trial subgroup analysis from ODYSSEY COMBO II stratified by baseline LDL-C (mg/dl)



F.3.2 Statin intensity

Figure 63: % change from baseline in LDL-C: within-trial subgroup analysis from ODYSSEY COMBO II stratified by statin intensity

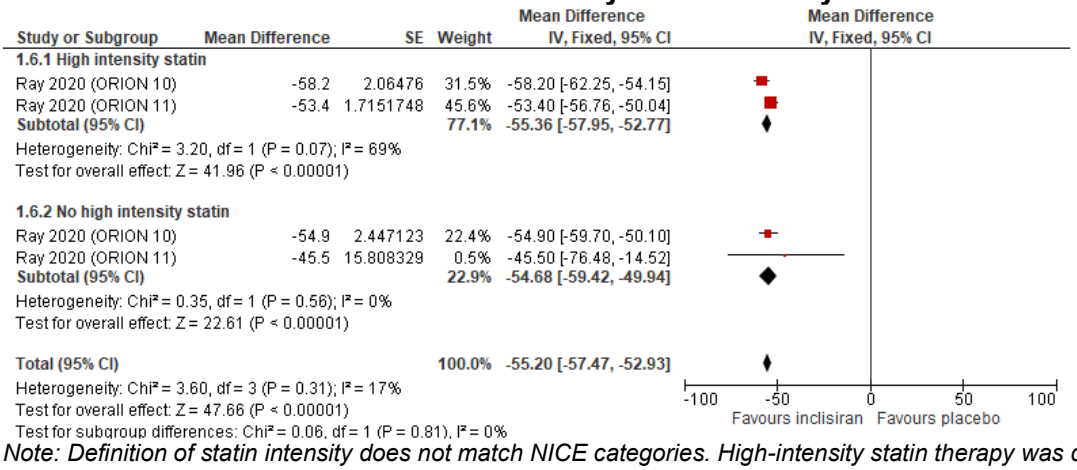


Note: Definition of statin intensity does not match NICE categories. High-intensity statin therapy was defined as taking atorvastatin 40–80 mg, rosuvastatin 20–40 mg.

F.4 Inclisiran versus placebo in CVD secondary prevention

F.4.1 Statin intensity

Figure 64: % change from baseline in LDL-C: within-trial subgroup analysis from ORION 10 and 11 stratified by statin intensity



Note: Definition of statin intensity does not match NICE categories. High-intensity statin therapy was defined as taking atorvastatin 40–80 mg, rosuvastatin 20–40 mg, or simvastatin 80 mg.

Appendix G GRADE tables

Table 10: Clinical evidence profile: ezetimibe + statin versus statin

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ezetimibe plus high or moderate intensity statins	High or moderate intensity statins alone or plus placebo	Relative (95% CI)	Absolute (95% CI)		
LDL-C; (% change) (follow-up: 6-12 months)												
3	randomised trials	not serious	not serious	not serious	serious[a,b]	none	160	162	-	MD **11.5 % lower** (15.66 lower to 7.33 lower)	⨁⨁⨁◯ Moderate	CRITICAL
LDL-C; mmol/l (Absolute MD: combined final and change) (follow-up: 12 weeks - 1 year)												
15	randomised trials	serious[c]	serious[d]	not serious	serious[a,b]	none	7589	7681	-	MD **0.41 lower** (0.47 lower to 0.34 lower)	⨁◯◯◯ Very low	CRITICAL
non-HDL-C; (% change) (follow-up: 6 months)												
1	randomised trials	Very serious[e]	not serious	not serious	serious[a,b]	none	21	19	-	MD **15.5 % lower** (26.61 lower to 4.39 lower)	⨁◯◯◯ Very low	CRITICAL
non-HDL-C; mmol/l (mean difference in absolute change) (follow-up: 12 weeks to 1 year)												
3	randomised trials	not serious	very serious[f]	not serious	serious[a,b]	none	6431	6523	-	MD **0.67 mmol/l lower** (1 lower to 0.33 lower)	⨁◯◯◯ Very low	CRITICAL
MACE (follow-up: 6 months to 7 years)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ezetimibe plus high or moderate intensity statins	High or moderate intensity statins alone or plus placebo	Relative (95% CI)	Absolute (95% CI)		
8	randomised trials	not serious	not serious	serious[g]	not serious	none	2618/9522 (27.5%)	2794/9545 (29.3%)	**RR 0.94** (0.90 to 0.98)	**18 fewer per 1,000** (from 29 fewer to 6 fewer)	⨁⨁⨁◯ Moderate	CRITICAL
MACE - follow up > 2 years (follow-up: 7 patient years)												
1	Randomised trials	Not serious	Not serious	serious[g]	Not serious	none	2572/9067 (28.4%)	2742/9077 (30.2%)	**RR 0.94** (0.90 to 0.98)	**18 fewer per 1,000** (from 30 fewer to 6 fewer)	⨁⨁⨁◯ Moderate	CRITICAL
MACE - follow up ≤ 2 years (follow-up: 6 months to 2 years)												
7	Randomised trials	Not serious	Not serious	Serious[h]	Serious[a]	none	46/4355 (10.1%)	52/4468 (11.1%)	**RR 0.88** (0.61 to 1.29)	**13 fewer per 1,000** (from 43 fewer to 32 more)	⨁⨁◯◯ Low	CRITICAL
MACE: HR (follow-up: 7 years)												
1	randomised trials	not serious	not serious	serious[g]	not serious	none	2572/9067 (28.4%)	2742/9077 (30.2%)	**HR 0.94** (0.89 to 0.98)		⨁⨁⨁◯ Moderate	CRITICAL
Adverse events - myopathy or rhabdomyolysis (follow-up: 6 months to 6 years)												
5	randomised trials	not serious	not serious	serious[g]	very serious[a]	none	27/9254 (0.3%)	28/9260 (0.3%)	**OR 0.97** (0.57 to 1.64)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)[i]	⨁◯◯◯ Very low	CRITICAL
Adverse events - raised liver transaminases (follow-up: 6 months to 6 years)												
6	randomised trials	not serious	not serious	Not serious	serious[a]	none	228/9344 (2.4%)	211/9352 (2.3%)	**RR 1.08** (0.90 to 1.30)	**0 fewer per 1,000** (from 0 fewer to 10 more)	⨁⨁⨁◯ Moderate	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ezetimibe plus high or moderate intensity statins	High or moderate intensity statins alone or plus placebo	Relative (95% CI)	Absolute (95% CI)		
Adverse events - cancer (follow-up: 6 years)												
1	randomised trials	not serious	not serious	Not serious	not serious	none	748/9067 (8.2%)	732/9077 (8.1%)	**RR 1.02** (0.93 to 1.13)	**2 more per 1,000** (from 6 fewer to 10 more)	⨁⨁⨁⨁ High	CRITICAL
Adverse events - gallbladder-related AE (follow-up: 6 years)												
1	randomised trials	not serious	not serious	Not serious	serious[a]	none	281/9067 (3.1%)	321/9077 (3.5%)	**RR 0.88** (0.75 to 1.03)	**4 fewer per 1,000** (from 9 fewer to 1 more)	⨁⨁⨁◯ Moderate	CRITICAL

a. Downgraded by 1 increment if the confidence interval crossed one MID and by 2 increments if the confidence interval crossed two MIDs (0.8 and 1.25 for dichotomous outcomes; 0.5 * median of baseline SD of the intervention and control group for continuous outcomes).

b. Continuous MIDs: % change LDL-C: 9.45; absolute change LDL-C:0.35; % change non-HDL-C: 8.85; absolute change non-HDL-C: 0.455

c. Majority of evidence at high risk of bias (random effects study weighting)

d. Serious inconsistency: I2 = 51%; ; random effects model was used for the analysis due to heterogeneity unexplained by subgroup analysis

e. Very serious risk of bias due to between-group differences in age at baseline and high rate of missing outcome data

f. Very serious inconsistency: I2 = 82%; random effects model was used for the analysis due to heterogeneity unexplained by subgroup analysis

g. All or the majority of evidence has serious intervention indirectness due to the proportion having the simvastatin dose increased from 40 to 80 mg being unbalanced between groups.

h. Follow up <12 months in the majority of evidence based on weight in the meta-analysis.

i. Absolute effect calculated from risk difference

Table 11: Clinical evidence profile: PCSK9i versus placebo or usual care

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PCSK9i	Placebo or usual care	Relative (95% CI)	Absolute (95% CI)		
% change LDL-C (follow-up: 12-52 weeks)												
8	randomised trials	not serious	very serious[a]	not serious	not serious[b]	none	15709	14935	-	MD **54.62 % lower** (59.28 lower to 49.97 lower)	⨁⨁◯◯ Low	CRITICAL
LDL-C absolute change or final value (follow-up: 12-52 weeks (one using time-weighted average from baseline to 18 months))												
10	randomised trials	not serious	very serious[a]	not serious	not serious[b]	none	15088	14966	-	MD **1.43 mmol/l lower** (1.56 lower to 1.3 lower)	⨁⨁◯◯ Low	CRITICAL
non-HDL-C % change (follow-up: 12-52 weeks)												
7	randomised trials	not serious	very serious[a]	not serious	not serious[b]	none	1933	1157	-	MD **42.47 % lower** (48.45 lower to 36.5 lower)	⨁⨁◯◯ Low	CRITICAL
non HDL-C absolute change or final value (mmol/l) (follow-up: 36-52 weeks (one using time-weighted average from baseline to 18 months))												
5	randomised trials	not serious	very serious[a]	not serious	not serious	none	958	867	-	MD **1.45 mmol/l lower** (1.67 lower to 1.22 lower)	⨁⨁◯◯ Low	CRITICAL
Major adverse CVD events/MACE (at 24 weeks to 4 years)												
7	randomised trials	not serious	not serious	not serious	serious[c]	none	1793/24165 (7.4%)	2150/24067 (8.9%)	**RR 0.83** (0.78 to 0.88)	**15 fewer per 1,000** (from 20 fewer to 11 fewer)	⨁⨁⨁◯ Moderate	CRITICAL
Major adverse CVD events/MACE - follow up > 2 years												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PCSK9i	Placebo or usual care	Relative (95% CI)	Absolute (95% CI)		
2	randomised trials	not serious	not serious	not serious	serious[c]	none	1719/23246 (7.4%)	2065/23242 (8.9%)	**RR 0.83** (0.78 to 0.88)	**15 fewer per 1,000** (from 20 fewer to 11 fewer)	⨁⨁⨁◯ Moderate	CRITICAL
Major adverse CVD events/MACE - follow up ≤ 2 years												
5	randomised trials	not serious	not serious	not serious	serious[c]	none	74/919 (8.1%)	85/825 (10.3%)	**RR 0.85** (0.63 to 1.14)	**15 fewer per 1,000** (from 38 fewer to 14 more)	⨁⨁⨁◯ Moderate	CRITICAL
MACE (at 36 months to 4 years)												
2	randomised trials	not serious	not serious	not serious	serious[c]	none	1719/23246 (7.4%)	2065/23242 (8.9%)	**HR 0.83** (0.78 to 0.88)		⨁⨁⨁◯ Moderate	CRITICAL
Myopathy/rhabdomyolysis												
2	randomised trials	serious[d]	not serious	not serious	very serious[c]	none	54/23153 (0.2%)	59/23118 (0.3%)	**RR 0.91** (0.63 to 1.32)	**0 fewer per 1,000** (from 1 fewer to 1 more)	⨁◯◯◯ Very low	CRITICAL
New onset diabetes (at 52 weeks to 4 years)												
4	randomised trials	not serious	not serious	not serious	not serious	none	1348/15681 (8.6%)	1343/15621 (8.6%)	**RR 1.00** (0.93 to 1.07)	**0 fewer per 1,000** (from 6 fewer to 6 more)	⨁⨁⨁⨁ High	CRITICAL
Increased liver transaminases (at 18-36 months)												
2	randomised trials	not serious	not serious	not serious	not serious	none	242/14268 (1.7%)	244/14264 (1.7%)	**RR 0.99** (0.83 to 1.18)	**0 fewer per 1,000** (from 3 fewer to 3 more)	⨁⨁⨁⨁ High	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PCSK9i	Placebo or usual care	Relative (95% CI)	Absolute (95% CI)		
Injection-site reactions (at 12 weeks to 4 years)												
7	randomised trials	not serious	not serious	not serious	not serious	none	691/24367 (2.8%)	436/24271 (1.8%)	**RR 1.57** (1.40 to 1.77)	**10 more per 1,000** (from 7 more to 14 more)	⨁⨁⨁⨁ High	CRITICAL
Nausea												
2	randomised trials	not serious	not serious	not serious	very serious[c]	none	4/213 (1.9%)	3/104 (2.9%)	**RR 0.65** (0.15 to 2.85)	**10 fewer per 1,000** (from 25 fewer to 53 more)	⨁⨁◯◯ Low	CRITICAL

a. I2 >75%; random effects model was used for the analysis due to heterogeneity unexplained by subgroup analysis.

b. Continuous outcome MIDs: % change LDL-C = 13.85; absolute LDL-C: 0.37; % change non-HDL-C: 12.5; absolute non-HDL-C: 0.32.

c. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs (standard MIDs for dichotomous outcomes: 0.8 and 1.25)

d. Downgraded by 1 increment because the majority of the evidence was at high risk of bias (due to event rate for outcome being similar to number lost to follow-up)

