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PCSK9 monoclonal antibodies for the primary and secondary prevention of cardiovascular disease (Review)

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[Intervention Review]

PCSK9 monoclonal antibodies for the primary and secondary prevention of cardiovascular disease

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ABSTRACT

Background

Despite the availability of effective drug therapies that reduce low-density lipoprotein (LDL)-cholesterol (LDL-C), cardiovascular disease (CVD) remains an important cause of mortality and morbidity. Therefore, additional LDL-C reduction may be warranted, especially for people who are unresponsive to, or unable to take, existing LDL-C-reducing therapies. By inhibiting the proprotein convertase subtilisin/kexin type 9 (PCSK9) enzyme, monoclonal antibodies (PCSK9 inhibitors) reduce LDL-C and CVD risk.

Objectives

Primary

To quantify the effects of PCSK9 inhibitors on CVD, all-cause mortality, myocardial infarction, and stroke, compared to placebo or active treatment(s) for primary and secondary prevention.

Secondary

To quantify the safety of PCSK9 inhibitors, with specific focus on the incidence of influenza, hypertension, type 2 diabetes, and cancer, compared to placebo or active treatment(s) for primary and secondary prevention.

Search methods

We identified studies by systematically searching CENTRAL, MEDLINE, Embase, and Web of Science in December 2019. We also searched ClinicalTrials.gov and the International Clinical Trials Registry Platform in August 2020 and screened the reference lists of included studies. This is an update of the review first published in 2017.

Selection criteria

All parallel-group and factorial randomised controlled trials (RCTs) with a follow-up of at least 24 weeks and adult participants with or without a history of CVD were eligible if they compared PCSK9 inhibitors alirocumab or evolocumab to placebo or active treatments such as statins, ezetimibe, or a combination of these.

Data collection and analysis

Two review authors independently reviewed and extracted data. Where data were available, we calculated pooled effect estimates. We used GRADE to assess certainty of evidence and in 'Summary of findings' tables.

Main results

We included 24 studies with data on 60,997 participants. Eighteen trials randomised participants to alirocumab and six to evolocumab. All participants received background lipid-lowering treatment or lifestyle counselling. Six alirocumab studies used an active treatment comparison group (the remaining used placebo), compared to three evolocumab active comparison trials. Follow-up ranged from 6 to 36 months for the comparisons with placebo and from 6 to 12 months for comparisons with active treatment. Most of the available studies preferentially enrolled people with either established CVD or at a high risk already, and evidence in low- to medium-risk settings is minimal.

Alirocumab compared with placebo decreased the risk of CVD events, with an absolute risk difference (RD) of –2% (odds ratio (OR) 0.87, 95% confidence interval (CI) 0.80 to 0.94; 10 studies, 23,868 participants; high-certainty evidence), decreased the risk of mortality (RD –1%; OR 0.83, 95% CI 0.72 to 0.96; 12 studies, 24,797 participants; high-certainty evidence), and MI (RD –2%; OR 0.86, 95% CI 0.79 to 0.94; 9 studies, 23,352 participants; high-certainty evidence) and for any stroke (RD 0%; OR 0.73, 95% CI 0.58 to 0.91; 8 studies, 22,835 participants; high-certainty evidence).

Alirocumab compared with ezetimibe and statins: for CVD, the RD was 1% (OR 1.37, 95% CI 0.65 to 2.87; 3 studies, 1379 participants; low-certainty evidence); for mortality, RD was –1% (OR 0.51, 95% CI 0.18 to 1.40; 5 studies, 1333 participants; low-certainty evidence); for MI, RD was 1% (OR 1.45, 95% CI 0.64 to 3.28, 5 studies, 1734 participants; low-certainty evidence); and for any stroke, RD was less than 1% (OR 0.85, 95% CI 0.13 to 5.61; 5 studies, 1734 participants; low-certainty evidence).

Evolocumab compared with placebo: for CVD, the RD was –2% (OR 0.84, 95% CI 0.78 to 0.91; 3 studies, 29,432 participants; high-certainty evidence); for mortality, RD was less than 1% (OR 1.04, 95% CI 0.91 to 1.19; 3 studies, 29,432 participants; high-certainty evidence); for MI, RD was –1% (OR 0.72, 95% CI 0.64 to 0.82; 3 studies, 29,432 participants; high-certainty evidence); and for any stroke RD was less than –1% (OR 0.79, 95% CI 0.65 to 0.94; 2 studies, 28,531 participants; high-certainty evidence).

Evolocumab compared with ezetimibe and statins: for any CVD event RD was less than –1% (OR 0.66, 95% CI 0.14 to 3.04; 1 study, 218 participants; very low-certainty evidence); for all-cause mortality, the RD was less than 1% (OR 0.43, 95% CI 0.14 to 1.30; 3 studies, 5223 participants; very low-certainty evidence); and for MI, RD was less than 1% (OR 0.66, 95% CI 0.23 to 1.85; 3 studies, 5003 participants; very low-certainty evidence). There were insufficient data on any stroke.

Authors' conclusions

The evidence for the clinical endpoint effects of evolocumab and alirocumab versus placebo were graded as high. There is a strong evidence base for the benefits of PCSK9 monoclonal antibodies to people who might not be eligible for other lipid-lowering drugs, or to people who cannot meet their lipid goals on more traditional therapies, which was the main patient population of the available trials.

The evidence base of PCSK9 inhibitors compared with ezetimibe and statins is much weaker (low very- to low-certainty evidence) and it is unclear whether evolocumab or alirocumab might be effectively used as *replacement* therapies.

Finally, there is very limited evidence on any potential safety issues of both evolocumab and alirocumab. While the current evidence synthesis does not reveal any adverse signals, neither does it provide evidence against such signals. This suggests careful consideration of alternative lipid lowering treatments before prescribing PCSK9 inhibitors.

PLAIN LANGUAGE SUMMARY

PCSK9 inhibitors for prevention of cardiovascular disease

Research question

What is the effectiveness and safety of PCSK9 inhibitors for cardiovascular disease (CVD) prevention?

Background

Despite the availability of effective medicines (such as statins (which works by blocking a substance your body needs to make cholesterol) or ezetimibe (which stops your body taking in cholesterol from food), or both) that reduce low-density lipoprotein (LDL) cholesterol (LDL-C) (sometimes called 'bad' cholesterol), CVD remains an important cause of death and illness. Additional LDL-C reduction may be needed, especially for people who are unresponsive to, or are unable to use, existing LDL-C-reducing therapies. Medicines called PCSK9 inhibitors are another way of lowering LDL-C and CVD risk.

Study characteristics

Review authors identified 23 studies that evaluated the effects of the PCSK9 inhibitors, alirocumab and evolocumab, in people at high risk of CVD. Studies were conducted in outpatient clinics. Review authors identified the studies included in this review through electronic literature searches conducted up to December 2019. This is an update of the review first published in 2017.

Key results

Both alirocumab and evolocumab decreased the risk of CVD when *added* to other LDL-C-lowering medicines (e.g. statins or ezetimibe). Alirocumab additionally showed a decrease in death from any cause; with insufficient evidence for evolocumab. Limited data, often of lower quality, was available comparing these PCSK9 inhibitors *against* other LDL-C-lowering drugs. Differences in risk between people treated with and without PCSK9 inhibitors suggest the absolute treatment benefit will likely be modest (e.g. less than 1% change in risk).

Quality of evidence

We found high-quality evidence when *adding* PCSK9 inhibitors to existing LDL-C-lowering treatments and low- to very low-quality evidence when *replacing* existing LDL-C-reducing medicines with PCSK9 inhibitors.

SUMMARY OF FINDINGS

Summary of findings 1. Alirocumab compared with placebo

Alirocumab compared with placebo

Patient or population: people at high risk of CVD (history of CVD or high LDL-C despite treatment)
Setting: outpatient care settings
Intervention: alirocumab PCSK9 monoclonal antibodies
Comparison: placebo

Outcomes	Illustrative comparative risk (95% CI)		Relative effect (95% CI)	RD (95% CI)	Number of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk using PCSK9 inhibition					
CVD Follow-up: 6–36 months	CVD risk was 229 per 1000 participants	CVD risk in the intervention group was 214 (205 to 222) per 1000 participants	**OR 0.87** (0.80 to 0.94)	**–0.02** (–0.02 to –0.01)	23,868 (10 RCTs)	⊕⊕⊕⊕ **High**	< 1 is beneficial
All-cause mortality Follow-up: 6–36 months	All-cause mortality risk was 59 per 1000 participants	All-cause mortality risk in the intervention group was 53 (49 to 58) per 1000 participants	**OR 0.83** (0.72 to 0.96)	**–0.01** (–0.01 to 0.00)	24,797 (12 RCTs)	⊕⊕⊕⊕ **High**	< 1 is beneficial
Myocardial infarction Follow-up: 6–36 months	Myocardial infarction risk was 143 per 1000 participants	Myocardial infarction risk in the intervention group was 128 (120 to 136) per 1000 participants	**OR 0.86** (0.79 to 0.94)	**–0.02** (–0.02 to –0.01)	23,352 (9 RCTs)	⊕⊕⊕⊕ **High**	< 1 is beneficial
Any stroke Follow-up: 6–36 months	Stroke risk was 27 per 1000 participants	Stroke risk in the intervention group was 23 (20 to 26) per 1000 participants	**OR 0.73** (0.58 to 0.91)	**–0.00** (–0.01 to 0.00)	22,835 (8 RCTs)	⊕⊕⊕⊕ **High**	< 1 is beneficial

CI: confidence interval; **CVD:** cardiovascular disease; **LDL-C:** low-density lipoprotein cholesterol; **OR:** odds ratio; **RCT:** randomised controlled trial; **RD:** risk difference.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to the estimate of effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of effect but may be substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Summary of findings 2. Evolocumab compared with placebo