Table 12: Clinical evidence profile: PCSK9i versus ezetimibe

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PCSK9i	Ezetimibe	Relative (95% CI)	Absolute (95% CI)		
% change LDL-C (follow-up: range 24 weeks to 52 weeks)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PCSK9i	Ezetimibe	Relative (95% CI)	Absolute (95% CI)		
2	randomised trials	not serious	not serious	not serious	not serious[a]	none	870	448	-	MD **33.5 % lower** (37.9 lower to 29.09 lower)	⨁⨁⨁⨁ High	CRITICAL
Final LDL-C (follow-up: 24 weeks)												
1	randomised trials	not serious	not serious	not serious	not serious	none	467	240	-	MD **0.8 mmol/l lower** (0.94 lower to 0.66 lower)	⨁⨁⨁⨁ High	CRITICAL
% change non-HDL-C (follow-up: range 24 weeks to 52 weeks)												
2	randomised trials	not serious	serious[b]	not serious	not serious[a]	none	870	448	-	MD **25.25 % lower** (29.86 lower to 20.64 lower)	⨁⨁⨁◯ Moderate	CRITICAL
MACE/ Positively adjudicated CVD events (at 24 to 104 weeks)												
2	randomised trials	not serious	not serious	serious[c]	very serious[d]	none	36/885 (4.1%)	18/447 (4.0%)	**RR 1.01** (0.58 to 1.76)	**0 fewer per 1,000** (from 17 fewer to 31 more)	⨁◯◯◯ Very low	CRITICAL
New-onset diabetes (at 24 to 104 weeks)												
2	randomised trials	not serious	not serious	serious[e]	very serious[d]	none	23/616 (3.7%)	13/322 (4.0%)	**RR 0.92** (0.47 to 1.80)	**3 fewer per 1,000** (from 21 fewer to 32 more)	⨁◯◯◯ Very low	CRITICAL
Increased liver transaminases- alanine aminotransferase >3 x ULN (follow-up: 104 weeks)												
1	randomised trials	not serious	not serious	not serious	very serious[d]	none	10/479 (2.1%)	2/241 (0.8%)	**RR 2.52** (0.56 to 11.39)	**13 more per 1,000** (from 4 fewer to 86 more)	⨁⨁◯◯ Low	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PCSK9i	Ezetimibe	Relative (95% CI)	Absolute (95% CI)		
Increased liver transaminases- aspartate aminotransferase >3 x ULN (follow-up: 104 weeks)												
1	randomised trials	not serious	not serious	not serious	very serious[d]	none	11/479 (2.3%)	1/241 (0.4%)	**RR 5.53** (0.72 to 42.62)	**19 more per 1,000** (from 1 fewer to 173 more)	⨁⨁◯◯ Low	CRITICAL
Injection site reactions (at 24 to 104 weeks)												
2	randomised trials	not serious	not serious	not serious	serious[d]	none	24/885 (2.7%)	5/447 (1.1%)	**RR 2.42** (0.93 to 6.31)	**16 more per 1,000** (from 1 fewer to 59 more)	⨁⨁⨁◯ Moderate	CRITICAL
Influenza at 104 weeks												
1	randomised trials	serious[f]	not serious	not serious	very serious[d]	none	22/479 (4.6%)	16/241 (6.6%)	**RR 0.69** (0.37 to 1.29)	**21 fewer per 1,000** (from 42 fewer to 19 more)	⨁◯◯◯ Very low	CRITICAL

a. Continuous outcome MIDs: % change LDL-C: 15.34; final LDL-C value: 4.5 mmol/l; % change non-HDL-C: 12.61

b. I2 >50%

c. Downgraded by 1 increment for serious indirectness due to one of 1/2 studies reporting outcome at 24 weeks

d. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs (standard MIDs for dichotomous outcomes: 0.8 and 1.25)

e. Unclear if diabetes referred to new onset in one of the studies with the higher weight in the meta-analysis.

f. Downgraded by 1 increment as the evidence was at high risk of bias, due to it being unclear if the outcome was consistently recorded

Table 13: Clinical evidence profile: PCSK9i +ezetimibe versus ezetimibe

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PCSK9i + ezetimibe	Ezetimibe	Relative (95% CI)	Absolute (95% CI)		
Final LDL-C (follow-up: 3 months)												
1	randomised trials	Very serious[a]	not serious	not serious	not serious[b]	none	68	61	-	MD **0.69 lower** (0.84 lower to 0.54 lower)	⨁⨁◯◯ Low	CRITICAL

a. Very high risk of bias due to recruitment and randomisation method not being specified (leading to potential selection bias), and treatment being adjusted according to lipid control during follow-up in combination with lack of blinding.

b. Continuous MID: final LDL-C: 0.25

Table 14: Clinical evidence profile: inclisiran versus placebo

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Inclisiran	Placebo	Relative (95% CI)	Absolute (95% CI)		
LDL-C % change (follow-up: weighted average between 90 and 540 days)												
2	randomised trials	not serious	serious[a]	not serious	not serious[b]	none	1591	1587	-	MD **51.49 lower** (56 lower to 46.99 lower)	⨁⨁⨁◯ Moderate	CRITICAL
LDL-C absolute change (mmol/l) (follow-up: weighted average between 90 and 540 days)												
2	randomised trials	not serious	serious[c]	not serious	not serious	none	1591	1587	-	MD **1.32 lower** (1.37 lower to 1.28 lower)	⨁⨁⨁◯ Moderate	CRITICAL
MACE (non-adjudicated terms) (follow-up: 540 days)												
2	randomised trials	not serious	not serious	not serious	serious[d]	none	121/1592 (7.6%)	162/1582 (10.2%)	**RR 0.74** (0.59 to 0.93)	**27 fewer per 1,000** (from 42 fewer to 7 fewer)	⨁⨁⨁◯ Moderate	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Inclisiran	Placebo	Relative (95% CI)	Absolute (95% CI)		
Increased liver transaminases - ALT >3xULN (follow-up: 540 days)												
2	randomised trials	not serious	serious[e]	not serious	very serious[d]	none	6/1592 (0.4%)	6/1582 (0.4%)	**RR 0.99** (0.32 to 3.07)	**0 fewer per 1,000** (from 3 fewer to 8 more)	⨁◯◯◯ Very low	CRITICAL
Increased liver transaminases - AST >3xULN (follow-up: 540 days)												
2	randomised trials	not serious	serious[e]	not serious	very serious[d]	none	6/1592 (0.4%)	9/1582 (0.6%)	**RR 0.66** (0.24 to 1.86)	**2 fewer per 1,000** (from 4 fewer to 5 more)	⨁◯◯◯ Very low	CRITICAL
Injection-site reactions (follow-up: 540 days)												
2	randomised trials	not serious	serious[e]	serious[f]	not serious	none	58/1592 (3.6%)	11/1582 (0.7%)	**RR 5.01** (1.52 to 16.54)	**28 more per 1,000** (from 4 more to 108 more)	⨁⨁◯◯ Low	CRITICAL

a. I2 = 86%; random effects model was used for the analysis due to heterogeneity unexplained by subgroup analysis.

b. Continuous MIDs: % change LDL-C; 12.3; absolute change LDL-C: 0.495

c. I2 = 84%; random effects model was used for the analysis due to heterogeneity unexplained by subgroup analysis.

d. Downgraded by 1 increment if the confidence interval crossed one MID and by 2 increments if the confidence interval crossed two MIDs (0.8 and 1.25 for dichotomous outcomes; 0.5 * median of baseline SD of the intervention and control group for continuous outcomes).

e. Event rate less than number lost to follow-up.

f. I2 = 69%; random effects model was used for the analysis due to heterogeneity unexplained by subgroup analysis.

Appendix H Economic evidence study selection

Not applicable

Appendix I Economic evidence tables

Not applicable.

Appendix J Health economic model

See separate economic analysis report.

Appendix K Excluded studies

K.1 Clinical studies

Table 15: Studies excluded from the clinical review

Study	Exclusion reason
(2020) Efficacy of Evolocumab in Patients with Hypercholesterolemia. Kosin med j 35(2): 125-132	- Population not relevant to this review protocol: proportion with CVD not stated
Ah, Young-Mi; Jeong, Minseob; Choi, Hye Duck (2022) Comparative safety and efficacy of low- or moderate-intensity statin plus ezetimibe combination therapy and high-intensity statin monotherapy: A meta-analysis of randomized controlled studies. PloS one 17(3): e0264437	- Systematic review with no data of additional relevance SR with insufficient risk of bias assessment - used as a source of primary studies
Alvarez-Sala, Luis A, Cachofeiro, Victoria, Masana, Luis et al. (2008) 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 30(1): 84-97	- Population not relevant to this review protocol: <50% CVD excluded people with CVD event in the previous 3 months
Bach, Richard G, Cannon, Christopher P, Giugliano, Robert P et al. (2019) Effect of Simvastatin-Ezetimibe Compared With Simvastatin Monotherapy After Acute Coronary Syndrome Among Patients 75 Years or Older: A Secondary Analysis of a Randomized Clinical Trial. JAMA cardiology 4(9): 846-854	- Secondary publication of an included study that does not provide any additional relevant information
Baigent, Colin, Landray, Martin J, Reith, Christina et al. (2011) 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. Lancet (London, England) 377(9784): 2181-92	- Population not relevant to this review protocol: <50% CVD
Ballantyne, Christie M, Abate, Nicola, Yuan, Zhong et al. (2005) Dose-comparison study of the combination of ezetimibe and simvastatin (Vytorin) versus atorvastatin in patients with hypercholesterolemia: the Vytorin Versus Atorvastatin (VYVA) study. American heart journal 149(3): 464-73	- Follow-up <3 months
Ballantyne, Christie M, Hoogeveen, Ron C, Raya, Joe L et al. (2014) Efficacy, safety and effect on biomarkers related to 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 232(1): 86-93	- Comparator in study does not match that specified in this review protocol Incorrect comparison: all arms have ezetimibe, comparing different statins in combination
Ballantyne, CM, Houri, J, Notarbartolo, A et al. (2003) Effect of ezetimibe coadministered with	- Population not relevant to this review protocol: <50% CVD

Study	Exclusion reason
atorvastatin in 628 patients with primary hypercholesterolemia: a prospective, randomized, double-blind trial. Circulation 107(19): 2409-2415	
Ballantyne, CM, Lipka, LJ, Sager, PT et al. (2004) Long-term safety and tolerability profile of ezetimibe and atorvastatin coadministration therapy in patients with primary hypercholesterolaemia. International journal of clinical practice 58(7): 653-658	- Population not relevant to this review protocol: <50% CVD Very low rate of people with previous CVD (12%); partially indirect comparison as intervention did not start with high-intensity statins but some of the participants were then titrated to high-intensity
Bang, Casper N, Greve, Anders M, Boman, Kurt et al. (2012) Effect of lipid lowering on new-onset atrial fibrillation in patients with asymptomatic aortic stenosis: the Simvastatin and Ezetimibe in Aortic Stenosis (SEAS) study. American heart journal 163(4): 690-6	- Population not relevant to this review protocol: <50% CVD Incorrect population: not CVD and not on statins for CV risk reduction
Barrios, V, Amabile, N, Paganelli, F et al. (2005) Lipid-altering efficacy of switching from atorvastatin 10 mg/day to ezetimibe/simvastatin 10/20 mg/day compared to doubling the dose of atorvastatin in hypercholesterolaemic patients with atherosclerosis or coronary heart disease. International journal of clinical practice 59(12): 1377-86	- Comparator in study does not match that specified in this review protocol: ezetimibe plus statin versus double dose of statin
Bays, H, Gaudet, D, Weiss, R et al. (2015) Alirocumab as Add-On to Atorvastatin Versus Other Lipid Treatment Strategies: ODYSSEY OPTIONS I Randomized Trial. Journal of clinical endocrinology and metabolism 100(8): 3140-3148	- Population not relevant to this review protocol: <80% CVD and suffiicient data from directly relevant populations
Bays, H, Sapre, A, Taggart, W et al. (2008) Long-term (48-week) safety of ezetimibe 10 mg/day coadministered with simvastatin compared to simvastatin alone in patients with primary hypercholesterolemia. Current medical research and opinion 24(10): 2953-2966	- Study does not include an intervention relevant to this protocol: includes low intensity statin Incorrect interventions (include S10 - low intensity; and S80 - contraindicated)
Bays, Harold E, Leiter, Lawrence A, Colhoun, Helen M et al. (2017) Alirocumab Treatment and Achievement of Non-High-Density Lipoprotein Cholesterol and Apolipoprotein B Goals in Patients With Hypercholesterolemia: Pooled Results From 10 Phase 3 ODYSSEY Trials. Journal of the American Heart Association 6(8)	- Secondary analysis of 10 trials with no data of additional relevance
Bays, Harold, Gaudet, Daniel, Weiss, Robert et al. (2015) Alirocumab as Add-On to Atorvastatin Versus Other Lipid Treatment Strategies: ODYSSEY OPTIONS I Randomized Trial. The Journal of clinical endocrinology and metabolism 100(8): 3140-8	- Population not relevant to this review protocol ASCVD 61% and sufficient evidence from studies with>80% CVD population
Bays, HE, Ose, L, Fraser, N et al. (2004) A multicenter, randomized, double-blind, placebo-controlled, factorial design study to evaluate the lipid-altering efficacy and safety profile of the ezetimibe/simvastatin tablet compared with ezetimibe and simvastatin monotherapy in	- Population not relevant to this review protocol: proportion with CVD not stated

Study	Exclusion reason
patients with primary hypercholesterolemia. Clinical therapeutics 26(11): 1758-1773	
Ben-Yehuda, Ori, Wenger, Nanette K, Constance, Christian et al. (2011) 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. Journal of geriatric cardiology : JGC 8(1): 1-11	- Comparator in study does not match that specified in this review protocol: ezetimibe plus statin versus higher dose of statin
Bittner, Vera A, Szarek, Michael, Aylward, Philip E et al. (2020) Effect of Alirocumab on Lipoprotein(a) and Cardiovascular Risk After Acute Coronary Syndrome. Journal of the American College of Cardiology 75(2): 133-144	- Secondary publication of an included study that does not provide any additional relevant information
Blazing, MAB, Giugliano, RPG, Wiviott, SDW et al. (2015) Muscle related complaints, serious adverse events vents and drug discontinuations in 17,706 subjects randomized to simvastatin or ezetimibe/simvastatin in the IMPROVE-IT study. European heart journal 36: 1151	- Conference abstract
Blazing, Michael A, Giugliano, Robert P, de Lemos, James A et al. (2016) On-treatment analysis of the Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT). American heart journal 182: 89-96	- Duplicate reference
Blom, DJ, Hala, T, Bolognese, M et al. (2014) A 52-week placebo-controlled trial of evolocumab in hyperlipidemia. New England journal of medicine 370(19): 1809-1819	- Population not relevant to this review protocol: <50% CVD
Boccara, Franck, Kumar, Princy N, Caramelli, Bruno et al. (2020) Evolocumab in HIV-Infected Patients With Dyslipidemia: Primary Results of the Randomized, Double-Blind BEIJERINCK Study. Journal of the American College of Cardiology 75(20): 2570-2584	- Population not relevant to this review protocol: <50% CVD
Bohula May, EA, Giugliano, RP, Cannon, CP et al. (2015) Achievement of dual LDL-C (<70 mg/dl) and hs-CRP (<2 mg/L) goals more frequent with addition of ezetimibe and associated with better outcomes in IMPROVE-IT. European heart journal 36: 1060	- Full text paper not available
Bohula, EA, Morrow, DA, Giugliano, RP et al. (2017) Atherothrombotic Risk Stratification and Ezetimibe for Secondary Prevention. Journal of the American College of Cardiology 69(8): 911-921	- Secondary publication of an included study that does not provide any additional relevant information Study testing a model to predict CV death, MI or IS (absolute risk reduction) in the IMPROVE-IT population divided in different level of risk categories (low, intermediate, high) based on different variables; not relevant to review protocol
Bohula, Erin A, Giugliano, Robert P, Cannon, Christopher P et al. (2015) Achievement of dual low-density lipoprotein cholesterol and high-sensitivity C-reactive protein targets more	- Secondary publication of an included study that does not provide any additional relevant information