Evolocumab compared with placebo

Patient or population: people at high risk of CVD (history of CVD or high LDL-C despite treatment)
Setting: outpatient care settings
Intervention: evolocumab PCSK9 monoclonal antibodies
Comparison: placebo

Outcomes	Illustrative comparative risk (95% CI)		Relative effect (95% CI)	RD (95% CI)	Number of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk using PCSK9 inhibition					
CVD Follow-up: 6–36 months	CVD risk was 229 per 1000 participants	CVD risk in the intervention group was 213 (206 lower to 220 lower) per 1000 participants	**OR 0.84** (0.78 to 0.91)	**–0.02** (–0.02 to –0.01)	29,432 (3 RCTs)	⊕⊕⊕⊕ **High**	< 1 is beneficial
All-cause mortality Follow-up: 6–36 months	All-cause mortality risk was 59 per 1000 participants	All-cause mortality risk in the intervention group was 60 higher (56 lower to 64 higher) per 1000 participants	**OR 1.04** (0.91 to 1.19)	**0.00** (–0.00 to 0.01)	29,432 (3 RCTs)	⊕⊕⊕⊕ **High**	< 1 is beneficial
Myocardial infarction Follow-up: 6–36 months	Myocardial infarction risk was 143 per 1000 participants	Myocardial infarction risk in the intervention group was 131(127 to 135) per 1000 participants	**OR 0.72** (0.64 to 0.82)	**–0.01** (–0.02 to –0.01)	29,432 (3 RCTs)	⊕⊕⊕⊕ **High**	< 1 is beneficial
Any stroke Follow-up: 6–36 months	Stroke risk was 27 per 1000 participants	Stroke risk in the intervention group was 23 (20 to 26) per 1000 participants	**OR 0.79** (0.65 to 0.94)	**–0.00** (–0.01 to –0.00)	28,531 (2 RCTs)	⊕⊕⊕⊕ **High**	< 1 is beneficial

CI: confidence interval; **CVD:** cardiovascular disease; **LDL-C:** low-density lipoprotein cholesterol; **OR:** odds ratio; **RCT:** randomised controlled trial; **RD:** risk difference.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to the estimate of effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of effect but may be substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Summary of findings 3. Alirocumab compared with ezetimibe and statins

Alirocumab compared with ezetimibe and statins

Patient or population: people at high risk of CVD (history of CVD or high LDL-C despite treatment)
Setting: outpatient care settings
Intervention: alirocumab PCSK9 monoclonal antibodies
Comparison: ezetimibe and statins

Outcomes	Illustrative comparative risk (95% CI)		Relative effect (95% CI)	RD (95% CI)	Number of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk with PCSK9 inhibition					
CVD Follow-up: 6–12 months	CVD risk was 28 per 1000 participants	CVD risk in the intervention group was 37 (20 to 50 higher) per 1000 participants	**OR 1.37** (0.65 to 2.87)	**0.01** (–0.01 to 0.03)	1379 (3 RCTs)	⊕⊕⊖⊖ **Low** [a]	< 1 is beneficial
All-cause mortality Follow-up: 6–12 months	All-cause mortality risk was 9 per 1000 participants	All-cause mortality risk in the intervention group was 3 (0 to 12) per 1000 participants	**OR 0.51** (0.18 to 1.40)	**–0.01** (–0.02 to 0.00)	1733 (5 RCTs)	⊕⊕⊖⊖ **Low** [a]	< 1 is beneficial
Myocardial infarction Follow-up: 6–12 months	Myocardial infarction risk was 28 per 1000 participants	Myocardial infarction risk in the intervention group was 35 (22 to 48) per 1000 participants	**OR 1.45** (0.64 to 3.28)	**0.01** (–0.01 to 0.02)	1734 (5 RCTs)	⊕⊕⊖⊖ **Low** [a]	< 1 is beneficial
Any stroke Follow-up: 6–12 months	Stroke risk was 27 per 1000 participants	Stroke risk in the intervention group was 23 (20 to 26) per 1000 participants	**OR 0.85** (0.13 to 5.61)	**0.00** (–0.01 to 0.01)	1734 (5 RCTs)	⊕⊕⊖⊖ **Low** [a]	< 1 is beneficial

CI: confidence interval; **CVD:** cardiovascular disease; **LDL-C:** low-density lipoprotein cholesterol; **OR:** odds ratio; **RCT:** randomised controlled trial; **RD:** risk difference.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to the estimate of effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of effect but may be substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Low event rates and confidence intervals crossed null effect included both appreciable harm and benefit. Downgraded two levels for imprecision.

Summary of findings 4. Evolocumab compared with ezetimibe and statins

Evolocumab compared with ezetimibe and statins

Patient or population: people at high risk of CVD (history of CVD or high LDL-C despite treatment)
Setting: outpatient care settings
Intervention: evolocumab PCSK9 monoclonal antibodies
Comparison: ezetimibe and statins

Outcomes	Illustrative comparative risk (95% CI)		Relative effect (95% CI)	RD (95% CI)	Number of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk with PCSK9 inhibition					
CVD Follow-up: 6–12 months	CVD risk was 28 per 1000 participants	CVD risk in the intervention group was 26 (22 to 29) per 1000 participants	**OR 0.66** (0.14 to 3.04)	**–0.01** (–0.07 to 0.04)	218 (1 RCTs)	⊕⊖⊖⊖ **Very low** [a,b]	< 1 is beneficial
All-cause mortality Follow-up: 6–12 months	All-cause mortality risk was 9 per 1000 participants	All-cause mortality risk in the intervention group was 7 (4 to 10) per 1000 participants	**OR 0.43** (0.14 to 1.30)	**–0.00** (–0.01 to 0.01)	5223 (3 RCTs)	⊕⊖⊖⊖ **Very low** [a,b]	< 1 is beneficial
Myocardial infarction Follow-up: 6–12 months	Myocardial infarction risk was 28 per 1000 participants	Myocardial infarction risk in the intervention group was 26 (22 to 29) per 1000 participants	**OR 0.66** (0.23 to 1.85)	**–0.00** (–0.00 to 0.00)	5003 (3 RCTs)	⊕⊖⊖⊖ **Very low** [a,b]	< 1 is beneficial
Any stroke Follow-up: 6–12 months	Stroke risk was 27 per 1000 participants	—	Insufficient data	Insufficient data	3899 (2 RCTs)	Insufficient data	< 1 is beneficial

CI: confidence interval; **CVD:** cardiovascular disease; **LDL-C:** low-density lipoprotein cholesterol; **OR:** odds ratio; **RCT:** randomised controlled trial; **RD:** risk difference.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to the estimate of effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of effect but may be substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Data were based on OSLER-1 and OSLER-2 (or both), which were open-label studies. Downgraded one level because of limitations in the design and implementation of available studies suggesting high likelihood of bias.
[b]Low event rates and confidence intervals crossed null effect included both appreciable harm and benefit. Downgraded two levels for imprecision.

BACKGROUND

Description of the condition

Cardiovascular disease event (CVD; coronary heart disease (CHD) and stroke) affects 85 million subjects across Europe (Willer 2013). Patients receive long-term medications for primary and secondary prevention (at a combined direct and indirect cost of €210 billion each year; Willer 2013) . This burden is especially high in people with familial hypercholesterolaemia (FH) who have a loss of function mutation, which affects 1 in 250 individuals of European descent (Benn 2012; Knowles 2014; Nordestgaard 2013). These mutations prevent removal of circulating low-density lipoprotein cholesterol (LDL-C), which is one of the most important modifiable risk factors for CVD (Grundy 2004), both in people with FH and in the general population. Autosomal-dominant FH is caused by heterozygous mutations in the low-density lipoprotein receptor (LDLR) (Sudhof 1985), apolipoprotein B (APOB) – the major constituent apoprotein of LDL-C (Garcia 2001; Innerarity 1987; Nordestgaard 2013), or the gene for proprotein convertase subtilisin/kexin type 9 (Abifadel 2003). A rare autosomal-recessive form of FH is caused by mutations in the gene for the low-density lipoprotein receptor adaptor protein 1 (LDRRAP1). People with FH have higher risk of premature coronary heart disease (CHD) that can be reduced with statin treatment. Polygenic elevation in LDL-C concentration, which is associated with higher risk of CHD, is caused by additive effects of common, largely independently inherited polymorphisms located in more than 50 loci throughout the genome (Willer 2013).

Description of the intervention

Interventions of confirmed efficacy in reducing cardiovascular events through lowering of LDL-C include statin drugs targeting 3-hydroxy-3-methyl-glutaryl-CoA (HMG-CoA) reductase and ezetimibe targeting the Niemann-Pick C1-like 1 intestinal cholesterol transporter protein (Cannon 2015; CTT 2005a; CTT 2005b; CTT 2012). Cardiovascular risk is reduced but not abolished among people receiving these medications, suggesting that additional LDL-C reduction via alternative pathways may result in further reduction in CVD events, especially among people who have an inadequate response to, or are intolerant of, statins or ezetimibe (Mancini 2011; Marks 2003).

A new pharmacological target for further reduction of LDL-C is the proprotein convertase subtilisin/kexin type 9 (PCSK9) enzyme. Two monoclonal antibodies (mAbs) against the PCSK9 enzyme (PCSK9 inhibitors), alirocumab and evolocumab, have been approved for high-risk people; both are administered subcutaneously.

How the intervention might work

PCSK9 is synthesised and secreted by hepatocytes and binds to the LDLR on the hepatocyte surface, promoting internalisation and degradation. Reduction in surface LDLR reduces uptake of LDL particles and increases LDL-C concentration in the blood (Cohen 2005; Cohen 2006). Therefore, inhibitors of PCSK9 are expected to lower LDL-C. Moreover, inhibition of PCSK9 may further enhance the lipid-lowering effects of statins, which are thought to be limited by a statin-induced increase in PCSK9 expression (Catapano 2013).

PCSK9 inhibitors bind to the PCSK9 enzyme with high affinity, disrupting its ability to bind with LDLR. By preventing PCSK9 from binding to LDLR, inhibitors against PCSK9 maintain surface LDLR expression with the aim of reducing LDL-C serum concentration. This is supported by the finding that variations in the *PCSK9* gene are associated with long-term elevations in LDL-C and higher risk of CHD (Benn 2010; Chasman 2012). Alternatively, loss of function mutations in *PCSK9* that lower LDL-C levels have also been associated with decreased CHD risk (Cohen 2006). Taken together, these gain- and loss-of-function PCSK9 genetic studies strongly validated PCSK9 as an efficacious target for prevention of CVD.

Why it is important to do this review

Statins are widely prescribed to reduce LDL-C levels and CVD risk in people at increased risk. People taking statins reduce their risk of CVD by around 20% to 25% for every 1 mmol/L decrease in LDL-C (CTT 2005a; CTT 2012), which may be further reduced by taking ezetimibe (Cannon 2015). Given the strong and positive associations, without clear threshold, between LDL-C and CVD as described in prospective studies (CTT 2005a; CTT 2012), it is expected that further reduction in LDL-C may lead to further prevention of CVD events. This could be especially important for people unable to tolerate statins, people with very high levels of LDL-C, and people at high cardiovascular risk. Large sample size phase 3 randomised controlled trials (RCTs) have shown that alirocumab and evolocumab both reduce CVD risk when prescribed in addition to statins (FOURIER; ODYSSEY OUTCOMES); however, information on the medium-term to long-term safety and efficacy of these drugs has not yet been reviewed. Furthermore, PCSK9 mAb effectiveness and safety compared to therapies such as statins or ezetimibe are unclear.

Statin prescriptions seem to increase the risk of the following unintended (safety) endpoints: type 2 diabetes mellitus (T2DM), weight gain (Sattar 2010; Swerdlow 2014), and rarely liver inflammation, and myositis (Collins 2016). It is uncertain if reducing LDL-C via a different mechanism might be associated with the same or a different set of adverse events. Furthermore, with recent Food and Drug Administration (FDA) and European Medicines Agency (EMA) approvals of alirocumab (Praluent) and evolocumab (Repatha), these drugs have become available to (selected) patients, and (remaining) questions on long-term efficacy and safety have become increasingly important to answer. Specifically, the EMA has approved Praluent and Repatha for people with primary hypercholesterolaemia, and the FDA has approved both drugs for people with heterozygous FH or a history of clinical atherosclerotic CVD. These recommendations have found their way into the 2016 European Society of Cardiology (ESC)/European Atherosclerosis Society (EAS) Guidelines for the Management of Dyslipidaemias, which recommend consideration of a PCSK9 inhibitor for pharmacological treatment of hypercholesterolaemia "in patients at very high-risk, with persistent high LDL-C despite treatment with maximal tolerated statin dose, in combination with ezetimibe or in patients with statin intolerance". The same guidelines recommend that "treatment with a PCSK9 antibody should be considered in FH patients with CVD or at very high-risk for CHD" (Catapano 2016). Pfizer discontinued the development of bococizumab, citing lack of long-term efficacy due to increased immunogenicity over time (Pfizer 2017). A number of large sample size PCSK9 mAb trials have been published since the previous version of the review, as such we sought to update the original results.

OBJECTIVES

Primary

To quantify the effects of PCSK9 inhibitors on CVD, all-cause mortality myocardial infarction, and stroke, compared to placebo or active treatment(s) for primary and secondary prevention.

Secondary

To quantify the safety of PCSK9 inhibitors, with specific focus on the incidence of influenza, hypertension, type 2 diabetes, and cancer, compared to placebo or active treatment(s) for primary and secondary prevention.

METHODS

Criteria for considering studies for this review

Types of studies

We included parallel-group and factorial RCTs with follow-up of at least 24 weeks. Cluster RCTs, cross-over trials, and non-randomised studies were ineligible for this review, and we excluded them during title and abstract screening; we noted a single cross-over trial that we have excluded for this reason (Nissen 2016). RCTs were eligible if they were reported as full-text articles or were published as abstracts, or if they were available only as unpublished data.

Types of participants

RCTs were eligible if they included adults 18 years of age or older, with or without a history of CVD. Participants could have had normal lipid levels or hypercholesterolaemia. We applied no restriction on comorbidities.

Types of interventions

We included trials if they randomised participants to the PCSK9 inhibitors alirocumab or evolocumab, and to placebo, or active treatments such as statins, ezetimibe, or a combination of these.

Types of outcome measures

This updated review no longer explored the effects of PCSK9 mAb with (lipid) biomarkers, large sample size trials have shown a persistent decreasing effect on these intermediate outcomes, to an extent that there is little uncertainty left on these effects (FOURIER; ODYSSEY Long Term; ODYSSEY OUTCOMES).

Reporting one or more of the outcomes listed here in the trial was not an inclusion criterion for the review. Where a published report did not report one of these outcomes, we accessed the trial protocol and contacted the trial authors to ascertain whether the outcomes were measured but not reported. Relevant trials which measured these outcomes but did not report the data at all, or not in a usable format, were included in the review as part of the narrative.

Primary outcomes

- Composite endpoint of CVD, defined as urgent coronary revascularisation, unstable angina pectoris, non-fatal and fatal myocardial infarction (MI), non-fatal and fatal stroke, and CHD death.
- All-cause mortality.
- MI.
- Stroke.

Secondary outcomes

- Adverse events, specifically:
  - influenza;
  - T2DM;
  - cancer;
  - hypertension.

Search methods for identification of studies

Electronic searches

We identified trials through systematic searches of the following databases (Lefebvre 2011):

- Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library (2019, Issue 11);
- MEDLINE and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily (Ovid, 1946 to 5 December 2019);
- Embase (Ovid, 1980 to 2 December 2019);
- Web of Science Core Collection (Clarivate Analytics, 1900 to 2 December 2019).

See Appendix 1 for the search strategies used. We applied the sensitivity-maximising version of the Cochrane RCT filter to MEDLINE and adaptations of it to Embase and Web of Science (Lefebvre 2011). We limited searches to records from 2005, as PCSK9 was discovered as a potential target in 2003 (Farnier 2014; Seidah 2003), hence we excluded papers published before 2005. We imposed no language restrictions.

Additionally, we searched ClinicalTrials.gov (www.ClinicalTrials.gov) and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) Search Portal (apps.who.int/trialsearch/) for relevant RCTs on 20 August 2020.

Searching other resources

We searched the following websites for unpublished studies on 20 August 2020:

- FDA (www.fda.gov/)
- Pharmaceutical company websites (Regeneron – www.regeneron.com/; Sanofi – en.sanofi.com/)
- ProQuest dissertations and theses (PQDT; www.proquest.com/products-services/pqdt.html).

Additionally, we screened reference lists of included studies for relevant RCTs.

Data collection and analysis

Selection of studies

Two review authors (AFS and JPLC) independently screened search results by title and abstract, and subsequently the full text, for potentially relevant studies. A third review author (JPC) resolved disagreements. We distilled multiple reports on a single RCT into a single entry. We provided a PRISMA flow diagram, and details of studies excluded after full-text assessment (see Characteristics of excluded studies table).

Data extraction and management

Two review authors (AFS and JPLC) independently extracted data and resolved differences by returning to the original publication and, if needed, by consulting a third review author (JPC). When appropriate, we extracted data on numbers of events versus no events, means, standard deviations, crude point estimates, or standard error estimates. When reported, we extracted results from an intention-to-treat (ITT) analysis. When available, we used the study protocol, appendices, and design papers as additional sources of information.

Assessment of risk of bias in included studies

We assessed risk of bias using the Cochrane 'Risk of bias' tool based on the following items (Higgins 2011).

- Random sequence generation (selection bias).
- Allocation (selection bias).
- Blinding of participants and personnel (performance bias).
- Blinding of outcome assessment (detection bias).
- Incomplete outcome data (attrition bias).
- Selective reporting (reporting bias).
- Other potential sources of bias.

We graded individual items as having 'low', 'unclear', or 'high' risk of bias.

Assessment of bias in conducting the systematic review

We conducted this Cochrane Review according to the published protocol (Schmidt 2015), and reported deviations from it in the Differences between protocol and review section.

Measures of treatment effect

We reported treatment effects as odds ratios (ORs) and risk differences (RDs) (Newcombe 2014), 95% with confidence intervals (CIs) calculated using the Wald method. Estimates are presented for the effect of alirocumab and evolocumab compared to placebo or active treatment (including statins and ezetimibe or other pharmacological interventions that lower LDL-C), resulting in four effect estimates for any one outcome.

Unit of analysis issues

The unit of analysis was the participant. This Cochrane Review focused exclusively on parallel-group designed RCTs, hence we had no unit of analysis issues.

Dealing with missing data

We contacted trial authors to request missing data.

Assessment of heterogeneity

We measured between-study heterogeneity by using the I^2 statistic with a one-sided CI (with a z value of –1.96) and tested it using a Q test.

Assessment of reporting biases

We explored reporting bias using funnel plots for outcomes with 10 or more studies.

Data synthesis

Before meta-analysing results, we grouped trials comparing alirocumab or evolocumab to placebo or active treatment. Trials comparing PCSK9 mAbs against statins only were unavailable. OR study-specific estimates were combined using Review Manager's inverse variance method for fixed-effect meta-analysis (Review Manager 2014). Similarly, we calculated fixed-effect RD estimates using generalised linear models with a random intercept for study (Bradburn 2007; Sweeting 2004).

In the case of multiple treatment or comparator arms, we pooled estimates across arms to facilitate a comparison between inhibitors and comparison therapy. Alternatively, we could have compared results from a single intervention arm versus multiple comparator groups (or vice versa), but this would have resulted in correlated effect estimates with erroneously small P values (i.e. increased type 1 errors).