Study	Exclusion reason
frequent with the addition of ezetimibe to simvastatin and associated with better outcomes in IMPROVE-IT. Circulation 132(13): 1224-33	
Bohula, Erin A, Giugliano, Robert P, Leiter, Lawrence A et al. (2018) Inflammatory and Cholesterol Risk in the FOURIER Trial. Circulation 138(2): 131-140	- Secondary publication of an included study that does not provide any additional relevant information
Bohula, Erin A, Wiviott, Stephen D, Giugliano, Robert P et al. (2017) Prevention of Stroke with the Addition of Ezetimibe to Statin Therapy in Patients With Acute Coronary Syndrome in IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial). Circulation 136(25): 2440-2450	- Secondary publication of an included study that does not provide any additional relevant information IMPROVE-IT but focusing on people with stroke before randomisation
Bonaca, Marc P, Nault, Patrice, Giugliano, Robert P et al. (2018) Low-Density Lipoprotein Cholesterol Lowering With Evolocumab and Outcomes in Patients With Peripheral Artery Disease: Insights From the FOURIER Trial (Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk). Circulation 137(4): 338-350	- Secondary publication of an included study that does not provide any additional relevant information
Brudi, P, Reckless, J P, Henry, D P et al. (2009) Efficacy of ezetimibe/simvastatin 10/40 mg compared to doubling the dose of low-, medium- and high-potency statin monotherapy in patients with a recent coronary event. Cardiology 113(2): 89-97	- Comparator in study does not match that specified in this review protocol: ezetimibe plus statin versus double dose of statin
Burnett, Heather, Fahrbach, Kyle, Cichewicz, Allie et al. (2022) Comparative efficacy of non-statin lipid-lowering therapies in patients with hypercholesterolemia at increased cardiovascular risk: a network meta-analysis. Current medical research and opinion 38(5): 777-784	- Network meta-analysis with population not relevant to this review protocol Population does not entirely match protocol; individual studies assessed for inclusion.
Califf, Robert M., Lokhnygina, Yuliya, Cannon, Christopher P. et al. (2010) An update on the IMProved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) design. American Heart Journal 159(5): 705-709	- Secondary publication of an included study that does not provide any additional relevant information discussion of additional interim analysis of IMPROVE-IT trial
Cariou, B, Leiter, LA, Müller-Wieland, D et al. (2017) Efficacy and safety of alirocumab in insulin-treated patients with type 1 or type 2 diabetes and high cardiovascular risk: rationale and design of the ODYSSEY DM-INSULIN trial. Diabetes & metabolism 43(5): 453-459	- Trial protocol for a study not yet completed/reported Paper reports on methodology/design and inclusion criteria, no data available to extract.
Chaiyasothi, Thanaputt, Nathisuwan, Surakit, Dilokthornsakul, Piyameth et al. (2019) Effects of Non-statin Lipid-Modifying Agents on Cardiovascular Morbidity and Mortality Among Statin-Treated Patients: A Systematic Review and Network Meta-Analysis. Frontiers in pharmacology 10: 547	- Network meta-analysis with outcomes not relevant to this review protocol

Study	Exclusion reason
Chiang, Chern-En, Schwartz, Gregory G, Elbez, Yedid et al. (2022) Alirocumab and Cardiovascular Outcomes in Patients With Previous Myocardial Infarction: Prespecified Subanalysis From ODYSSEY OUTCOMES. The Canadian journal of cardiology 38(10): 1542-1549	- Secondary publication of an included study that does not provide any additional relevant information
Constance, Christian, Ben-Yehuda, Ori, Wenger, Nanette K et al. (2014) Atorvastatin 10 mg plus ezetimibe versus titration to atorvastatin 40 mg: attainment of European and Canadian guideline lipid targets in high-risk subjects >=65 years. Lipids in health and disease 13: 13	- Comparator in study does not match that specified in this review protocol: ezetimibe plus statin versus higher dose of statin
Cruz-Fernandez, J M, Bedarida, G V, Adgey, J et al. (2005) 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 59(6): 619-27	- Follow-up <3 months
Daviglus, Martha L, Ferdinand, Keith C, Lopez, J Antonio G et al. (2021) Effects of Evolocumab on Low-Density Lipoprotein Cholesterol, Non-High Density Lipoprotein Cholesterol, Apolipoprotein B, and Lipoprotein(a) by Race and Ethnicity: A Meta-Analysis of Individual Participant Data From Double-Blind and Open-Label Extension Studies. Journal of the American Heart Association 10(1): e016839	- Systematic review with no data of additional relevance SR/MA of population subgroups not relevant to the protocol (by ethnicity, statin intolerant, T2D, HeFH, duration of follow-up)
Desai, Nihar R, Giugliano, Robert P, Zhou, Jing et al. (2014) AMG 145, a monoclonal antibody against PCSK9, facilitates achievement of national cholesterol education program-adult treatment panel III low-density lipoprotein cholesterol goals among high-risk patients: an analysis from the LAPLACE-TIMI 57 trial (LDL-C assessment with PCSK9 monoclonal antibody inhibition combined with statin thErapy-thrombolysis in myocardial infarction 57). Journal of the American College of Cardiology 63(5): 430-3	- Secondary publication of an included study that does not provide any additional relevant information
Desai, Nihar R, Kohli, Payal, Giugliano, Robert P et al. (2013) AMG145, a monoclonal antibody against proprotein convertase subtilisin kexin type 9, significantly reduces lipoprotein(a) in hypercholesterolemic patients receiving statin therapy: an analysis from the LDL-C Assessment with Proprotein Convertase Subtilisin Kexin Type 9 Monoclonal Antibody Inhibition Combined with Statin Therapy (LAPLACE)-Thrombolysis in Myocardial Infarction (TIMI) 57 trial. Circulation 128(9): 962-9	- Secondary publication of an included study that does not provide any additional relevant information
Eisen, Alon, Cannon, Christopher P, Blazing, Michael A et al. (2016) The benefit of adding ezetimibe to statin therapy in patients with prior coronary artery bypass graft surgery and acute	- Secondary publication of an included study that does not provide any additional relevant information

Study	Exclusion reason
coronary syndrome in the IMPROVE-IT trial. European heart journal 37(48): 3576-3584	
El Shahawy, Mahfouz, Cannon, Christopher, Blom, Dirk et al. (2016) Alirocumab Versus Ezetimibe Over 104 Weeks In Individuals With Hypercholesterolemia And High Cardiovascular Risk: Final Results From ODYSSEY COMBO II. Journal of Clinical Lipidology 10(3): 717-718	- Conference abstract Conference abstract relevant to included study
El-Tamalawy, Mona Mohammed, Ibrahim, Osama Mohamed, Hassan, Timour Mostafa et al. (2018) Effect of Combination Therapy of Ezetimibe and Atorvastatin on Remnant Lipoprotein Versus Double Atorvastatin Dose in Egyptian Diabetic Patients. Journal of clinical pharmacology 58(1): 34-41	- Comparator in study does not match that specified in this review protocol: ezetimibe plus statin versus double dose of statin
Ennezat, Pierre Vladimir, Guerbaai, Raphaelle-Ashley, Marechaux, Sylvestre et al. (2023) Extent of Low-density Lipoprotein Cholesterol Reduction and All-cause and Cardiovascular Mortality Benefit: A Systematic Review and Meta-analysis. Journal of cardiovascular pharmacology 81(1): 35-44	- Systematic review with no data of additional relevance SR does not contain outcome of interest : CV and all cause mortality only
Farmer, John (2009) The Vytorin on Carotid-Media Thickness and Overall Arterial Rigidity (VYCTOR) study. Expert review of cardiovascular therapy 7(9): 1057-60	- Study design not relevant to this review protocol: not randomised not a trial report: commentary piece
Farnier, Michel, Jones, Peter, Severance, Randall et al. (2016) Efficacy and safety of adding alirocumab to rosuvastatin versus adding ezetimibe or doubling the rosuvastatin dose in high cardiovascular-risk patients: The ODYSSEY OPTIONS II randomized trial. Atherosclerosis 244: 138-46	- Population not relevant to this review protocol: <80% CVD and suffiicient data from directly relevant populations
Farnier, Michel, Volpe, Massimo, Massaad, Rachid et al. (2005) 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 102(2): 327-32	- Follow-up <3 months Insufficient follow-up: 6 weeks; partially incorrect comparison with some participants receiving low statin intensity as background treatment
Feldman, Theodore, Koren, Michael, Insull, William Jr et al. (2004) Treatment of high-risk patients with ezetimibe plus simvastatin co-administration versus simvastatin alone to attain National Cholesterol Education Program Adult Treatment Panel III low-density lipoprotein cholesterol goals. The American journal of cardiology 93(12): 1481-6	- Population not relevant to this review protocol: <50% CVD 66% had coronary heart disease or risk equivalent, exact number of people with coronary heart disease was not specified and is likely <50%
Ference, Brian A, Cannon, Christopher P, Landmesser, Ulf et al. (2018) Reduction of low density lipoprotein-cholesterol and cardiovascular events with proprotein convertase subtilisin-kexin type 9 (PCSK9) inhibitors and statins: an analysis of FOURIER, SPIRE, and the Cholesterol Treatment Trialists	- Review article but not a systematic review

Study	Exclusion reason
Collaboration. European heart journal 39(27): 2540-2545	
Foody, JoAnne M, Brown, W Virgil, Zieve, Franklin et al. (2010) 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). The American journal of cardiology 106(9): 1255-63	- Population not relevant to this review protocol: <50% CVD
Fujisue, K, Nagamatsu, S, Shimomura, H et al. (2018) Impact of statin-ezetimibe combination on coronary atheroma plaque in patients with and without chronic kidney disease - Sub-analysis of PRECISE-IVUS trial. International journal of cardiology 268: 23-26	- Secondary publication of an included study that does not provide any additional relevant information Not relevant subgroup analysis of included trial (originally excluded as population less than 50% of the population had previous statin use and intensity was unclear)
Fujisue, Koichiro, Yamanaga, Kenshi, Nagamatsu, Suguru et al. (2021) Effects of Statin Plus Ezetimibe on Coronary Plaques in Acute Coronary Syndrome Patients with Diabetes Mellitus: Sub-Analysis of PRECISE-IVUS Trial. Journal of atherosclerosis and thrombosis 28(2): 181-193	- Secondary publication of an included study that does not provide any additional relevant information
Ganda, Om P, Plutzky, Jorge, Sanganalmath, Santosh K et al. (2018) Efficacy and safety of alirocumab among individuals with diabetes mellitus and atherosclerotic cardiovascular disease in the ODYSSEY phase 3 trials. Diabetes, obesity & metabolism 20(10): 2389-2398	- Secondary publication of an included study that does not provide any additional relevant information
Gao, Fei, Li, Yue Ping, Ma, Xiao Teng et al. (2022) Effect of Alirocumab on Coronary Calcification in Patients With Coronary Artery Disease. Frontiers in cardiovascular medicine 9: 907662	- Secondary publication of an included study that does not provide any additional relevant information
Gao, Jing, Liu, Jing-Yu, Lu, Peng-Ju et al. (2021) Effects of Evolocumab Added to Moderate-Intensity Statin Therapy in Chinese Patients With Acute Coronary Syndrome: The EMSIACS Trial Study Protocol. Frontiers in physiology 12: 750872	- Trial protocol for a study not yet completed/reported
Gencer, Baris, Mach, Francois, Murphy, Sabina A et al. (2020) Efficacy of Evolocumab on Cardiovascular Outcomes in Patients With Recent Myocardial Infarction: A Prespecified Secondary Analysis From the FOURIER Trial. JAMA cardiology 5(8): 952-957	- Secondary publication of an included study that does not provide any additional relevant information
Geng, Qiang, Li, Xuan, Sun, Qingjiao et al. (2022) Efficacy and safety of PCSK9 inhibition in cardiovascular disease: a meta-analysis of 45 randomized controlled trials. Cardiology journal 29(4): 574-581	- Systematic review does not fully match review PICO - used as a source of primary studies
Ginsberg, HN, Rader, DJ, Raal, FJ et al. (2016) Efficacy and Safety of Alirocumab in Patients with Heterozygous Familial	- Population not relevant to this review protocol: >20% familial hypercholesterolaemia

Study	Exclusion reason
Hypercholesterolemia and LDL-C of 160 mg/dl or Higher. Cardiovascular drugs and therapy / sponsored by the International Society of Cardiovascular Pharmacotherapy 30(5): 473-483	
Giugliano, Robert P, Gencer, Baris, Wiviott, Stephen D et al. (2020) Prospective Evaluation of Malignancy in 17,708 Patients Randomized to Ezetimibe Versus Placebo: Analysis From IMPROVE-IT. JACC. CardioOncology 2(3): 385-396	- Secondary publication of an included study that does not provide any additional relevant information gives HR and cancer locations (not required per protocol); N with cancer already available in primary report
Giugliano, Robert P, Keech, Anthony, Murphy, Sabina A et al. (2017) Clinical Efficacy and Safety of Evolocumab in High-Risk Patients Receiving a Statin: Secondary Analysis of Patients With Low LDL Cholesterol Levels and in Those Already Receiving a Maximal-Potency Statin in a Randomized Clinical Trial. JAMA cardiology 2(12): 1385-1391	- Secondary publication of an included study that does not provide any additional relevant information
Giugliano, Robert P, Pedersen, Terje R, Park, Jeong-Gun et al. (2017) Clinical efficacy and safety of achieving very low LDL-cholesterol concentrations with the PCSK9 inhibitor evolocumab: a prespecified secondary analysis of the FOURIER trial. Lancet (London, England) 390(10106): 1962-1971	- Secondary publication of an included study that does not provide any additional relevant information FOURIER sub-analysis by statin intensity already reported in primary report.
Giugliano, Robert P, Pedersen, Terje R, Saver, Jeffrey L et al. (2020) Stroke Prevention With the PCSK9 (Proprotein Convertase Subtilisin-Kexin Type 9) Inhibitor Evolocumab Added to Statin in High-Risk Patients With Stable Atherosclerosis. Stroke 51(5): 1546-1554	- Secondary publication of an included study that does not provide any additional relevant information Sub analysis of included study with no additional data of relevance (subgroup with prior stroke)
Giugliano, Robert P, Wiviott, Stephen D, Blazing, Michael A et al. (2017) Long-term Safety and Efficacy of Achieving Very Low Levels of Low-Density Lipoprotein Cholesterol : A Prespecified Analysis of the IMPROVE-IT Trial. JAMA cardiology 2(5): 547-555	- Secondary publication of an included study that does not provide any additional relevant information Subgroup analysis for safety and efficacy outcomes based on LDL-C levels achieved at 1 month not baseline LDL-C levels.
Giugliano, RP, Cannon, C, Blazing, M et al. (2015) Baseline LDL-C and clinical outcomes with addition of ezetimibe to statin in 18,144 patients post ACS. Journal of the American College of Cardiology 65(10suppl1): a4	- Conference abstract Poster/abstract about IMPROVE-IT trial, no extractable data
Giugliano, RP, Cannon, CP, Blazing, MA et al. (2018) Benefit of Adding Ezetimibe to Statin Therapy on Cardiovascular Outcomes and Safety in Patients With Versus Without Diabetes Mellitus: results From IMPROVE-IT (Improved Reduction of Outcomes: vytorin Efficacy International Trial). Circulation 137(15): 1571-1582	- Secondary publication of an included study that does not provide any additional relevant information Subgroup analysis of data from included trial, subgroups not of interest based on review protocol. Diabetes. New onset not reported
Giugliano, RP, Wiviott, SD, Fuchs, CS et al. (2015) Prospectivev evaluation of cancer in 18,144 patients randomized to ezetimibe vs placebo: a prespecified analysis from the	- Conference abstract Conference abstract: malignancy endpoints of IMPROVE-IT trial, no new data