Subgroup analysis and investigation of heterogeneity

Subgroup analysis and meta-regression of the LDL-C estimates were employed in a previous version of this review (Schmidt 2017), finding clinically *insignificant* heterogeneity in LDL-C effect. Given the availability of large sample size RCTs, finding limited longitudinal variation in LDL-C (and other biomarkers), we chose to focus on clinical endpoints data in the current update and readers interested in the biomarker evidence are referred to the previous publication.

Due to the unavailability of subgroup specific reports, these analyses could not be performed for clinical endpoints. In the previous version of the review, we did contact the trialists requesting additional results, which were never shared.

Sensitivity analysis

We evaluated the effect of PCSK9 mAbs on the individual components of major CVD, specifically any stroke and MI.

Summary of findings and assessment of the certainty of the evidence

We created 'Summary of findings' tables (using the GRADE approach to assess the certainty of evidence; Grade Working Group 2004) for each comparison separately, and (based on the protocol) for CVD, mortality outcomes, MI, and any stroke. We calculated risk under the intervention using RDs; we included odds ratios in the table but did not use them to calculate (reduced) risk under treatment. The absolute risk of disease, without PCSK9 treatment, was estimated by dividing the total number of events in the placebo arm by the total number of participants allocated to placebo (per compound, summed across trials).

RESULTS

Description of studies

We searched to include randomiaed controlled trials.

Results of the search

The search yielded 1873 hits, which we supplemented by 15 additional records obtained by cross-referencing trial registry sites and other sources (see Figure 1 for a flow diagram). After screening titles and abstracts, we retrieved 68 full-text articles and excluded

36 of these. We included 34 references describing 24 studies. Most studies had multiple publications (e.g. conference abstracts) that we distilled into a single entry. The alirocumab trial, focussing on plaque phenotypes, did not report on any outcomes relevant for the present review (Sugizaki 2019). For the ODYSSEY trials, we extracted additional information from an FDA report (FDA 2015).

Figure 1. Study flow diagram. RCT: randomised controlled trial.

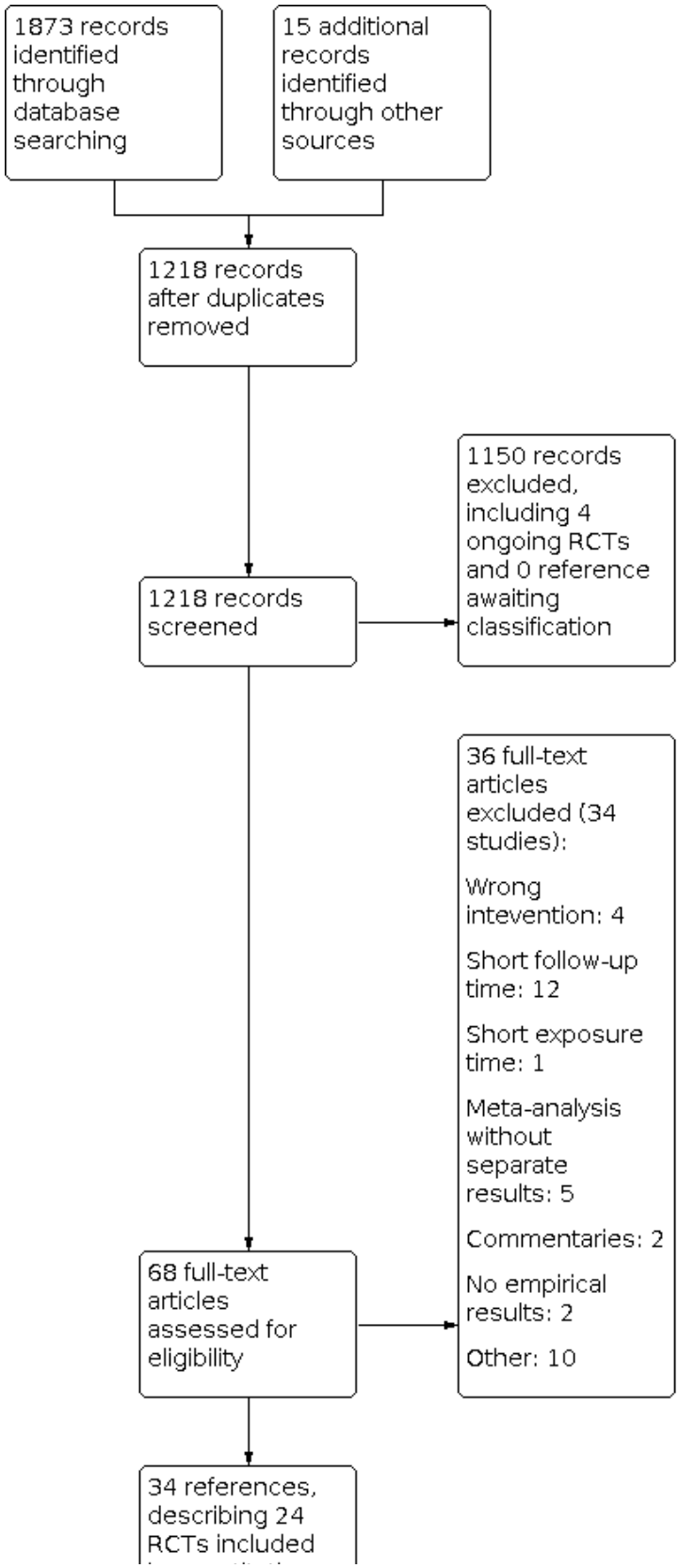


Figure 1. (Continued)

describing 24 RCTs included in quantitative synthesis (meta-analysis)

Compared to the 2017 version of the review, the terminated bococizumab (three) and RG7652 (one) trials were removed. We included seven additional studies evaluating alirocumab or evolocumab.

Included studies

PCSK9 inhibitors; settings and participants

Investigators collected a combined sample of 60,997 participants, with 26,538 randomised to alirocumab (in 18 trials), and 34,435 to evolocumab (six trials). Out of the unique participants, 17,682 were women (7721 (29%) alirocumab participants and 9961 (29%) evolocumab participants for whom gender was reported), 4590 had no history of CVD (10% of the alirocumab participants and 7% of the evolocumab participants), 1879 had FH (22% of the alirocumab participants and 38% of the evolocumab participants), 18,908 had a T2DM diagnosis at baseline (32% in alirocumab and 34% evolocumab trials; out of participants with reported T2DM status). We noted that the three FH studies focused exclusively on participants with FH (self-identified). Caucasians were the predominant ethnic group included in these studies (50,804 participants). All trials included participants treated in outpatient care settings.

Comparison group

All, but one study (Sugizaki 2019), were industry-sponsored, multi-centre trials. Twelve alirocumab trials were placebo controlled (ODYSSEY CHOICE II; ODYSSEY CHOICE I; ODYSSEY COMBO I; ODYSSEY DM-DYSLIPIDEMIA; ODYSSEY FH I; ODYSSEY FH II; ODYSSEY HIGH FH; ODYSSEY JAPAN; ODYSSEY Long Term; ODYSSEY DM-INSULIN; ODYSSEY KT; ODYSSEY OUTCOMES), on the background of lipid-lowering treatments such as statin or ezetimibe therapies. Six studies randomised participants to either ezetimibe only, or to ezetimibe with statins combined (ODYSSEY ALTERNATIVE; ODYSSEY COMBO II; ODYSSEY MONO; ODYSSEY OPTIONS I; ODYSSEY OPTIONS II; Sugizaki 2019). For evolocumab trials, three (Descartes; FOURIER; GLAGOV) studies were placebo controlled, and three (GLAGOV; OSLER-1; OSLER-2) randomised subjects to active treatments including statins and/or ezetimibe.

Note that the ODYSSEY OPTIONS I and OPTIONS II trials compared alirocumab with ezetimibe and atorvastatin, atorvastatin, or rosuvastatin. As described in the Data synthesis section, to prevent erroneously small P values (due to use of the same alirocumab arm twice), we combined multiple arms of comparison groups and estimated effects of alirocumab versus ezetimibe and statin.

Researchers administered PCSK9 inhibitors every two weeks, every four weeks, or every eight weeks; for the sake of comparison, we calculated the two weeks' equivalence dosage (see Characteristics of included studies table), which ranged from 50 mg to 210 mg every two weeks. In most studies (except Descartes; ODYSSEY FH II; ODYSSEY HIGH FH; ODYSSEY Long Term; OSLER-1), participants received different dosages of PCSK9, often depending on a predefined uptitration criterion such as LDL-C reduction or history of CVD.

Excluded studies

We excluded 34 trials, predominantly owing to follow-up time less than 24 weeks (see main objectives), or because trials described a meta-analysis while providing little to no detail on individual studies (which were already included separately) (Characteristics of excluded studies table).

Ongoing studies

We identified four ongoing trials that may fit our inclusion criteria and may be included at a later review update (Characteristics of ongoing studies table).