Study	Exclusion reason
IMPROVE IT trial. European heart journal 36: 181	
Goldberg, AC, Sapre, A, Liu, J et al. (2004) Efficacy and safety of ezetimibe coadministered with simvastatin in patients with primary hypercholesterolemia: a randomized, double-blind, placebo-controlled trial. Mayo Clinic proceedings 79(5): 620-629	- Population not relevant to this review protocol: <50% CVD
Greve, Anders M, Bang, Casper N, Berg, Ronan M G et al. (2015) Resting heart rate and risk of adverse cardiovascular outcomes in asymptomatic aortic stenosis: the SEAS study. International journal of cardiology 180: 122-8	- Population not relevant to this review protocol Incorrect population: heart failure and no other qualifying condition
Greve, Anders M, Boman, Kurt, Gohlke-Baerwolf, Christa et al. (2012) Clinical implications of electrocardiographic left ventricular strain and hypertrophy in asymptomatic patients with aortic stenosis: the Simvastatin and Ezetimibe in Aortic Stenosis study. Circulation 125(2): 346-53	- Population not relevant to this review protocol Incorrect population: heart failure and no other qualifying condition
Guedeney, Paul, Sorrentino, Sabato, Giustino, Gennaro et al. (2021) Indirect comparison of the efficacy and safety of alirocumab and evolocumab: a systematic review and network meta-analysis. European heart journal. Cardiovascular pharmacotherapy 7(3): 225-235	- Network meta-analysis with intervention/comparisons not relevant to this review protocol (alirocumab vs evolocumab)
Hamdan, Righab, Hajj, Fouad, Kadry, Zeina et al. (2011) Benefit and tolerability of the coadministration of ezetimibe and atorvastatin in acute coronary syndrome patients. Le Journal medical libanais. The Lebanese medical journal 59(2): 65-9	- Comparator in study does not match that specified in this review protocol: ezetimibe plus statin versus double dose of statin
Han, YL, Ma, YY, Su, GH et al. (2020) Efficacy and safety of alirocumab versus ezetimibe in high cardiovascular risk Chinese patients with hyperlipidemia: ODYSSEY EAST Study-Chinese sub-population analysis. Zhonghua xin xue guan bing za zhi 48(7): 593-599	- Study not reported in English
Hao, Qiukui, Aertgeerts, Bert, Guyatt, Gordon et al. (2022) PCSK9 inhibitors and ezetimibe for the reduction of cardiovascular events: a clinical practice guideline with risk-stratified recommendations. BMJ (Clinical research ed.) 377: e069066	- Data not reported in an extractable format or a format that can be analysed Clinical practice guideline
Hibi, K, Sonoda, S, Kawasaki, M et al. (2018) Effects of Ezetimibe-Statin Combination Therapy on Coronary Atherosclerosis in Acute Coronary Syndrome. Circulation journal 82(3): 757-766	- Comparator in study does not match that specified in this review protocol Incorrect comparison, pitavastatin not part of the review protocol
Hirayama, A, Honarpour, N, Yoshida, M et al. (2014) Effects of evolocumab (AMG 145), a monoclonal antibody to PCSK9, in hypercholesterolemic, statin-treated Japanese patients at high cardiovascular risk--primary results from the phase 2 YUKAWA study. Circulation journal 78(5): 1073-1082	- Population not relevant to this review protocol: <50% CVD

Study	Exclusion reason
Hirayama, Atsushi, Yamashita, Shizuya, Ruzza, Andrea et al. (2019) Long-Term Treatment With Evolocumab Among Japanese Patients - Final Report of the OSLER Open-Label Extension Studies. Circulation journal : official journal of the Japanese Circulation Society 83(5): 971-977	- Secondary publication of an included study that does not provide any additional relevant information
Holme, Ingar, Boman, Kurt, Brudi, Philippe et al. (2010) Observed and predicted reduction of ischemic cardiovascular events in the Simvastatin and Ezetimibe in Aortic Stenosis trial. The American journal of cardiology 105(12): 1802-8	- Population not relevant to this review protocol: <50% CVD previous CVD was part of the exclusion criteria
Hougaard, M, Hansen, HS, Junker, A et al. (2014) Effect of ezetimibe in addition to statin therapy in statin naive STEMI patients assessed by optical coherence tomography and intravascular ultrasound with iMap (the OCTIVUS trial). Journal of the American College of Cardiology 64(11suppl1): b112	- Conference abstract
Hougaard, Mikkel, Hansen, Henrik Steen, Thayssen, Per et al. (2020) Influence of Ezetimibe on Plaque Morphology in Patients with ST Elevation Myocardial Infarction Assessed by Optical Coherence Tomography: An OCTIVUS Sub-Study. Cardiovascular revascularization medicine : including molecular interventions 21(11): 1417-1424	- Secondary publication of an included study that does not provide any additional relevant information
Huang, Yen-Chu, Chang, Chia-Hao, Tsai, Yuan-Hsiung et al. (2022) PCSK9 inhibition in patients with acute stroke and symptomatic intracranial atherosclerosis: protocol for a prospective, randomised, open-label, blinded end-point trial with vessel-wall MR imaging. BMJ open 12(4): e060068	- Trial protocol for a study not yet completed/reported
Inazawa, Takeshi, Sakamoto, Kentaro, Kohro, Takahide et al. (2013) 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 12: 142	- Comparator in study does not match that specified in this review protocol: ezetimibe plus statin versus double dose of statin Population: history of CAD in 10-15%, stroke <3%; incorrect comparison - double dose statin
Jackowska, Paulina, Chalubinski, Maciej, Luczak, Emilia et al. (2019) The influence of statin monotherapy and statin-ezetimibe combined therapy on FoxP3 and IL 10 mRNA expression in patients with coronary artery disease. Advances in clinical and experimental medicine : official organ Wroclaw Medical University 28(9): 1243-1248	- Comparator in study does not match that specified in this review protocol: ezetimibe plus statin versus higher dose of statin
Janik, Matthew J, Urbach, Dorothea V, van Nieuwenhuizen, Elane et al. (2021) Alirocumab treatment and neurocognitive function according to the CANTAB scale in patients at increased cardiovascular risk: A prospective, randomized,	- Population not relevant to this review protocol Proportion with CVD not stated

Study	Exclusion reason
placebo-controlled study. Atherosclerosis 331: 20-27	
Japaridze, L; Sadunishvili, M; Megreladze, I (2016) COMBINATION THERAPY EFFECTIVENESS OF EZETIMIBE AND ATORVASTATIN IN PATIENTS WITH ACUTE CORONARY SYNDROME. Georgian medical news: 15-22	- Comparator in study does not match that specified in this review protocol: ezetimibe plus statin versus double dose of statin
Japaridze, Lasha and Sadunishvili, Maia (2017) The short-term effect of atorvastatin plus ezetimibe therapy versus atorvastatin monotherapy on clinical outcome in acute coronary syndrome patients by gender. Kardiologia polska 75(8): 770-778	- Comparator in study does not match that specified in this review protocol: ezetimibe plus statin versus double dose of statin
Jukema, J Wouter, Szarek, Michael, Zijlstra, Laurien E et al. (2019) Alirocumab in Patients With Polyvascular Disease and Recent Acute Coronary Syndrome: ODYSSEY OUTCOMES Trial. Journal of the American College of Cardiology 74(9): 1167-1176	- Secondary publication of an included study that does not provide any additional relevant information
Jukema, J Wouter, Zijlstra, Laurien E, Bhatt, Deepak L et al. (2019) Effect of Alirocumab on Stroke in ODYSSEY OUTCOMES. Circulation 140(25): 2054-2062	- Secondary publication of an included study that does not provide any additional relevant information
Kanbayashi, K, Yamaguchi, J, Fujii, S et al. (2017) The impact of serum sitosterol level on clinical outcomes in acute coronary syndrome patients with dyslipidemia: a subanalysis of HIJ PROPER. European heart journal. Conference: european society of cardiology, ESC congress 2017. Spain 38(supplement1): 237	- Conference abstract
Kasmas, S H, Izar, M C, Franca, C N et al. (2012) Differences in synthesis and absorption of cholesterol of two effective lipid-lowering therapies. Brazilian journal of medical and biological research = Revista brasileira de pesquisas medicas e biologicas 45(11): 1095-101	- Comparator in study does not match that specified in this review protocol: ezetimibe plus statin versus higher dose of statin
Kastelein, JJ, Ginsberg, HN, Langslet, G et al. (2015) ODYSSEY FH I and FH II: 78 week results with alirocumab treatment in 735 patients with heterozygous familial hypercholesterolaemia. European heart journal 36(43): 2996-3003	- Population not relevant to this review protocol: >20% familial hypercholesterolaemia
Kastelein, JJ, Strony, J, Sager, PT et al. (2004) The ENHANCE trial: ezetimibe and simvastatin in hypercholesterolemia enhances atherosclerosis regression. Stroke 35(6): e258	- Population not relevant to this review protocol: >20% familial hypercholesterolaemia People with familial hypercholesterolemia (100%)
Kastelein, JJP, Sager, PT, De Groot, E et al. (2005) Comparison of ezetimibe plus simvastatin versus simvastatin monotherapy on atherosclerosis progression in familial hypercholesterolemia: design and rationale of the Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis	- Population not relevant to this review protocol: >20% familial hypercholesterolaemia People with familiar hypercholesterolemia (100%)

Study	Exclusion reason
Regression (ENHANCE) trial. American heart journal 149(2): 234-239	
Kastelein, John J P, Kereiakes, Dean J, Cannon, Christopher P et al. (2017) Effect of alirocumab dose increase on LDL lowering and lipid goal attainment in patients with dyslipidemia. Coronary artery disease 28(3): 190-197	- Secondary analysis of trials with no data of additional relevance to the protocol
Katoh, A, Hattori, Y, Yoshikwa, N et al. (2017) The effects of ezetimibe on coronary plaque volume in patients with stable angina pectoris previously treated with statins. European heart journal. Conference: european society of cardiology, ESC congress 2017. Spain 38(supplement1): 188	- Conference abstract
Kawada-Watanabe, E, Ogawa, H, Koyanagi, R et al. (2017) Rationale, design features, and baseline characteristics: the Heart Institute of Japan-PRoper level of lipid lOwering with Pitavastatin and Ezetimibe in acute coRonary syndrome (HIJ-PROPER). Journal of cardiology 69(3): 536-541	- Comparator in study does not match that specified in this review protocol Incorrect comparison, pitavastatin not part of the review protocol
Kawamura, M, Watanabe, T, Sakamoto, K et al. (2015) 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 58(1suppl1): 82	- Conference abstract
Kereiakes, Dean J, Lepor, Norman E, Gerber, Robert et al. (2018) Efficacy and safety of alirocumab in patients with or without prior coronary revascularization: Pooled analysis of eight ODYSSEY phase 3 trials. Atherosclerosis 277: 211-218	- Data not reported in an extractable format or a format that can be analysed
Khan, Safi U, Riaz, Haris, Rahman, Hammad et al. (2019) Association of baseline LDL-C with total and cardiovascular mortality in patients using proprotein convertase subtilisin-kexin type 9 inhibitors: A systematic review and meta-analysis. Journal of clinical lipidology 13(4): 538-549	- Systematic review with no data of additional relevance does not contain any outocmes of relevance to this protocol
Khan, Safi U, Talluri, Swapna, Riaz, Haris et al. (2018) A Bayesian network meta-analysis of PCSK9 inhibitors, statins and ezetimibe with or without statins for cardiovascular outcomes. European journal of preventive cardiology 25(8): 844-853	- Systematic review with no data of additional relevance SR does not contain any outocomes of relevance to this protocol
Khan, Safi U, Yedlapati, Siva H, Lone, Ahmad N et al. (2022) PCSK9 inhibitors and ezetimibe with or without statin therapy for cardiovascular risk reduction: a systematic review and network meta-analysis. BMJ (Clinical research ed.) 377: e069116	- Network meta-analysis with outcomes not relevant to this review protocol
Khan, Sajjad A, Naz, Arshi, Qamar Masood, Muhammad et al. (2020) Meta-Analysis of Inclisiran for the Treatment of	- Systematic review with no data of additional relevance Included ORION 9, which was in those with Familial Hypercholesterolemia which was not