Risk of bias in included studies

We have provided, a per-study, risk of bias assessment with rationale in the Characteristics of included studies table. All studies described used a randomised trial design; we have discussed risk of bias in the following sections and have summarised this information in Figure 2 and Figure 3.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

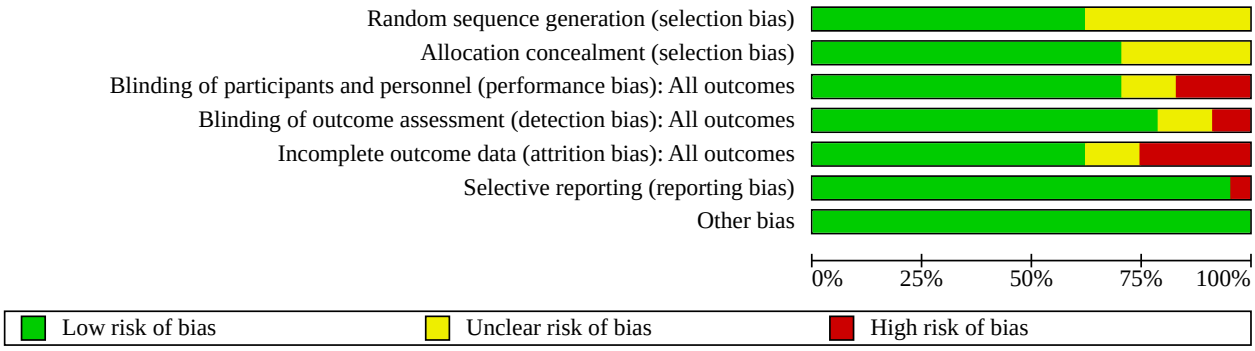


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

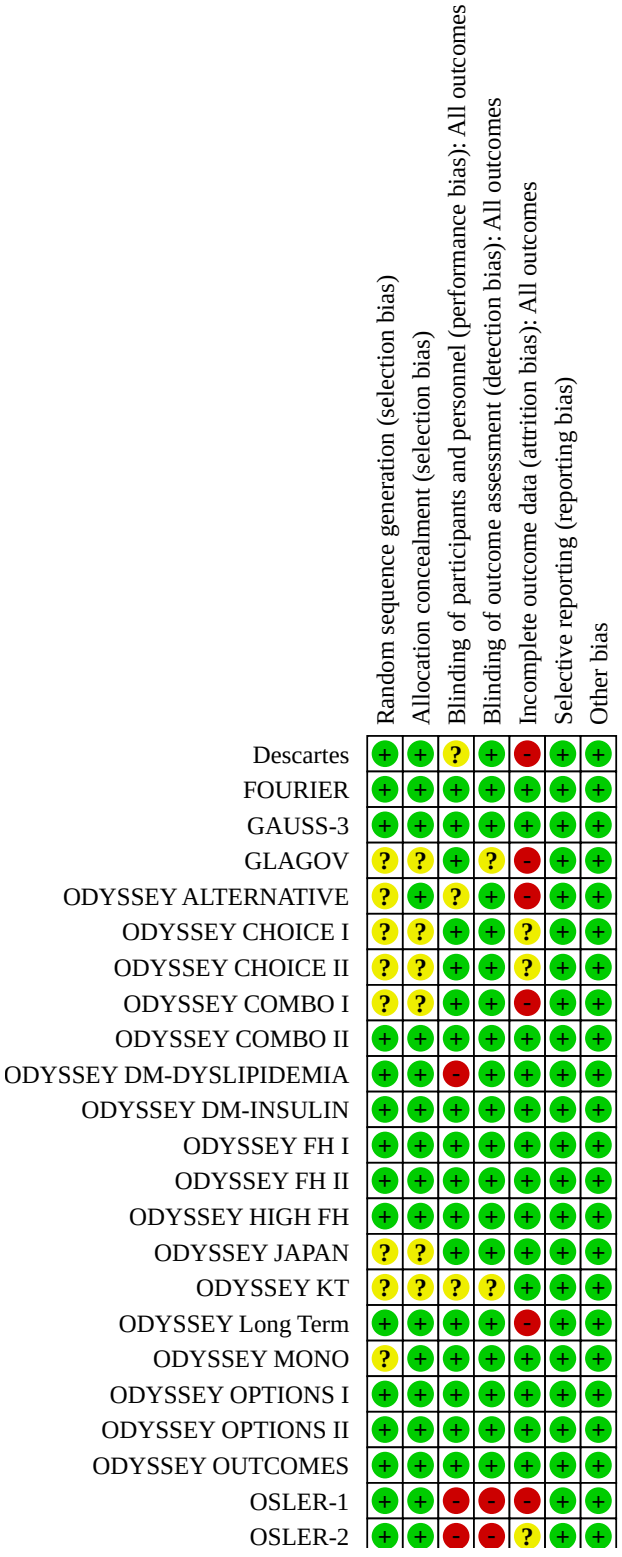
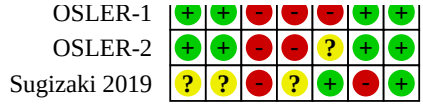


Figure 3. (Continued)



Allocation

Eight trials provided insufficient detail on how randomisation was achieved (unclear risk of bias) (GLAGOV; ODYSSEY ALTERNATIVE; ODYSSEY CHOICE I; ODYSSEY CHOICE II; ODYSSEY COMBO I; ODYSSEY JAPAN; ODYSSEY KT; ODYSSEY MONO; Sugizaki 2019). The remaining studies typically used a voice-based or Internet-based centralised response system, and we perceived them to have low risk of bias.

Most RCTs ensured allocation concealment by using centralised allocation and in some cases permuted blocks. Six RCTs did not sufficiently report on this item, and we perceived them as having unclear risk of bias (GLAGOV; ODYSSEY CHOICE I; ODYSSEY CHOICE II; ODYSSEY COMBO I; ODYSSEY JAPAN; ODYSSEY KT; Sugizaki 2019).

Blinding

Owing to the open-label design, the ODYSSEY DM-DYSLIPIDEMIA; OSLER-1; OSLER-2; and Sugizaki 2019 studies were at high risk of performance bias and detection bias. The open-label design makes it conceivable that knowledge of allocated drugs could influence participant behaviour, and similar might influence physician diagnoses.

The following trials were judged to be at an unclear risk of performance or detection bias due to insufficient reporting details: Descartes; GLAGOV; ODYSSEY ALTERNATIVE; ODYSSEY KT.

Incomplete outcome data

Loss due to follow-up (attrition bias) was typically low (arbitrarily defined as less than 5%), except in Descartes; GLAGOV; ODYSSEY ALTERNATIVE; ODYSSEY COMBO I; ODYSSEY Long Term; OSLER-1; and OSLER-2. Most studies used advanced analytics, such as mixed-effects models or (multiple) imputations, to ameliorate loss due to follow-up (even if this was minor) and to ensure the ITT analysis. However, information on both performance of these methods and appropriateness of assumptions underlying these methods was missing.

Three trials (ODYSSEY CHOICE I; ODYSSEY CHOICE II; OSLER-2) provided insufficient information to evaluate attrition bias and were evaluated to be at an unclear risk of bias.

Selective reporting

We compared endpoints described in study protocols and on ClinicalTrials.gov versus endpoints reported in the primary publication, and generally found good agreement. Despite moderate 36-week follow-up, the non-industry sponsored Sugizaki 2019 did not report on the incidence of CVD outcomes and was at high risk of reporting bias (reported only as abstract).

Other potential sources of bias

We identified no other potential sources of bias.

Effects of interventions

See: **Summary of findings 1** Alirocumab compared with placebo; **Summary of findings 2** Evolocumab compared with placebo; **Summary of findings 3** Alirocumab compared with ezetimibe and statins; **Summary of findings 4** Evolocumab compared with ezetimibe and statins

See 'Summary of findings' tables for the following.

- Alirocumab PCSK9 mAb versus placebo (Summary of findings 1).
- Evolocumab PCSK9 mAb versus placebo (Summary of findings 2).
- Alirocumab PCSK9 mAb versus active treatment (Summary of findings 3).
- Evolocumab PCSK9 mAb versus active treatment (Summary of findings 4).

Alirocumab PCSK9 monoclonal antibody compared with placebo

Comparing alirocumab with placebo, the intended effects were as follows: RD −2%, OR 0.87 (95% CI 0.80 to 0.94; 10 studies, 23,868 participants; high-certainty evidence; Analysis 1.1) for any CVD event; RD −1%; OR 0.83 (95% CI 0.72 to 0.96; 12 studies, 24,797 participants; high-certainty evidence; Analysis 1.2) for all-cause mortality; RD −2%, OR 0.86 (95% CI 0.79 to 0.94; 9 studies, 23,352 participants; high-certainty evidence; Analysis 1.3) for any MI; and RD less than −1%, OR 0.73 (95% CI 0.58 to 0.91; 8 studies, 22,835 participants; high-certainty evidence; Analysis 1.4) for any stroke.

Treatment effect estimates of unintended effects were as follows: RD 1%, OR 1.09 (95% CI 0.83 to 1.42) for influenza; RD less than −1%, OR 0.96 (95% CI 0.86 to 1.07) for T2DM; RD less than −1%, OR 0.88 (95% CI 0.61 to 1.26) for any cancer diagnosis; and RD less than −1%, OR 0.92 (95% CI 0.72 to 1.18) for hypertension. Evaluation of these treatment effect estimates on the RD scale revealed that the effect of PCSK9 inhibitors on the risk of an event was typically modest, with changes in risk often less than 1% (see Table 1 and Analysis 1.5; Analysis 1.6; Analysis 1.7; Analysis 1.8).

Evolocumab PCSK9 monoclonal antibody compared with placebo

Comparing evolocumab with placebo, the intended effects were as follows: RD −2%, OR 0.84 (95% CI 0.78 to 0.91; 3 studies, 29,432 participants; high-certainty evidence; Analysis 2.1) for any CVD event; RD less than 1%, OR 1.04 (95% CI 0.91 to 1.19; 3 studies, 29,432 participants; high-certainty evidence; Analysis 2.2) for all-cause mortality; RD −1%, OR 0.72 (95% CI 0.64 to 0.82; 3 studies, 29,432 participants; high-certainty evidence; Analysis 2.3) for any MI; and RD less than 1%, OR 0.79 (95% CI 0.65 to 0.94; 2 studies, 28,531 participants; high-certainty evidence; Analysis 2.4) for any stroke.

Treatment effect estimates of unintended effects were as follows: RD 1%, OR 1.21 (95% CI 0.69 to 2.11) for influenza; RD less than –1%, OR 1.05 (95% CI 0.94 to 1.17) for T2DM; with an absence of information on hypertension and cancer diagnoses (see Table 2 and Analysis 2.5; Analysis 2.6).

Alirocumab PCSK9 monoclonal antibody compared with active treatment

Comparing alirocumab with active treatment, the intended effects were as follows: RD 1%, OR 1.37 (95% CI 0.65 to 2.87; 3 studies, 1379 participants; low-certainty evidence; Analysis 3.1) for any CVD event; RD –1%, OR 0.51 (95% CI 0.18 to 1.40; 5 studies, 1733 participants; low-certainty evidence; Analysis 3.2) for all-cause mortality; RD 1%, OR 1.45 (95% CI 0.64 to 3.28, 5 studies, 1734 participants; low-certainty evidence; Analysis 3.3) for any MI; and RD less than –1%, OR 0.85 (95% CI 0.13 to 5.61; 5 studies, 1734 participants; low-certainty evidence; Analysis 3.4) for any stroke.

Treatment effect estimates of unintended effects were as follows: RD 1%, OR 1.72 (95% CI 0.91 to 3.25) for influenza; RD –2%, OR 0.28 (95% CI 0.05 to 1.55) for T2DM; RD less than 1%, OR 1.08 (95% CI 0.43 to 2.69) for any cancer diagnosis; and RD less than –1%, OR 1.01 (95% CI 0.57 to 1.79) for hypertension (see Table 3 and Analysis 3.5; Analysis 3.6; Analysis 3.7; Analysis 3.8).

Evolocumab PCSK9 monoclonal antibody compared with active treatment

Comparing evolocumab with active treatment, the intended effects were as follows: RD –1%, OR 0.66 (95% CI 0.14 to 3.04; 1 study; 218 participants; very low-certainty evidence; Analysis 4.1) for any CVD event; RD less than –1%, OR 0.43 (95% CI 0.14 to 1.30; 3 studies, 5223 participants; very low-certainty evidence; Analysis 4.2) for all-cause mortality; and RD less than –1%, OR 0.66 (95% CI 0.23 to 1.85; 3 studies, 5003 participants; very low-certainty evidence; Analysis 4.3) for MI.

Treatment effect estimates of unintended effects were as follows: RD 1%, OR 1.22 (95% CI 0.88 to 1.70) for influenza; RD less than 1%, OR 3.52 (95% CI 0.18 to 68.33) for T2DM; and RD less than 1%, OR 1.51 (95% CI 0.06 to 37.04) for hypertension, with an absence of information on any stroke and any cancer (Table 4 and Analysis 4.4; Analysis 4.5; Analysis 4.6).

Outcomes and comparisons without data

See respective sections for details on missing outcome data that were unavailable for some comparisons. Data on quality of life were unavailable for all studies. Finally, while we did present evidence for MI and any stroke, we did not have sufficient data to present further details on the individual components of any CVD such as angina pectoris, urgent revascularisation and so on. The alirocumab trial, focusing on plaque phenotypes, did not at present, report on any outcomes relevant for the present review (Sugizaki 2019).

Reporting bias and small-study heterogeneity (funnel plots)

Following the protocol funnel plots were generated for comparisons with 10 or more studies, that is for the alirocumab versus placebo effects on CVD and influenza: Figure 4; Figure 5. The CVD analysis shows a degree of asymmetry were small sample size studies with a protective effect (favouring alirocumab) appear absent.

Figure 4. A funnel plot of the alirocumab versus placebo cardiovascular disease effects.

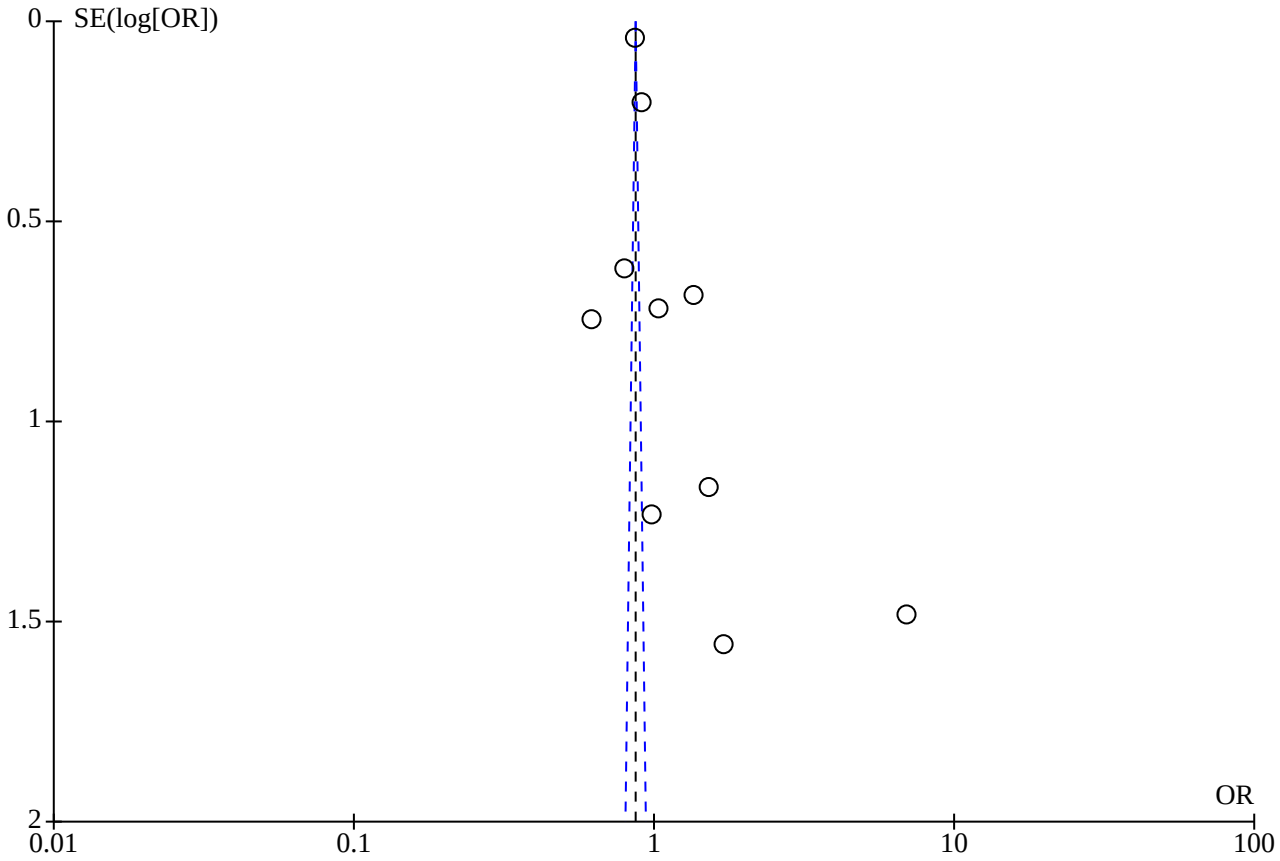
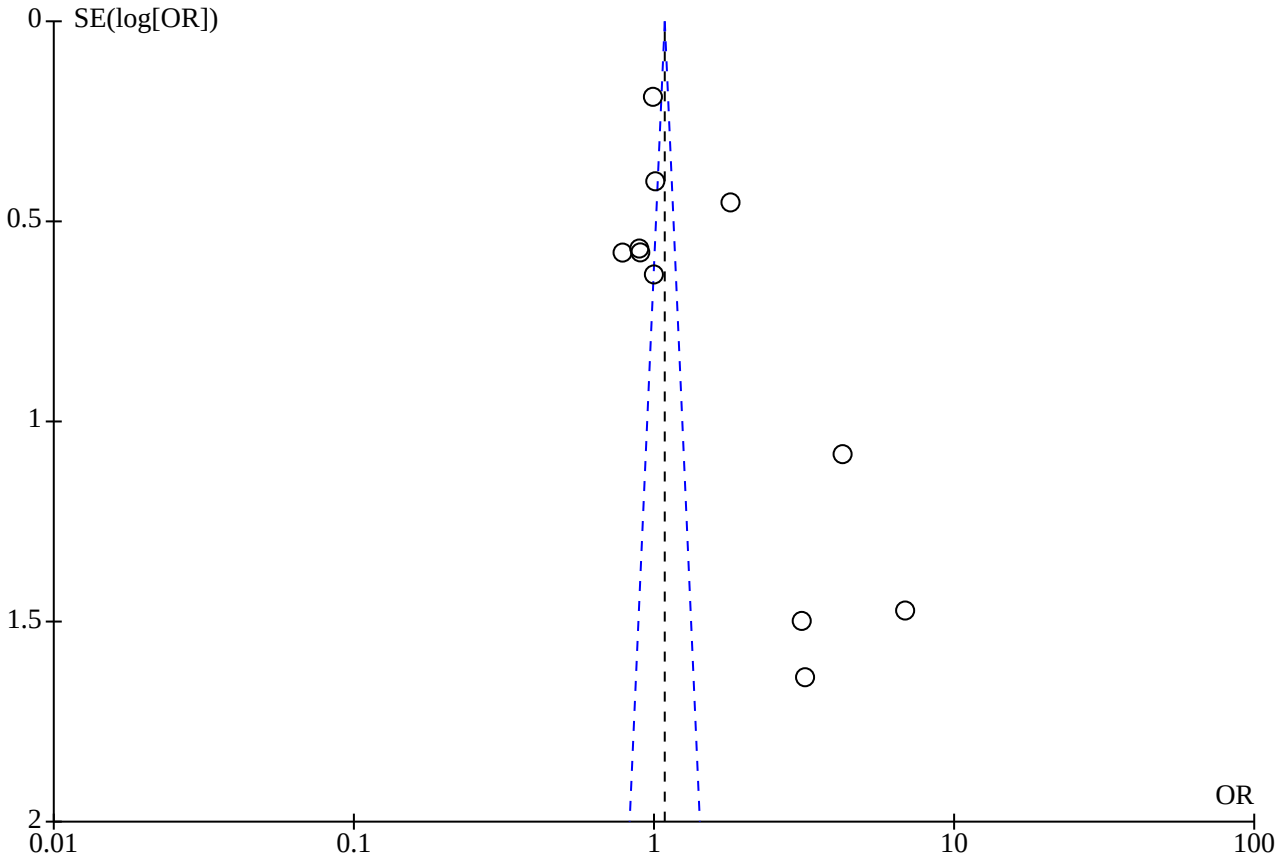


Figure 5. A funnel plot of the alirocumab versus placebo influenza effects.