Study	Exclusion reason
Hypercholesterolemia. The American journal of cardiology 134: 69-73	relevant to the protocol. Paper added no extra relevant data on ORION 10 and 11 already identified.
Kim, Byeong-Keuk, Hong, Sung-Jin, Lee, Yong-Joon et al. (2022) Long-term efficacy and safety of moderate-intensity statin with ezetimibe combination therapy versus high-intensity statin monotherapy in patients with atherosclerotic cardiovascular disease (RACING): a randomised, open-label, non-inferiority trial. Lancet (London, England) 400(10349): 380-390	- Comparator in study does not match that specified in this review protocol: ezetimibe plus statin versus double dose of statin
Kinouchi, K, Ichihara, A, Bokuda, K et al. (2013) Effects of adding ezetimibe to fluvastatin on kidney function in patients with hypercholesterolemia: a randomized control trial. Journal of atherosclerosis and thrombosis 20(3): 245-256	- Population not relevant to this review protocol: <50% CVD Population with hypercholesterolemia and no previous CVD
Kinouchi, K, Ichihara, A, Bokuda, K et al. (2012) Ezetimibe preserves renal function in hypercholesterolemic patients treated with fluvastatin. Journal of hypertension 30: e214	- Conference abstract
Kiyosue, Arihiro, Honarpour, Narimon, Kurtz, Christopher et al. (2016) A Phase 3 Study of Evolocumab (AMG 145) in Statin-Treated Japanese Patients at High Cardiovascular Risk. The American journal of cardiology 117(1): 40-7	- Population not relevant to this review protocol: <50% CVD
Koenig, W., Conde, L.G., Landmesser, U. et al. (2022) Efficacy and Safety of Inclisiran in Patients with Polyvascular Disease: Pooled, Post Hoc Analysis of the ORION-9, ORION-10, and ORION-11 Phase 3 Randomized Controlled Trials. Cardiovascular Drugs and Therapy	- Systematic review with no data of additional relevance Included ORION 9, which was in those with Familial Hypercholesterolemia which was not relevant to the protocol. Paper added no extra relevant data on ORION 10 and 11 already identified.
Koh, KK, Nam, C-W, Chao, T-H et al. (2017) A randomized, double-blind, placebo-controlled, parallel group study to evaluate the efficacy and safety of alirocumab in high cardiovascular risk patients with hypercholesterolemia not adequately controlled with their lipidmodifying therapy in South Korea and Taiwan. Journal of the American College of Cardiology 69(11): 1664	- Conference abstract
Koren, M, Sabatine, M, Giugliano, R et al. (2019) Final Report of the OSLER-1 Study: long-Term Evolocumab for the Treatment of Hypercholesterolemia. Journal of clinical lipidology 13(3): e53-e54	- Conference abstract
Koren, MJ, Giugliano, RP, Raal, FJ et al. (2014) Efficacy and safety of longer-term administration of evolocumab (AMG 145) in patients with hypercholesterolemia: 52-week results from the Open-Label Study of Long-Term Evaluation Against LDL-C (OSLER) randomized trial. Circulation 129(2): 234-243	- Population not relevant to this review protocol: <50% CVD

Study	Exclusion reason
Koren, MJ, Roth, EM, McKenney, JM et al. (2015) Safety and efficacy of alirocumab 150 mg every 2 weeks, a fully human proprotein convertase subtilisin/kexin type 9 monoclonal antibody: a phase II pooled analysis. Postgraduate medicine. 127 (2) (pp 125-132), 2015. Date of publication: 01 jan 2015.	- Secondary analysis of trials with no data of additional relevance to the protocol
Koren, MJ, Sabatine, MS, Giugliano, RP et al. (2017) Long-term low-density lipoprotein cholesterol-lowering efficacy, persistence, and safety of evolocumab in treatment of hypercholesterolemia: results up to 4 years from the open-label OSLER-1 extension study. JAMA cardiology 2(6): 598-607	- Population not relevant to this review protocol: <50% CVD
Koskinas, Konstantinos C, Siontis, George C M, Piccolo, Raffaele et al. (2018) Effect of statins and non-statin LDL-lowering medications on cardiovascular outcomes in secondary prevention: a meta-analysis of randomized trials. European heart journal 39(14): 1172-1180	- Systematic review does not fully match review PICO - used as a source of primary studies SR includes comparisons not relevant to the protocl. Used as a source of primary studies (only 2 relevant and both already ordered)
Kouvelos, GN, Arnaoutoglou, EM, Milionis, HJ et al. (2015) The effect of adding ezetimibe to rosuvastatin on renal function in patients undergoing elective vascular surgery. Angiology 66(2): 128-135	- Secondary publication of an included study that does not provide any additional relevant information
Landmesser, Ulf, Haghikia, Arash, Leiter, Lawrence A et al. (2021) Effect of inclisiran, the small-interfering RNA against proprotein convertase subtilisin/kexin type 9, on platelets, immune cells, and immunological biomarkers: a pre-specified analysis from ORION-1. Cardiovascular research 117(1): 284-291	- Secondary publication of an included study that does not provide any additional relevant information
Landmesser, Ulf, McGinniss, Jennifer, Steg, Ph Gabriel et al. (2022) Achievement of ESC/EAS LDL-C treatment goals after an acute coronary syndrome with statin and alirocumab. European journal of preventive cardiology 29(14): 1842-1851	- Secondary publication of an included study that does not provide any additional relevant information
Lee, Ju-Hee, Kang, Hyun-Jae, Kim, Hyo-Soo et al. (2013) Effects of ezetimibe/simvastatin 10/20 mg vs. atorvastatin 20 mg on apolipoprotein B/apolipoprotein A1 in Korean patients with type 2 diabetes mellitus: results of a randomized controlled trial. American journal of cardiovascular drugs : drugs, devices, and other interventions 13(5): 343-51	- Population not relevant to this review protocol: <50% CVD
Lee, Yong-Joon, Cho, Jae Young, You, Seng Chan et al. (2022) Moderate-intensity statin with ezetimibe vs. high-intensity statin in patients with diabetes and atherosclerotic cardiovascular disease in the RACING trial. European heart journal	- Comparator in study does not match that specified in this review protocol: ezetimibe plus statin versus double dose of statin
Leiter, LA, Cariou, B, Müller-Wieland, D et al. (2017) Efficacy and safety of alirocumab in insulin-treated individuals with type 1 or type 2 diabetes and high cardiovascular risk: the	- Population not relevant to this review protocol: <50% CVD

Study	Exclusion reason
ODYSSEY DM-INSULIN randomized trial. Diabetes, obesity & metabolism 19(12): 1781-1792	
Leiter, Lawrence A, Teoh, Hwee, Kallend, David et al. (2019) Inclisiran Lowers LDL-C and PCSK9 Irrespective of Diabetes Status: The ORION-1 Randomized Clinical Trial. Diabetes care 42(1): 173-176	- Population not relevant to this review protocol: <80% CVD and suffiicient data from directly relevant populations - Comparator in study does not match that specified in this review protocol Inclisiran not at licensed dose.
Liu, Zhi, Hao, Hengjian, Yin, Chunlin et al. (2017) Therapeutic effects of atorvastatin and ezetimibe compared with double-dose atorvastatin in very elderly patients with acute coronary syndrome. Oncotarget 8(25): 41582-41589	- Comparator in study does not match that specified in this review protocol: ezetimibe plus statin versus double dose of statin
Lorenzatti, AJ, Eliaschewitz, FG, Chen, Y et al. (2019) Randomised study of evolocumab in patients with type 2 diabetes and dyslipidaemia on background statin: primary results of the BERSON clinical trial. Diabetes, obesity & metabolism 21(6): 1455-1463	- Population not relevant to this review protocol: <80% CVD and suffiicient data from directly relevant populations
Lorenzatti, Alberto J, Eliaschewitz, Freddy G, Chen, Yundai et al. (2018) Rationale and design of a randomized study to assess the efficacy and safety of evolocumab in patients with diabetes and dyslipidemia: The BERSON clinical trial. Clinical cardiology 41(9): 1117-1122	- Population not relevant to this review protocol: <50% CVD Population does not match protocol: not all on statins and not all CVD
Lorenzi, Maria, Ambegaonkar, Baishali, Baxter, Carl A et al. (2019) Ezetimibe in high-risk, previously treated statin patients: a systematic review and network meta-analysis of lipid efficacy. Clinical research in cardiology : official journal of the German Cardiac Society 108(5): 487-509	- Network meta-analysis with intervention/comparisons not relevant to this review protocol adding ezetimibe vs doubling the dose of statin
Luan, Yi, Wang, Min, Zhao, Liding et al. (2021) Safety and Efficacy of Perioperative Use of Evolocumab in Myocardial Infarction Patients: Study Protocol for a Multicentre Randomized Controlled Trial. Advances in therapy 38(4): 1801-1810	- Trial protocol for a study not yet completed/reported
Luo, L, Yuan, X, Huang, W et al. (2015) Safety of coadministration of ezetimibe and statins in patients with hypercholesterolaemia: a meta-analysis. Internal medicine journal 45(5): 546-57	- Systematic review does not fully match review PICO - used as a source of primary studies SR: insufficient reporting of included study caracteristics. majority of studies have follow up <3 months. Remaining studies cross checked for relevance and ordered if appropriate
Ma, Wenfang, Guo, Xiying, Ma, Yiming et al. (2021) Meta-analysis of randomized clinical trials comparing PCSK9 monoclonal antibody versus ezetimibe/placebo in patients at high cardiovascular risk. Atherosclerosis 326: 25-34	- Systematic review does not fully match review PICO - used as a source of primary studies SR does not contain a comparison relevant to the protocol (pooled 'ezetimibe and placebo, and includes populations not relevant to the protocol (FH, non CVD, statin naïve)
Ma, Wenrui, Pan, Qinyuan, Pan, Defeng et al. (2021) Efficacy and Safety of Lipid-Lowering	- Systematic review does not fully match review PICO - used as a source of primary studies

Study	Exclusion reason
Drugs of Different Intensity on Clinical Outcomes: A Systematic Review and Network Meta-Analysis. Frontiers in pharmacology 12: 713007	
Madan, Mina, Vira, Tasnim, Rampakakis, Emmanouil et al. (2012) 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: 103728	- Comparator in study does not match that specified in this review protocol: ezetimibe plus statin versus higher dose of statin
Magnuson, EA, Chinnakondepalli, K, Vilain, K et al. (2015) Impact of ezetimibe on hospitalization-related costs among patients with a recent acute coronary syndrome: results from the improve-it trial. Circulation 132(nopagination)	- Conference abstract
Matsue, Yuya, Matsumura, Akihiko, Suzuki, Makoto et al. (2013) Differences in action of atorvastatin and ezetimibe in lowering low-density lipoprotein cholesterol and effect on endothelial function: randomized controlled trial. Circulation journal : official journal of the Japanese Circulation Society 77(7): 1791-8	- Comparator in study does not match that specified in this review protocol: ezetimibe plus statin versus double dose of statin
McCormack, T, Harvey, P, Gaunt, R et al. (2010) Incremental cholesterol reduction with ezetimibe/simvastatin, atorvastatin and rosuvastatin in UK General Practice (IN-PRACTICE): randomised controlled trial of achievement of Joint British Societies (JBS-2) cholesterol targets. International journal of clinical practice 64(8): 1052-61	- Follow-up <3 months
Meaney, Alejandra, Ceballos, Guillermo, Asbun, Juan et al. (2009) The VYtorin on Carotid intima-media thickness and overall arterial rigidity (VYCTOR) study. Journal of clinical pharmacology 49(7): 838-47	- Study does not include an intervention relevant to this protocol: includes low intensity statin Population & comparison not relevant: majority had previously received statins at low and very low doses, comparison included statin not relevant to review protocol, unclear if population had previous CVD
Moreira, Flavio Tocci, Ramos, Silvia Cristina, Monteiro, Andrea Moreira et al. (2014) Effects of two lipid lowering therapies on immune responses in hyperlipidemic subjects. Life sciences 98(2): 83-7	- Comparator in study does not match that specified in this review protocol: ezetimibe plus statin versus higher dose of statin
Moriarty, PM, Thompson, PD, Cannon, CP et al. (2015) Efficacy and safety of alirocumab vs ezetimibe in statin-intolerant patients, with a statin rechallenge arm: the ODYSSEY ALTERNATIVE randomized trial. Journal of clinical lipidology 9(6): 758-769	- Population not relevant to this review protocol: >50% statin intolerant Population does not meet protocol: participants were intolerant to statins and approximately 50% had CVD with results not given separately for CVD vs CV risk factors populations
Morrone, Doralisa, Weintraub, William S, Toth, Peter P et al. (2012) Lipid-altering efficacy of ezetimibe plus statin and statin monotherapy and identification of factors associated with treatment response: a pooled analysis of over 21,000 subjects from 27 clinical trials. Atherosclerosis 223(2): 251-61	- Systematic review does not fully match review PICO - used as a source of primary studies SR with majority of studies not reporting at time point reelvant to the protocol (<12 weeks); and limited to Merck-sopnsored studies (not truly systematic)

Study	Exclusion reason
Mortensen, Martin B, Sand, Niels-Peter, Busk, Martin et al. (2022) Influence of intensive lipid-lowering on CT derived fractional flow reserve in patients with stable chest pain: Rationale and design of the FLOWPROMOTE study. Clinical cardiology 45(10): 986-994	- Data not reported in an extractable format or a format that can be analysed Design and data analysis plan but no results presented
Mu, Guangyan, Xiang, Qian, Zhou, Shuang et al. (2020) Efficacy and Safety of PCSK9 Monoclonal Antibodies in Patients at High Cardiovascular Risk: An Updated Systematic Review and Meta-Analysis of 32 Randomized Controlled Trials. Advances in therapy 37(4): 1496-1521	- Systematic review does not fully match review PICO - used as a source of primary studies SR population doesn't match protocpl: CVD or high CV risk population; all relevant studies already identified.
Muller-Wieland, D, Rader, DJ, Moriarty, PM et al. (2019) Efficacy and Safety of Alirocumab 300 mg Every 4 Weeks in Individuals with Type 2 Diabetes on Maximally Tolerated Statin. Journal of clinical endocrinology and metabolism	- Population not relevant to this review protocol: <80% CVD and suffiicient data from directly relevant populations
Murphy, Sabina A, Cannon, Christopher P, Blazing, Michael A et al. (2016) Reduction in Total Cardiovascular Events With Ezetimibe/Simvastatin Post-Acute Coronary Syndrome: The IMPROVE-IT Trial. Journal of the American College of Cardiology 67(4): 353-361	- Duplicate reference FOURIER sub-analysis already reported in primary report.
Murphy, Sabina A, Pedersen, Terje R, Gaciong, Zbigniew A et al. (2019) Effect of the PCSK9 Inhibitor Evolocumab on Total Cardiovascular Events in Patients With Cardiovascular Disease: A Prespecified Analysis From the FOURIER Trial. JAMA cardiology 4(7): 613-619	- Secondary publication of an included study that does not provide any additional relevant information
Nakamura, Takamitsu, Hirano, Mitsumasa, Kitta, Yoshinobu et al. (2012) A comparison of the efficacy of combined ezetimibe and statin therapy with doubling of statin dose in patients with remnant lipoproteinemia on previous statin therapy. Journal of cardiology 60(1): 12-7	- Comparator in study does not match that specified in this review protocol: ezetimibe plus statin versus double dose of statin
Nakano, Yasuhiro, Yamamoto, Mitsutaka, Matoba, Tetsuya et al. (2022) Association between Serum Oxysterols and Coronary Plaque Regression during Lipid-Lowering Therapy with Statin and Ezetimibe: Insights from the CuVIC Trial. Journal of atherosclerosis and thrombosis	- Comparator in study does not match that specified in this review protocol: ezetimibe plus statin versus higher dose of statin Statins could be chosen by investigator from any high, medium or low dose options and proportions used not stated
Navar, Ann Marie, Roe, Matthew T, White, Jennifer A et al. (2019) Medication Discontinuation in the IMPROVE-IT Trial. Circulation. Cardiovascular quality and outcomes 12(1): e005041	- Secondary publication of an included study that does not provide any additional relevant information
Navarese, Eliano P, Robinson, Jennifer G, Kowalewski, Mariusz et al. (2018) Association Between Baseline LDL-C Level and Total and Cardiovascular Mortality After LDL-C Lowering: A Systematic Review and Meta-analysis. JAMA 319(15): 1566-1579	- Systematic review does not fully match review PICO - used as a source of primary studies SR does not contain outcomes of relevance to the protocol: total or CV mortality only

Study	Exclusion reason
Nicholls, Stephen J, Ray, Kausik K, Ballantyne, Christie M et al. (2017) Comparative effects of cholesteryl ester transfer protein inhibition, statin or ezetimibe on lipid factors: The ACCENTUATE trial. Atherosclerosis 261: 12-18	- Population not relevant to this review protocol: <80% CVD and suffiicient data from directly relevant populations
Nielsen, Olav W, Sajadieh, Ahmad, Sabbah, Muhammad et al. (2016) Assessing Optimal Blood Pressure in Patients With Asymptomatic Aortic Valve Stenosis: The Simvastatin Ezetimibe in Aortic Stenosis Study (SEAS). Circulation 134(6): 455-68	- Population not relevant to this review protocol: <50% CVD Incorrect population: not CVD and not on statins for CV risk reduction
Nissen, SE, Stroes, E, Dent-Acosta, RE et al. (2016) Efficacy and Tolerability of Evolocumab vs Ezetimibe in Patients With Muscle-Related Statin Intolerance: the GAUSS-3 Randomized Clinical Trial. JAMA 315(15): 1580-1590	- Population not relevant to this review protocol: >50% statin intolerant
Nissen, Steven E and Nicholls, Stephen J (2017) Results of the GLAGOV trial. Cleveland Clinic journal of medicine 84(12suppl4): e1-e5	- Secondary publication of an included study that does not provide any additional relevant information
Oh, Minyoung, Kim, Hyunji, Shin, Eon Woo et al. (2020) Comparison of High-Dose Rosuvastatin Versus Low-Dose Rosuvastatin Plus Ezetimibe on Carotid Atherosclerotic Plaque Inflammation in Patients with Acute Coronary Syndrome. Journal of cardiovascular translational research 13(6): 900-907	- Comparator in study does not match that specified in this review protocol: ezetimibe plus statin versus higher dose of statin
Oh, Minyoung, Kim, Hyunji, Shin, Eon Woo et al. (2019) Effects of ezetimibe/simvastatin 10/10 mg versus Rosuvastatin 10 mg on carotid atherosclerotic plaque inflammation. BMC cardiovascular disorders 19(1): 201	- Study does not include an intervention relevant to this protocol: includes low intensity statin
Oh, Pyung Chun, Jang, Albert Youngwoo, Ha, Kyungeun et al. (2021) Effect of Atorvastatin (10 mg) and Ezetimibe (10 mg) Combination Compared to Atorvastatin (40 mg) Alone on Coronary Atherosclerosis. The American journal of cardiology 154: 22-28	- Comparator in study does not match that specified in this review protocol: ezetimibe plus statin versus higher dose of statin
Oikawa, S, Yamashita, S, Nakaya, N et al. (2017) Efficacy and Safety of Long-term Coadministration of Fenofibrate and Ezetimibe in Patients with Combined Hyperlipidemia: results of the EFECTL Study. Journal of atherosclerosis and thrombosis 24(1): 77-94	- Population not relevant to this review protocol: <50% CVD Incorrect comparison; Very low rate of previous CVD (<50%)
Okada, K, Kimura, K, Iwahashi, N et al. (2012) The mechanism of long-term low-density lipoprotein cholesterol lowering effect of ezetimibe-plus-statin combination therapy in coronary artery disease patients; compared with double-dose statin therapy. Journal of the American College of Cardiology 59(13suppl1): e1541	- Conference abstract
Okada, Kozo, Iwahashi, Noriaki, Endo, Tsutomu et al. (2012) Long-term effects of ezetimibe-plus-statin therapy on low-density lipoprotein cholesterol levels as compared with double-dose	- Comparator in study does not match that specified in this review protocol: ezetimibe plus statin versus double dose of statin

Study	Exclusion reason
statin therapy in patients with coronary artery disease. Atherosclerosis 224(2): 454-6	
Okada, Kozo, Kimura, Kazuo, Iwahashi, Noriaki et al. (2011) Clinical usefulness of additional treatment with ezetimibe in patients with coronary artery disease on statin therapy. -From the viewpoint of cholesterol metabolism.-. Circulation journal : official journal of the Japanese Circulation Society 75(10): 2496-504	- Comparator in study does not match that specified in this review protocol: ezetimibe plus statin versus double dose of statin
Otake, Hiromasa, Sugizaki, Yoichiro, Toba, Takayoshi et al. (2019) Efficacy of alirocumab for reducing plaque vulnerability: Study protocol for ALTAIR, a randomized controlled trial in Japanese patients with coronary artery disease receiving rosuvastatin. Journal of cardiology 73(3): 228-232	- Population not relevant to this review protocol
Otake, Hiromasa, Tanimura, Kosuke, Sugizaki, Yoichiro et al. (2019) Effect of Alirocumab and Rosuvastatin or Rosuvastatin Alone on Lipid Core Plaque in Coronary Artery Disease Seen on Near-Infrared Spectroscopy Intravascular Ultrasound (ANTARES). Circulation reports 1(2): 107-111	- Trial protocol for a study not yet completed/reported
Oyama, Kazuma, Giugliano, Robert P, Tang, Minao et al. (2021) Effect of evolocumab on acute arterial events across all vascular territories : results from the FOURIER trial. European heart journal 42(47): 4821-4829	- Secondary publication of an included study that does not provide any additional relevant information post-hoc analysis of included study with no additional data of relevance
Palathingal, J.T., Vijayan, D., Drisya Rajan, C. et al. (2020) A randomised controlled study of high dose statin versus statin plus ezetimibe therapy in patients with acute coronary syndrome. International Journal of Biomedical Science 16(4): 52-67	- Data not reported in an extractable format or a format that can be analysed Study only reports mean LDL-C at baseline and follow-up in graph format so data cannot be utilised
Pearson, Thomas, Denke, Margo, McBride, Patrick et al. (2005) 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. The American journal of geriatric pharmacotherapy 3(4): 218-28	- Follow-up <3 months
Pokharel, Yashashwi, Chinnakondepalli, Khaja, Vilain, Katherine et al. (2017) Impact of Ezetimibe on the Rate of Cardiovascular-Related Hospitalizations and Associated Costs Among Patients With a Recent Acute Coronary Syndrome: Results From the IMPROVE-IT Trial (Improved Reduction of Outcomes: Vytorin Efficacy International Trial). Circulation. Cardiovascular quality and outcomes 10(5)	- Secondary publication of an included study that does not provide any additional relevant information
Pytel, Edyta, Bukowska, Bozena, Koter-Michalak, Maria et al. (2017) Effect of intensive lipid-lowering therapies on cholinesterase	- Comparator in study does not match that specified in this review protocol: ezetimibe plus statin versus higher dose of statin

Study	Exclusion reason
activity in patients with coronary artery disease. Pharmacological reports : PR 69(1): 150-155	
Pytel, Edyta, Jackowska, Paulina, Chwatko, Grazyna et al. (2016) Intensive statin therapy, used alone or in combination with ezetimibe, improves homocysteine level and lipid peroxidation to a similar degree in patients with coronary artery diseases. Pharmacological reports : PR 68(2): 344-8	- Comparator in study does not match that specified in this review protocol: ezetimibe plus statin versus higher dose of statin
Qian, Juying, Li, Zhanquan, Zhang, Xuelian et al. (2022) Efficacy and Tolerability of Ezetimibe/Atorvastatin Fixed-dose Combination Versus Atorvastatin Monotherapy in Hypercholesterolemia: A Phase III, Randomized, Active-controlled Study in Chinese Patients. Clinical therapeutics 44(10): 1282-1296	- Comparator in study does not match that specified in this review protocol: ezetimibe plus statin versus double dose of statin
Ray, Kausik K, Colhoun, Helen M, Szarek, Michael et al. (2019) Effects of alirocumab on cardiovascular and metabolic outcomes after acute coronary syndrome in patients with or without diabetes: a prespecified analysis of the ODYSSEY OUTCOMES randomised controlled trial. The lancet. Diabetes & endocrinology 7(8): 618-628	- Secondary publication of an included study that does not provide any additional relevant information
Ray, Kausik K, Ginsberg, Henry N, Davidson, Michael H et al. (2016) Reductions in Atherogenic Lipids and Major Cardiovascular Events: A Pooled Analysis of 10 ODYSSEY Trials Comparing Alirocumab With Control. Circulation 134(24): 1931-1943	- Secondary analysis of 10 trials with no data of additional relevance
Ray, Kausik K, Landmesser, Ulf, Leiter, Lawrence A et al. (2017) Inclisiran in Patients at High Cardiovascular Risk with Elevated LDL Cholesterol. The New England journal of medicine 376(15): 1430-1440	- Population not relevant to this review protocol: <80% CVD and suffiicient data from directly relevant populations Previous CVD was less than 80% in each treatment arm and not licensed dose
Ray, Kausik K, Raal, Frederick J, Kallend, David G et al. (2023) Inclisiran and cardiovascular events: a patient-level analysis of phase III trials. European heart journal 44(2): 129-138	- Secondary analysis of trials with no data of additional relevance to the protocol
Ray, Kausik K, Troquay, Roel P T, Visseren, Frank L J et al. (2023) Long-term efficacy and safety of inclisiran in patients with high cardiovascular risk and elevated LDL cholesterol (ORION-3): results from the 4-year open-label extension of the ORION-1 trial. The lancet. Diabetes & endocrinology	- Study design not relevant to this review protocol: not randomised incorrect study design: non-randomised open label extension study
Ray, KK, Ginsberg, HN, Davidson, MH et al. (2016) Reductions in Atherogenic Lipids and Major Cardiovascular Events: a Pooled Analysis of 10 ODYSSEY Trials Comparing Alirocumab to Control. Circulation	- Secondary analysis of 10 trials with no data of additional relevance - Duplicate reference
Ray, KK, Leiter, LA, M?ller-Wieland, D et al. (2018) Alirocumab vs usual lipid-lowering care as add-on to statin therapy in individuals with type 2 diabetes and mixed dyslipidaemia: the ODYSSEY DM-DYSLIPIDEMIA randomized	- Population not relevant to this review protocol: <50% CVD

Study	Exclusion reason
trial. Diabetes, obesity & metabolism 20(6): 1479-1489	
Ray, KK, Stoekenbroek, RM, Kallend, D et al. (2019) Effect of 1 or 2 Doses of Inclisiran on Low-Density Lipoprotein Cholesterol Levels: one-Year Follow-up of the ORION-1 Randomized Clinical Trial. JAMA cardiology 4(11): 1067-1075	- Population not relevant to this review protocol: <80% CVD and suffiicient data from directly relevant populations - Study does not contain an intervention relevant to this review protocol; inclisiran not at licensed dose
Reckless, J P D, Henry, P, Pomykaj, T et al. (2008) 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 62(4): 539-54	- Comparator in study does not match that specified in this review protocol: ezetimibe plus statin versus double dose of statin
Reith, C, Staplin, N, Herrington, WG et al. (2017) Effect on non-vascular outcomes of lowering LDL cholesterol in patients with chronic kidney disease: results from the Study of Heart and Renal Protection. BMC nephrology 18(1): 147	- Population not relevant to this review protocol: <50% CVD CKD patients receiving maintenance dialysis; excluding people with prior MI or coronary revascularization; 15% had history of vascular disease; no further info to suggest participants matched the protocol definition of CVD
Robinson, J.G., Davidson, M.H., Shah, A. et al. (2007) Efficacy and safety of ezetimibe and ezetimibe plus statin therapy in patients aged under 65, 65-74 and 75 years and older. Aging Health 3(6): 691-705	- Population not relevant to this review protocol: <80% CVD and suffiicient data from directly relevant populations
Robinson, Jennifer G, Ballantyne, Christie M, Grundy, Scott M et al. (2009) Lipid-altering efficacy and safety of ezetimibe/simvastatin versus atorvastatin in patients with hypercholesterolemia and the metabolic syndrome (from the VYMET study). The American journal of cardiology 103(12): 1694-702	- Population not relevant to this review protocol: <50% CVD
Robinson, Jennifer G, Colhoun, Helen M, Bays, Harold E et al. (2014) Efficacy and safety of alirocumab as add-on therapy in high-cardiovascular-risk patients with hypercholesterolemia not adequately controlled with atorvastatin (20 or 40 mg) or rosuvastatin (10 or 20 mg): design and rationale of the ODYSSEY OPTIONS Studies. Clinical cardiology 37(10): 597-604	- Population not relevant to this review protocol: <80% CVD and suffiicient data from directly relevant populations
Robinson, Jennifer G, Rogers, William J, Nedergaard, Bettina S et al. (2014) Rationale and design of LAPLACE-2: a phase 3, randomized, double-blind, placebo- and ezetimibe-controlled trial evaluating the efficacy and safety of evolocumab in subjects with hypercholesterolemia on background statin therapy. Clinical cardiology 37(4): 195-203	- Population not relevant to this review protocol: <50% CVD 32% CVD
Robinson, JG, Nedergaard, BS, Rogers, WJ et al. (2014) Effect of evolocumab or ezetimibe added to moderate- or high-intensity statin	- Population not relevant to this review protocol: <50% CVD