The currently available trials have all been conducted for market authorisation proposes, hence, it seems highly unlikely that any of such studies (given the FDA and EMA scrutiny), especially favouring a protective effect, would have remain unpublished. Instead, what is more likely, is that this seemingly asymmetry is a result of smaller studies selecting a different (possibly higher risk) patient population to increase power.

DISCUSSION

Summary of main results

In this systematic review and meta-analysis, we confirmed that PCSK9 inhibitors (alirocumab and evolocumab; mAbs) compared with placebo reduce the risk (high-certainty evidence) of CVD (as a composite), MI, stroke (combination of ischaemic and haemorrhagic events), and all-cause mortality (for alirocumab).

While most of the evidence focused on placebo-controlled trials, there were some trials (six for alirocumab and three for evolocumab) that made direct comparisons against active lipid-lowering treatment such as statins or ezetimibe. Due to a relatively low number of accrued events, most comparisons did not favour a protective or harmful effect. Results were of lower certainty (low to very low) due to the low number of events, or due to design choices such as open-label treatment allocation. As such we are uncertain whether PCSK9 mAb would elicit a similar decrease in risk as statins or ezetimibe. In general, there was no convincing evidence for between-study heterogeneity, which provides a crude indicator of the degree of between patient treatment response variation. Likely this lack of observed heterogeneity is closely related to the often modest number of studies available (typically fewer than 10). Trials published to date did not show any potential safety signal on influenza, hypertension, cancer diagnosis, or T2DM. Importantly, the results also do not exclude a potential harmful effect, for which the number of events and precision are too low.

Estimation of the same associations on an RD scale (Table 1; Table 2; Table 3; Table 4) indicates that PCSK9 inhibitors only modestly changed the outcome risk, with an absolute risk (reduction) often less than 1% over the follow-up period considered.

Overall completeness and applicability of evidence

Most of the evidence was obtained from people with established atherosclerotic CVD or at high risk of cardiovascular events; therefore, evidence regarding the use of PCSK9 inhibitors for treatment of people at lower risk remains uncertain. Second, information on clinical endpoints for the placebo comparison was based on the large sample size in the FOURIER and ODYSSEY OUTCOMES trials. Often these trials dominated the meta-analysed results. Although these trials were large, median follow-up was less than three years, hence information on long-term efficacy and safety is absent.

Further, in this review, we focused on any CVD and all-cause mortality, where possible exploring individual elements of CVD such as MI and stroke. In future, it will be important to explore the possible PCSK9 mAb effect on heart failure, atrial fibrillation and stroke subtypes. In a previous version of this review (Schmidt 2017), we additionally explored the possible association between PCSK9 mAb and cognitive function. The EBBINGHAUS trial (EBBINGHAUS: nested within the FOURIER), utilising a non-inferiority design, disproved such a relation existed over the short to medium follow-up currently available, and hence we did not explore this endpoint further.

Quality of the evidence

Although all available data were derived from industry-sponsored RCTs, most trials were at low risk of bias, reflecting observations that industry trials are often robustly designed (Zwierzyna 2018). Exceptions were the open-label OSLER trials, which were at high risk of performance bias. Another important potential source of bias was attrition bias, whereby some RCTs included missing observations for more than 5% of enrolled participants. Most trials tried to minimise this bias by using advanced analytics that explicitly (multiple imputation) or implicitly (mixed-effects models) imputed these missing observations, thus ensuring that all comparisons were made on an ITT basis. The appropriateness of these models (and their underlying assumptions) was not reported, hence these imputation algorithms may have failed to correct for potential attrition bias.

For intended effect and clinical outcomes (i.e. CVD, and all-cause mortality) with PCSK9 inhibitors compared with placebo, we graded the certainty of the evidence as high. In the active treatment comparisons, we graded the certainty of the evidence as low (alirocumab), and very low (evolocumab). In the case of alirocumab, we downgraded the evidence because of a reliance on trials with very few outcome events, resulting in a lack of precision and possible small sample size bias. In the case of evolocumab, this was compounded by reliance on open-label designed trials, the data presented separately for the OSLER-2 on ClinicalTrials.gov.

Finally, we observed a discrepancy between the data presented in the published joint analysis of OSLER-1 and OSLER-2 (OSLER-1; OSLER-2), and the data presented separately for the OSLER-2 on ClinicalTrials.gov. To exclude confounding by centre, we decide to use the ClinicalTrials.gov data and meta-analyse this with other evolocumab trials.

Potential biases in the review process

The meta-analysis presented may show some weaknesses. First, the meta-analysis explored a large number of endpoints, increasing the probability of a false-positive finding. Second, despite our best efforts, we may have failed to identify certain PCSK9 inhibitor trials.

Agreements and disagreements with other studies or reviews

We are aware of two previous systematic reviews and meta-analyses on PCSK9 inhibitors (Navarese 2015; Zhang 2015); both included a large number of RCTs with short follow-up of 12 weeks, which we excluded here, as well as several longer-term follow-up studies that we did include.

The meta-analysis of Zhang 2015 revealed a protective effect on mortality of alirocumab versus placebo (OR 0.43, 95% CI 0.19 to 0.96) and of alirocumab versus ezetimibe (OR 0.48, 95% CI 0.16 to 1.45); these effects are similar to those reported here.

Navarese 2015 reported a similarly protective effect of PCSK9 inhibitors (versus all types of comparators) for all-cause mortality (OR 0.45, 95% CI 0.23 to 0.86), as well as protective effects for cardiovascular mortality (OR 0.50, 95% CI 0.23 to 1.10) and MI (OR 0.49, 95% CI 0.26 to 0.93).

More recently, three independent meta-analyses found no significant effect of PCSK9 mAb on all-cause mortality (contrary to the alirocumab versus placebo effect reported here) (AlTurki 2019; Casula 2019; Torgeon 2018). However, all three meta-analyses not only combined placebo and active therapy arms, they also pooled alirocumab and evolocumab, with AlTurki 2019 even including the terminated PCSK9 mAb bococizumab. However, they did report a similar stroke and MI reduction of PCSK9 inhibition. As expected, based on the EBBINGHAUS results, Torgeon 2018 showed a fairly precise neutral effect of PCSK9 mAb on neurocognitive events (OR 1.02, 95% CI 0.89 to 1.16). There were similar precise estimates for T2DM (OR 0.96, 95% CI 0.91 to 1.02); however, this also included "worsening T2DM" as an endpoint.

The ODYSSEY OUTCOMES trial showed a very similar OR (0.88, 95% CI 0.74 to 1.05) for fatal-CVD (comparing alirocumab versus placebo) as to the all-cause mortality effect presented here.

AUTHORS' CONCLUSIONS

Implications for practice

Taken together, there is a strong evidence base for PCSK9 monoclonal antibodies in people who might not be eligible for other lipid-lowering drugs, or to people who cannot meet lipid goals on more traditional therapies.

The evidence base of PCSK9 inhibitors compared with active treatment is much weaker (low- to very low-certainty evidence) and it is unclear whether evolocumab or alirocumab might be effectively used as *replacement* therapies. Related, most of the available studies preferentially enrolled patients with either established CVD or at a high risk already, and evidence in medium- to low-risk settings is minimal.

Finally, there is very limited evidence on any potential safety issues of both evolocumab and alirocumab. While the current evidence synthesis does not reveal any signals, neither does it provide evidence against such signals. This suggests careful considerations of alternative lipid-lowering treatment before prescribing PCSK9 inhibitors.

Implications for research

Give the high certainty of evidence for alirocumab and evolocumab (versus placebo) and the similar effects profile on clinical endpoints of both drugs (again versus placebo), it seems highly likely that PCSK9 monoclonal antibodies prevent cardiovascular disease. While evolocumab did not show a significant effect on all-cause mortality, considering the overall agreement with alirocumab, which did show an all-cause mortality effect, this is likely an issue of sample size.

The most pressing need for longer-term follow-up studies is to elucidate the possible adverse effect profile of both alirocumab and evolocumab, which the current evidence base is not able to address (favouring a protective, harmful, or neutral effect). Depending on the medical need, further studies might consider the effects of alirocumab and evolocumab versus active treatment, for example in primary prevention settings. Despite the similarities of both compounds, this is only based on indirect comparisons and direct comparisons might provide further insights.

ACKNOWLEDGEMENTS

We are grateful to Carlo Piccini for his constructive peer-review comments.