Study	Exclusion reason
therapy on LDL-C lowering in patients with hypercholesterolemia: the LAPLACE-2 randomized clinical trial. JAMA 311(18): 1870-1882	35% of High intensity statin population had CVD and 21% of moderate intensity statins
Rodney, RA, Sugimoto, D, Wagman, B et al. (2006) Efficacy and safety of coadministration of ezetimibe and simvastatin in African-American patients with primary hypercholesterolemia. Journal of the National Medical Association 98(5): 772-778	- Population not relevant to this review protocol: <50% CVD 10% had coronary heart disease and participants with a CV event 3 months prior to randomisation were excluded; no further details to suggest population had CVD
Roeters van Lennep, Henk W O, Liem, An Ho, Dunselman, Peter H J M et al. (2008) The efficacy of statin monotherapy uptitration versus switching to ezetimibe/simvastatin: results of the EASEGO study. Current medical research and opinion 24(3): 685-94	- Comparator in study does not match that specified in this review protocol: ezetimibe plus statin versus double dose of statin
Rosen, Jeffrey B, Jimenez, Jose G, Pirags, Valdis et al. (2013) 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 10(3): 277-86	- Follow-up <3 months
Rosenson, Robert S, Daviglus, Martha L, Handelsman, Yehuda et al. (2019) Efficacy and safety of evolocumab in individuals with type 2 diabetes mellitus: primary results of the randomised controlled BANTING study. Diabetologia 62(6): 948-958	- Population not relevant to this review protocol: <80% CVD and suffiicient data from directly relevant populations
Rossebo, Anne B, Pedersen, Terje R, Allen, Christopher et al. (2007) Design and baseline characteristics of the simvastatin and ezetimibe in aortic stenosis (SEAS) study. The American journal of cardiology 99(7): 970-3	- Population not relevant to this review protocol: <50% CVD Incorrect publication type : PhD thesis; incorrect population: heart vavle disease
Roth, Eli M, Moriarty, Patrick M, Bergeron, Jean et al. (2016) A phase III randomized trial evaluating alirocumab 300 mg every 4 weeks as monotherapy or add-on to statin: ODYSSEY CHOICE I. Atherosclerosis 254: 254-262	- Population not relevant to this review protocol: <50% CVD Population with CV risk not previous CVD
Roth, Eli M, Taskinen, Marja-Riitta, Ginsberg, Henry N et al. (2014) Monotherapy with the PCSK9 inhibitor alirocumab versus ezetimibe in patients with hypercholesterolemia: results of a 24 week, double-blind, randomized Phase 3 trial. International journal of cardiology 176(1): 55-61	- Population not relevant to this review protocol: <50% CVD
Sabatine, Marc S, De Ferrari, Gaetano M, Giugliano, Robert P et al. (2018) Clinical Benefit of Evolocumab by Severity and Extent of Coronary Artery Disease: Analysis From FOURIER. Circulation 138(8): 756-766	- Secondary publication of an included study that does not provide any additional relevant information
Sabatine, Marc S, Giugliano, Robert P, Keech, Anthony C et al. (2017) Evolocumab and Clinical Outcomes in Patients with Cardiovascular	- Review article but not a systematic review

Study	Exclusion reason
Disease. The New England journal of medicine 376(18): 1713-1722	
Sabatine, Marc S, Giugliano, Robert P, Wiviott, Stephen D et al. (2015) Efficacy and safety of evolocumab in reducing lipids and cardiovascular events. The New England journal of medicine 372(16): 1500-9	- Population not relevant to this review protocol: <50% CVD
Sabatine, Marc S, Leiter, Lawrence A, Wiviott, Stephen D et al. (2017) Cardiovascular safety and efficacy of the PCSK9 inhibitor evolocumab in patients with and without diabetes and the effect of evolocumab on glycaemia and risk of new-onset diabetes: a prespecified analysis of the FOURIER randomised controlled trial. The lancet. Diabetes & endocrinology 5(12): 941-950	- Secondary publication of an included study that does not provide any additional relevant information
Sakamoto, K, Kawamura, M, Watanabe, T et al. (2017) Effect of ezetimibe add-on therapy over 52 weeks extension analysis of prospective randomized trial (RESEARCH study) in type 2 diabetes subjects. Lipids in health and disease 16(1): 122	- Comparator in study does not match that specified in this review protocol: ezetimibe plus statin versus double dose of statin Pitavastatin (received by 36.7% of the study population, not part of the review protocol); Paper linked to Inazawa paper where very low % of previous CVD
Samuel, Essie, Watford, Maya, Egolum, Ugochukwu O et al. (2022) Inclisiran: A First-in-Class siRNA Therapy for Lowering Low-Density Lipoprotein Cholesterol. The Annals of pharmacotherapy: 10600280221105169	- Review article but not a systematic review narrative review used as source of references
Sattar, Naveed, Preiss, David, Robinson, Jennifer G et al. (2016) Lipid-lowering efficacy of the PCSK9 inhibitor evolocumab (AMG 145) in patients with type 2 diabetes: a meta-analysis of individual patient data. The lancet. Diabetes & endocrinology 4(5): 403-10	- Systematic review does not fully match review PICO - used as a source of primary studies systematic review includes populations not relevant to the protocol (FH). Used as a source of primary studies
Sawayama, Y (2011) Low-dose pravastatin plus ezetimibe verus standard-dose pravastatin: the effect on the carotid atherosclerosis of patients with hypercholesterolemia. Atherosclerosis supplements 12(1): 180	- Conference abstract
Sawayama, Yasunori, Maeda, Shinji, Ohnishi, Hachiro et al. (2010) Efficacy and safety of ezetimibe for Japanese patients with dyslipidaemia: The ESSENTIAL Study. Clinical drug investigation 30(3): 157-66	- Comparator in study does not match that specified in this review protocol Incorrect comparison: ezetimibe alone vs ezetimibe + low intensity statin
Schmidt, A.F., Pearce, L.S., Wilkins, J.T. et al. (2015) PCSK9 monoclonal antibodies for the primary and secondary prevention of cardiovascular disease. Cochrane Database of Systematic Reviews 2015(6): cd011748	- More recent systematic review included that covers the same topic Cochrane review including studies with people without CVD; included studies were checked for inclusion in the present review individually using a more recent version (2020) of the same Cochrane review
Schmidt, A.F., Pearce, L.S., Wilkins, J.T. et al. (2017) PCSK9 monoclonal antibodies for the primary and secondary prevention of cardiovascular disease. Cochrane Database of Systematic Reviews 2017(4): cd011748	- More recent systematic review included that covers the same topic Cochrane review including studies with people without CVD; included studies were checked for inclusion in the present review individually using

Study	Exclusion reason
	a more recent version (2020) of the same Cochrane review
Schmidt, Amand F, Pearce, Lucy S, Wilkins, John T et al. (2017) PCSK9 monoclonal antibodies for the primary and secondary prevention of cardiovascular disease. The Cochrane database of systematic reviews 4: cd011748	- Duplicate reference
Schwartz, Gregory G, Gabriel Steg, Philippe, Bhatt, Deepak L et al. (2021) Clinical Efficacy and Safety of Alirocumab After Acute Coronary Syndrome According to Achieved Level of Low-Density Lipoprotein Cholesterol: A Propensity Score-Matched Analysis of the ODYSSEY OUTCOMES Trial. Circulation 143(11): 1109-1122	- Secondary publication of an included study that does not provide any additional relevant information
Schwartz, Gregory G, Szarek, Michael, Bittner, Vera A et al. (2021) Lipoprotein(a) and Benefit of PCSK9 Inhibition in Patients With Nominally Controlled LDL Cholesterol. Journal of the American College of Cardiology 78(5): 421-433	- Secondary publication of an included study that does not provide any additional relevant information
Sharp Collaborative, Group (2010) Study of Heart and Renal Protection (SHARP): randomized trial to assess the effects of lowering low-density lipoprotein cholesterol among 9,438 patients with chronic kidney disease. American heart journal 160(5): 785-794e10	- Population not relevant to this review protocol: <50% CVD
Shaya, Fadia Tohme, Sing, Krystal, Milam, Robert et al. (2020) Lipid-Lowering Efficacy of Ezetimibe in Patients with Atherosclerotic Cardiovascular Disease: A Systematic Review and Meta-Analyses. American journal of cardiovascular drugs : drugs, devices, and other interventions 20(3): 239-248	- Systematic review with no data of additional relevance 12 included studies already assessed for inclusion
Stanifer, JW, Charytan, DM, White, J et al. (2017) Benefit of Ezetimibe Added to Simvastatin in Reduced Kidney Function. Journal of the American Society of Nephrology : JASN 28(10): 3034-3043	- Secondary publication of an included study that does not provide any additional relevant information Subgroup under investigation (different levels of kidney function) not relevant to the current review
Steg, P.G., Szarek, M., Bhatt, D.L. et al. (2019) Effect of Alirocumab on Mortality after Acute Coronary Syndromes: An Analysis of the ODYSSEY OUTCOMES Randomized Clinical Trial. Circulation 140(2): 103-112	- Secondary publication of an included study that does not provide any additional relevant information
Stiekema, LCA, Stroes, ESG, Verweij, SL et al. (2019) Persistent arterial wall inflammation in patients with elevated lipoprotein(a) despite strong low-density lipoprotein cholesterol reduction by proprotein convertase subtilisin/kexin type 9 antibody treatment. European heart journal 40(33): 2775-2781	- Population not relevant to this review protocol: <50% CVD
Stoekenbroek, Robert M, Kallend, David, Wijngaard, Peter Lj et al. (2018) Inclisiran for the treatment of cardiovascular disease: the ORION	- Review article but not a systematic review

Study	Exclusion reason
clinical development program. Future cardiology 14(6): 433-442	
Stojakovic, T, de Campo, A, Scharnagl, H et al. (2010) 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 40(3): 187-94	- Population not relevant to this review protocol: <50% CVD
Stroes, E, Guyton, JR, Farnier, M et al. (2015) Efficacy and safety of 150 mg and 300 mg every 3 weeks in patients with poorly controlled hypercholesterolemia: the ODYSSEY CHOICE I and CHOICE II studies. Journal of the American College of Cardiology abstract: exhibit991	- Population not relevant to this review protocol: >50% statin intolerant
Stroes, E, Guyton, JR, Lepor, N et al. (2016) Efficacy and Safety of Alirocumab 150 mg Every 4 Weeks in Patients With Hypercholesterolemia Not on Statin Therapy: the ODYSSEY CHOICE II Study. Journal of the American Heart Association 5(9)	- Population not relevant to this review protocol: >50% statin intolerant
Strony, John, Yang, Bo, Hanson, Mary E et al. (2008) Long-term safety and tolerability of ezetimibe coadministered with simvastatin in hypercholesterolemic patients: a randomized, 12-month double-blind extension study. Current medical research and opinion 24(11): 3149-57	- Study does not include an intervention relevant to this protocol: includes low intensity statin
Suzuki, H, Watanabe, Y, Kumagai, H et al. (2013) Comparative efficacy and adverse effects of the addition of ezetimibe to statin versus statin titration in chronic kidney disease patients. Therapeutic advances in cardiovascular disease 7(6): 306-315	- Population not relevant to this review protocol: <50% CVD Population: no previous CVD/ CVD presence in approximately 3% of the study population
Szarek, Michael, Steg, Ph Gabriel, DiCenso, Dina et al. (2019) Alirocumab Reduces Total Hospitalizations and Increases Days Alive and Out of Hospital in the ODYSSEY OUTCOMES Trial. Circulation. Cardiovascular quality and outcomes 12(11): e005858	- Secondary publication of an included study that does not provide any additional relevant information
Szarek, Michael, White, Harvey D, Schwartz, Gregory G et al. (2019) Alirocumab Reduces Total Nonfatal Cardiovascular and Fatal Events: The ODYSSEY OUTCOMES Trial. Journal of the American College of Cardiology 73(4): 387-396	- Secondary publication of an included study that does not provide any additional relevant information
Takase, Susumu, Matoba, Tetsuya, Nakashiro, Soichi et al. (2017) Ezetimibe in Combination With Statins Ameliorates Endothelial Dysfunction in Coronary Arteries After Stenting: The CuVIC Trial (Effect of Cholesterol Absorption Inhibitor Usage on Target Vessel Dysfunction After Coronary Stenting), a Multicenter Randomized Controlled Trial. Arteriosclerosis, thrombosis, and vascular biology 37(2): 350-358	- Comparator in study does not match that specified in this review protocol Incorrect comparison: statin dosing not matched in control and intervention groups. Exact statin use unclear and mostly moderate intensity, including Pitavastatin
Talasaz, Azita H, Ho, Ai-Chen Jane, Bhatty, Fawzia et al. (2021) Meta-analysis of clinical	- Systematic review does not fully match review PICO - used as a source of primary studies

Study	Exclusion reason
outcomes of PCSK9 modulators in patients with established ASCVD. Pharmacotherapy 41(12): 1009-1023	RoB per study not per outcome, limited selection of relevant studies due to restrictions on comparators and duration of follow up being stricter than protocol
Tan, Huilian, Liu, Ling, Zheng, Qinghou et al. (2021) Effects of Combined Lipid-Lowering Therapy on Low-Density Lipoprotein Cholesterol Variability and Cardiovascular Adverse Events in Patients with Acute Coronary Syndrome. Advances in therapy 38(6): 3389-3398	- Comparator in study does not match that specified in this review protocol: ezetimibe plus statin versus higher dose of statin
Teramoto, T, Kobayashi, M, Tasaki, H et al. (2016) Efficacy and Safety of Alirocumab in Japanese Patients With Heterozygous Familial Hypercholesterolemia or at High Cardiovascular Risk With Hypercholesterolemia Not Adequately Controlled With Statins?- ODYSSEY JAPAN Randomized Controlled Trial. Circulation journal 80(9): 1980-1987	- Population not relevant to this review protocol: <50% CVD
Teramoto, Tamio, Kiyosue, Arihiro, Ishigaki, Yasushi et al. (2019) Efficacy and safety of alirocumab 150mg every 4 weeks in hypercholesterolemic patients on non-statin lipid-lowering therapy or lowest strength dose of statin: ODYSSEY NIPPON. Journal of cardiology 73(3): 218-227	- Population not relevant to this review protocol: >20% familial hypercholesterolaemia Incorrect population: majority not on statin, >20% FH and <50% CVD
Teramoto, Tamio, Kondo, Akira, Kiyosue, Arihiro et al. (2017) Efficacy and safety of alirocumab in patients with hypercholesterolemia not adequately controlled with non-statin lipid-lowering therapy or the lowest strength of statin: ODYSSEY NIPPON study design and rationale. Lipids in health and disease 16(1): 121	- Population not relevant to this review protocol: >50% statin intolerant
Toth, Peter P, Bray, Sarah, Villa, Guillermo et al. (2022) Network Meta-Analysis of Randomized Trials Evaluating the Comparative Efficacy of Lipid-Lowering Therapies Added to Maximally Tolerated Statins for the Reduction of Low-Density Lipoprotein Cholesterol. Journal of the American Heart Association 11(18): e025551	- Systematic review with no data of additional relevance SR not entirely matching protocol in terms of populations and various comparisons; included studies checked for inclusion
Toth, Peter P, Worthy, Gillian, Gandra, Shravanthi R et al. (2017) Systematic Review and Network Meta-Analysis on the Efficacy of Evolocumab and Other Therapies for the Management of Lipid Levels in Hyperlipidemia. Journal of the American Heart Association 6(10)	- Systematic review does not fully match review PICO - used as a source of primary studies SR not entirely matching protocol in terms of populations and various comparisons; individual studies checked for inclusion
Tripoten, M.I., Pogorelova, O.A., Zubareva, M.Y. et al. (2010) Arterial wall function in patients with coronary heart disease and dyslipidemia, comparative efficacy of ezetimibe, statins and their combination. Artery Research 4(4): 157-158	- Conference abstract
Tsujita, K, Yamanaga, K, Komura, N et al. (2016) Lipid profile associated with coronary plaque regression in patients with acute coronary syndrome: subanalysis of PRECISE-IVUS trial. Atherosclerosis 251: 367-372	- Secondary publication of an included study that does not provide any additional relevant information no relevant outcomes

Study	Exclusion reason
Tsujita, Kenichi, Yamanaga, Kenshi, Komura, Naohiro et al. (2016) Synergistic effect of ezetimibe addition on coronary atheroma regression in patients with prior statin therapy: Subanalysis of PRECISE-IVUS trial. European journal of preventive cardiology 23(14): 1524-8	- Secondary publication of an included study that does not provide any additional relevant information
Turgeon, Ricky D, Tsuyuki, Ross T, Gyenes, Gabor T et al. (2018) Cardiovascular Efficacy and Safety of PCSK9 Inhibitors: Systematic Review and Meta-analysis Including the ODYSSEY OUTCOMES Trial. The Canadian journal of cardiology 34(12): 1600-1605	- Systematic review does not fully match review PICO - used as a source of primary studies Population does not directly meet protocol: not limited to people with previous CVD; individual references checked
Vallejo-Vaz, Antonio J, Ray, Kausik K, Ginsberg, Henry N et al. (2019) Associations between lower levels of low-density lipoprotein cholesterol and cardiovascular events in very high-risk patients: Pooled analysis of nine ODYSSEY trials of alirocumab versus control. Atherosclerosis 288: 85-93	- Secondary publication of an included study that does not provide any additional relevant information subgroup analysis of included study with no relevant additional data
Wang, Hong-Fei, Mao, Yu-Cheng, Xu, Xin-Yi et al. (2022) Effect of alirocumab and evolocumab on all-cause mortality and major cardiovascular events: A meta-analysis focusing on the number needed to treat. Frontiers in cardiovascular medicine 9: 1016802	- Systematic review with no GRADE assessment - used as a source of primary studies SR with ROB by study only, includes studies with and without CVD.
Wang, Nelson, Fulcher, Jordan, Abeysuriya, Nishan et al. (2020) Intensive LDL cholesterol-lowering treatment beyond current recommendations for the prevention of major vascular events: a systematic review and meta-analysis of randomised trials including 327 037 participants. The lancet. Diabetes & endocrinology 8(1): 36-49	- Systematic review does not fully match review PICO - used as a source of primary studies SR including comparisons not relevant to this protocol (majority of studies were statin vs placebo); used as source of primary studies
Wang, Nelson, Woodward, Mark, Huffman, Mark D et al. (2022) Compounding Benefits of Cholesterol-Lowering Therapy for the Reduction of Major Cardiovascular Events: Systematic Review and Meta-Analysis. Circulation. Cardiovascular quality and outcomes 15(6): e008552	- Systematic review does not fully match review PICO - used as a source of primary studies SR including comparisons not relevant to this protocol (majority of stuides were statin vs placebo); used as source of primary stydies
Wang, Shifei, Xiu, Jiancheng, Liao, Wangjun et al. (2019) Relative Effect of Current Intensive Lipid-Lowering Drugs on Cardiovascular Outcomes in Secondary Prevention - A Meta-Analysis of 12 Randomized Trials. Circulation journal : official journal of the Japanese Circulation Society 83(6): 1356-1367	- Systematic review does not fully match review PICO - used as a source of primary studies does not contain a comparison relevant to the protocol (pooled 'more' vs 'less' intensive lipid lowering strategies
Wang, Wanting; Feng, Zhaoqiang; Bai, Jinghui (2021) Effects of alirocumab on cardiovascular events and all-cause mortality: a systematic review and meta-analysis. Reviews in cardiovascular medicine 22(3): 873-881	- Systematic review with no data of additional relevance all relevant studies included in more directly relevant SR
Wang, Xing, Wen, Dingke, Chen, Yuqi et al. (2022) PCSK9 inhibitors for secondary prevention in patients with cardiovascular	- Systematic review with no data of additional relevance NMA not including all relevant comparators. Used as a source of primary studies

Study	Exclusion reason
diseases: a bayesian network meta-analysis. Cardiovascular diabetology 21(1): 107	
West, AMA (2010) Type of lipid lowering therapy impacts atherosclerosis progression in peripheral arterial disease as assessed by CMR. Journal of cardiovascular magnetic resonance: 192	- Conference abstract
Wiviott, Stephen D, Giugliano, Robert P, Morrow, David A et al. (2020) Effect of Evolocumab on Type and Size of Subsequent Myocardial Infarction: A Prespecified Analysis of the FOURIER Randomized Clinical Trial. JAMA cardiology 5(7): 787-793	- Secondary publication of an included study that does not provide any additional relevant information
Wright, R Scott, Ray, Kausik K, Raal, Frederick J et al. (2021) Pooled Patient-Level Analysis of Inclisiran Trials in Patients With Familial Hypercholesterolemia or Atherosclerosis. Journal of the American College of Cardiology 77(9): 1182-1193	- Secondary publication of an included study that does not provide any additional relevant information
Wu, Na-Qiong, Guo, Yuan-Lin, Zhu, Cheng-Gang et al. (2018) Comparison of statin plus ezetimibe with double-dose statin on lipid profiles and inflammation markers. Lipids in health and disease 17(1): 265	- Comparator in study does not match that specified in this review protocol: ezetimibe plus statin versus higher dose of statin
Xia, Jiachun, Wang, Xinyue, Zhou, Jun et al. (2022) Impact of early PCSK9 inhibitor treatment on heart after percutaneous coronary intervention in patients with STEMI: Design and rationale of the PERFECT II trial. Frontiers in cardiovascular medicine 9: 1009674	- Trial protocol for a study not yet completed/reported
Yamanaga, K, Tsujita, K, Sugiyama, S et al. (2015) The impact of statin-ezetimibe combination therapy in patients with decreased cholesterol absorption ability. Circulation 132(nopagination)	- Conference abstract
Zhan, S., Xia, P., Tang, M. et al. (2017) Ezetimibe for the prevention of cardiovascular disease and all-cause mortality events. Cochrane Database of Systematic Reviews 2017(1): cd012502	- More recent systematic review included that covers the same topic
Zhang, Yue, Suo, Yanrong, Yang, Lin et al. (2022) Effect of PCSK9 Inhibitor on Blood Lipid Levels in Patients with High and Very-High CVD Risk: A Systematic Review and Meta-Analysis. Cardiology research and practice 2022: 8729003	- Systematic review with no data of additional relevance systematic review includes populations not relevant to the protocol (FH). Used as a source of primary studies
Zhao, Zinan, Hu, Xin, Zhang, Yatong et al. (2020) Cardiovascular and safety events of PCSK9 inhibitors in statin-treated patients with cardiovascular risk: A Systematic Review and Meta-Analysis. Journal of pharmacy & pharmaceutical sciences : a publication of the Canadian Society for Pharmaceutical Sciences, Societe canadienne des sciences pharmaceutiques 23: 422-436	- Systematic review with no data of additional relevance overlaps with included SR (Cochrane review), and includes no additional studies or outcomes of relevance. Includes fewer studies and outcomes.

Study	Exclusion reason
Zhao, Zonglei, Du, Song, Shen, Shuxin et al. (2019) Comparative efficacy and safety of lipid-lowering agents in patients with hypercholesterolemia: A frequentist network meta-analysis. Medicine 98(6): e14400	- Systematic review with no data of additional relevance overlaps with included SR (Cochrane review), and includes no additional studies or outcomes of relevance. Includes fewer studies and outcomes.
Zieve, Franklin, Wenger, Nanette K, Ben-Yehuda, Ori et al. (2010) Safety and efficacy of ezetimibe added to atorvastatin versus up titration of atorvastatin to 40 mg in Patients > or = 65 years of age (from the ZETia in the ELDerly [ZETELD] study). The American journal of cardiology 105(5): 656-63	- Comparator in study does not match that specified in this review protocol: ezetimibe plus statin versus double dose of statin
Zinellu, A, Sotgia, S, Loriga, G et al. (2012) Oxidative stress improvement is associated with increased levels of taurine in CKD patients undergoing lipid-lowering therapy. Amino acids 43(4): 1499-1507	- Population not relevant to this review protocol: <50% CVD Patients with CKD, but no evidence of CVD
Zinellu, A, Sotgia, S, Mangoni, AA et al. (2015) Impact of cholesterol lowering treatment on plasma kynurenine and tryptophan concentrations in chronic kidney disease: relationship with oxidative stress improvement. Nutrition, metabolism, and cardiovascular diseases : NMCD 25(2): 153-159	- Population not relevant to this review protocol: <50% CVD Patients with CKD, but no evidence of CVD
Zinellu, A, Sotgia, S, Mangoni, AA et al. (2016) Effect of cholesterol lowering treatment on plasma markers of endothelial dysfunction in chronic kidney disease. Journal of pharmaceutical and biomedical analysis 129: 383-388	- Population not relevant to this review protocol: <50% CVD Patients with CKD, but no evidence of CVD
Zinellu, A, Sotgia, S, Pisanu, E et al. (2012) LDL S-homocysteinylation decrease in chronic kidney disease patients undergone lipid lowering therapy. European journal of pharmaceutical sciences 47(1): 117-123	- Population not relevant to this review protocol: <50% CVD Patients with CKD, but no evidence of CVD
Nutrition, metabolism, and cardiovascular diseases: NMCD 27(9): 822-829	- Population not relevant to this review protocol: <50% CVD Patients with CKD, but no evidence of CVD
Zou, YC, Lu, Y, Bai, J et al. (2016) Effect of ezetimibe combined with low-dose atorvastain calcium on carotid atherosclerosis in elderly patients with coronary heart disease. Journal of the american geriatrics society. Conference: 5th chinese congress on gerontology and health industry, CCGI 2016. China. Conference start: 20160902. Conference end: 20160904 64: 328	- Study does not include an intervention relevant to this protocol: includes low intensity statin Paper not available; no relevant treatment: low dose statins

K.2 Health Economic studies

Not applicable.

Appendix L Expert witness testimony

Andrew Black – GP, Vice Chair of the NICE Indicator Advisory Committee.

- The below information was provided to the cardiovascular disease prevention guideline committee at the meeting on 30 March 2023. It reflects AB's opinions and not necessarily those of the NICE Indicator Advisory Committee.

The NICE Indicator Advisory Committee (IAC) operationalise guidelines and quality standards (QS) for the NHS and wider audience. Providing indicators for cholesterol levels has been a challenge over the years. In mid-2022 NICE received a referral from NHS England to develop indicators that were suitable for the Quality and Outcomes Framework (QOF) ideally for the following QOF year (2023/24).

Indicators usually take 12-18 months to develop but the IAC was asked to develop an indicator around cholesterol targets in October 2022 for possible QOF adoption in April 2023. The particular issue was that in NICE guideline CG181 the recommendations state that a greater than 40% reduction in non-HDL cholesterol should be aimed for at 3 months for both primary and secondary prevention. However, the NICE IAC have consistently heard that this cannot be measured and extracted from electronic GP IT systems using the national General Practice Extraction Service (GPES). NHS digital cannot extract the 2 readings and calculate a percentage from that.

The IAC were asked to produce something for the 2023/24 QOF cycle. A sub-committee of the IAC was formed to develop an indicator as a holding measure, with a pragmatic threshold, pending the guidance from NICE's clinical guideline committee. This was challenging for a number of reasons; determining an acceptable evidence-based target that would upset the least amount people, but also because there is evidence from the CVDPREVENT audit showing that recording of non-HDL cholesterol is poor. In March 2022 (using data from the previous 12 months), these data were missing in 52% of GP records, there was also a range where people were above 2.9mmol/litre and potentially 80% of practice population outside of this level (data are from academic in confidence analysis undertaken from CVDPREVENT audit for the IAC). The IAC discussed the different guidelines on the topic including the European Society Cardiology, Joint British Societies JBS 3 and British Heart Foundation recommendations, but all have slightly different targets levels.

There was discussion amongst the GPs on the IAC and cardiologists as to what they should do, taking these guidelines and relevant technology appraisals into account, as to where to put a holding threshold. The sub-committee decided on a non-HDL cholesterol level of 3.3mmol/l. Reasons for this included a feeling that a 40% reduction, based on baseline non-HDL cholesterol, would be getting towards a level of 3.3mmol/l. Furthermore, a NICE technology appraisal had used an LDL cholesterol level of 2.6mmol/litre which the sub-committee heard could be very broadly be translated into a non-HDL cholesterol of around 3.3mmol/litre for the initiation of a drug which was thought not to be primary care led, so it would be difficult to put levels below this in a QOF, where the level should be achievable by primary care alone. Another major factor was that the committee do not just take the QS or guideline and transfer recommendations directly into indicators. They take into consideration acceptability to the profession more generally and, to an extent, workload implications.

Once an indicator is agreed it goes to the NICE guidance executive to ratify and then goes to the NICE menu. NHS England and the BMA's General Practitioners Committee (GPC) then decide if it should be included in QOF or not.

A number of indicators in the menu are not a straight carry across from the clinical guidelines. Indicators may start further away with a measured plan to bring them closer to the clinical / quality standard within 2 years, recognising the implications.

The level of 3.3 mmol/litre was put out for consultation as a proposed indicator. Response was negative on both sides. They received quite a lot of complaints saying it was too onerous, not practical and not feasible. However, there was also a strong pushback from the other side saying 3.3 mmol/litre was not hard enough and argued for a much lower level. As a result the proposed level was universally unpopular on both sides of the argument and it was difficult for the committee to justify a level without a guideline behind it. It was therefore decided to wait for the guideline committee to consider this issue. It is hoped the indicator will be in the system for next year after the guideline has published.

It was noted that NHS England has decided to create its own indicator for the 2023/24 QOF outside of the NICE process with a non-HDL cholesterol level of 2.5mmol/l. From the IAC discussions there was a steer from cardiologists that 2.5mmol/litre was becoming the more recognised standard, based on the accelerated access collaborative guidance, but the IAC did not proceed with this value as the proposed NICE indicator because of the lack of assurance that the methodology or health economics behind were as robust as would be expected for a NICE standard.

The indicator is: Percentage of patients on the QOF Coronary Heart Disease, Peripheral Arterial Disease, or Stroke/TIA Register, who have a recording of non-HDL cholesterol in the preceding 12 months that is lower than 2.5mmol/l, or where non-HDL cholesterol is not recorded a recording of LDL cholesterol in the preceding 12 months that is lower than 1.8mmol/l.

This has a points ratio of 16, with a threshold of 20-35% of patients.

The IAC will still create an indicator based on the NICE guideline for the NICE menu. There can be more acceptance of a NICE badged indicator because it is evidence based and will have gone through some degree of piloting and consultation. The GPC and other interested parties tend to trust indicators produced by NICE for QOF as being of higher standard than those that come through other routes.