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GLAGOV *{published data only (unpublished sought but not used)}*

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ODYSSEY ALTERNATIVE *{published data only}*

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Descartes

Study characteristics	
Methods	**Type of RCT:** 2:1 parallel-group, double-blind RCT with stratified randomisation **Settings:** outpatient care **Duration:** 52 weeks **Start and stop dates:** January 2012 and November 2013
Participants	**Number of participants:** 905 (901 with baseline data) **Number lost to follow-up:** 134 **Women:** 471 (52%) **Mean age (SD), years:** 56 (11)

Descartes *(Continued)*

	History of CVD: 136 (15%) **Participants with FH:** NA Participants with fasting LDL-C ≥ 75 mg/dL and fasting TG 400 mg/dL
Interventions	**Background therapy:** SOC, which consisted of diet only, daily atorvastatin 10 mg, 80 mg, or 80 mg + ezetimibe 10 mg **Randomised therapy:** evolocumab every 4 weeks vs placebo **Evolocumab dose:** 48 weeks of 420 mg each 4 weeks. 2-week equivalent dose of 210 mg
Outcomes	CVD, all-cause mortality
Notes	• All lipid analyses performed by Medpace Reference Laboratories (MRL). Laboratories maintained Part III certification according to the CDC Lipid Standardization Program throughout the study. • LDL-C and very low-density lipoprotein cholesterol measured after preparative ultracentrifugation (β-quantification). Calculated LDL-C using Friedewald formula. • TGs and cholesterol measured with enzymatic colorimetric tests (Olympus AU2700 or AU5400 Analyzer, Olympus, Center Valley, PA) with calibration directly traceable to CDC reference procedures. • ApoB-containing lipoproteins precipitated with dextran sulphate, and HDL-C was measured in the supernatant. ApoA1 and ApoB were measured with rate immunonephelometry (Dade Behring BNII nephelometer, Siemens Healthcare Diagnostics, Deerfield, IL), and Lp(a) was measured by immuno turbidimetry (Denka Seiken Co. Ltd. Lp(a) assay from Polymedco, Cortlandt Manor, NY, on the Olympus Analyzer). • NCT01516879 • Parent trial of OSLER-2 • Funded by Amgen

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation performed centrally using an interactive voice-response system.
Allocation concealment (selection bias)	Low risk	Randomisation performed centrally using an interactive system.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Although paper and appendix described the study as double-blind, it was unclear how this was maintained and who was blinded. Lack of blinding will likely cause a change in adherence or participant choices regarding SOC/lifestyle (or both), which may influence outcomes.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Although paper and appendix described the study as double-blind, it was unclear how this was maintained and who was blinded. However, any lack of blinding of participants and personnel seems unlikely to bias LDL-C assessment, which was performed in independent laboratories. Outcomes such as adverse events may be biased owing to detection bias.
Incomplete outcome data (attrition bias) All outcomes	High risk	4 participants were randomised but were not included in the ITT (small number, good). However, at 2 weeks of follow-up, the number of available participants had decreased by about 15% (number of missing measurements 44 (14.57%) in comparison arm, and 90 (15.03%) in intervention arm). In some cases, missing participants were likely due to different enrolment times, limiting follow-up; however, reported numbers of discontinued participants were similarly high: 73 in the evolocumab arm and 28 in the placebo arm. Missing LDL-C data were imputed using linear-mixed models, including baseline mea-

Descartes *(Continued)*

		surements. Other missing lipid measurements were imputed using a last observation carried forward approach and were analysed by ANCOVA.
Selective reporting (reporting bias)	Low risk	Reported most endpoints.
Other bias	Low risk	No concerns outside the assessed risk of bias domains.

FOURIER

Study characteristics	
Methods	**Type of RCT:** 1:1 parallel-group, double-blind RCT **Settings:** outpatient care **Duration:** 157 weeks (36 months) **Start and stop dates:** February 2013 and November 2016
Participants	**Number of participants:** 27,564 (39 did not receive treatment) **Number lost to follow-up:** 1558 participants had observed LDL-C measurements at 36 months, 1375 completed follow-up of 36 months for the primary endpoint of CVD **Women:** 6769 (25%) **Mean age (SD), years:** 63 (9) **History of CVD:** 27,564 (100%), not reported but inferred based on inclusion criteria **Participants with FH:** NA Inclusion criteria • Men or women 40–85 years of age • History of clinically evident CVD at high risk for a recurrent event • Fasting LDL-C ≥ 70 mg/dL (≥ 1.8 mmol/L) or non-HDL-C ≥ 100 mg/dL (> 2.6 mmol/L) • Fasting TGs ≤ 400 mg/dL (4.5 mmol/L) Exclusion criteria • NYHA class III or IV, or last known left ventricular ejection fraction < 30% • Uncontrolled hypertension • Uncontrolled or recurrent ventricular tachycardia • Untreated hyperthyroidism or hypothyroidism • Homozygous FH • Low-density lipoprotein or plasma apheresis
Interventions	**Background therapy:** statin therapy **Randomised therapy:** evolocumab compared to placebo **Evolocumab dose:** 140 mg/2 weeks or to 420 mg/4 weeks. Resulting in a 2-week equivalent dose of 140–210 mg
Outcomes	CVD defined as: CV death, myocardial infarction, stroke, hospitalisation for unstable angina, or coronary revascularisation

FOURIER *(Continued)*

Notes	Funded by Amgen

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Central computerised system.
Allocation concealment (selection bias)	Low risk	Central allocation.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Both were blinded.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Central laboratory and blinded adjudication.
Incomplete outcome data (attrition bias) All outcomes	Low risk	27,564 participants were randomised of whom 39 did not receive any treatment. The number of participants available reduced considerably over time to only 1375 participants remaining at study end. However, as reported, loss to follow-up was only 0.1% and the decrease in number reflects different enrolment times.
Selective reporting (reporting bias)	Low risk	Reported most endpoints.
Other bias	Low risk	No concerns outside the assessed risk of bias domain./

GAUSS-3

Study characteristics

Methods	**Type of RCT:** 1:1 parallel-group, double-blind RCT (after a run-in phase) **Settings:** outpatient care **Duration:** 24 weeks (6 months) **Start and stop dates:** February 2016 and August 2017
Participants	**Number of participants:** 291 (in phase B, after the run-in phase), statin intolerant participants **Number lost to follow-up:** 2 **Women:** 106 (49%) **Mean age (SD), years:** 59 (10) **History of CVD:** unknown **Participants with FH:** NA Inclusion criteria

GAUSS-3 *(Continued)*

- Men or women 18–80 years of age
- Inability to tolerate atorvastatin 10 mg and any other statin at any dose or, alternatively, ≥ 3 statins, with 1 at the lowest mean daily starting dose and 2 other statins at any dose. The lowest mean starting dose was defined as rosuvastatin 5 mg, simvastatin 10 mg, pravastatin 40 mg, lovastatin 20, fluvastatin 40 mg, or pitavastatin 2 mg
- For people with diagnosed CHD, lipid inclusion criteria required LDL-C ≥ 100 mg/dL. People without CHD were required to have LDL-C ≥ 130 mg/dL with ≥ 2 risk factors, ≥ 160 mg/dL with ≥ 1 risk factors, or ≥ 190 mg/dL with 0 additional risk factors.

Exclusion criteria

- Myocardial infarction, unstable angina, coronary revascularisation, or stroke within 3 months before randomisation
- Personal or family history of hereditary muscular disorders
- Moderate-to-severe heart failure or uncontrolled cardiac arrhythmia
- Recently diagnosed or poorly controlled diabetes
- Hypertension or hyper/hypothyroidism
- Known active infection
- Major haematological, renal, hepatic, metabolic, gastrointestinal, or endocrine dysfunction

Interventions	**Background therapy:** none **Randomised therapy:** evolocumab vs ezetimibe (10 mg) **Evolocumab dose:** 420 mg/4 weeks
Outcomes	CVD, all-cause mortality
Notes	Funded by Amgen

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Central computerised system.
Allocation concealment (selection bias)	Low risk	Central allocation.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Both were blinded.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Central laboratory and blinded adjudication.
Incomplete outcome data (attrition bias) All outcomes	Low risk	2 participants were lost to follow-up.
Selective reporting (reporting bias)	Low risk	Reported most endpoints.
Other bias	Low risk	No concerns outside the assessed risk of bias domains.

GLAGOV

Study characteristics	
Methods	**Type of RCT:** 1:1 parallel-group, double-blind RCT **Settings:** outpatient care **Duration:** 76 weeks **Start and stop dates:** April 2013 and July 2016
Participants	**Number of participants:** 968 **Number lost to follow-up:** 124 participants excluded from the primary analysis **Women:** 269 (28%) **Mean age (SD), years:** 59.8 (9.2) **History of CVD:** 628 (65%) **Participants with FH:** unknown Inclusion criteria • Men or women aged > 18 years • Clinically indicated coronary angiogram, evidence of coronary disease • Stable statin dose for ≥ 4 weeks prior to screening • LDL-C criteria met within 4 weeks of screening visit or, if applicable, at the end of lipid stabilisation 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 (1 required): non-coronary atherosclerotic vascular disease as evidenced by documented peripheral arterial disease, documented abdominal aortic aneurysm, or documented cerebrovascular disease; documented myocardial infarction or hospitalisation for unstable angina within the last 2 years; documented T2DM • Minor risk factors (3 required): cigarette smoking (current); hypertension (blood pressure ≥ 140/90 mmHg or current use of antihypertensive medications); low HDL-C (men: < 40 mg/dL; women < 50 mg/dL); family history of premature CHD (first-degree male relative aged < 55 years or first-degree female relative aged < 65 years); age (men ≥ 50 years; women ≥ 55 years); hs-CRP ≥ 2 mg 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, replacement during the study, or a combination of these • Heart failure of New York Heart Failure Association (NYHA) class III or IV or last known left ventricular ejection fraction < 30% • Coronary artery bypass surgery < 6 week prior to the qualifying IVUS • Cardiac arrhythmia within 3 months prior to randomisation that was not controlled by medication • Uncontrolled hypertension at day 1, defined as a resting systolic blood pressure ≥ 180 mmHg • TG > 400 mg/dL at screening • Type 1 diabetes mellitus or poorly controlled T2DM (HbA1c 9%) at screening • TSH lower limit of normal or TSH > 1.5 × ULN • Estimated glomerular filtration rate < 30 mL/minute per 1.73 m^2 • Aspartate aminotransferase or alanine aminotransferase > 2 × ULN • Creatine kinase > 3 × ULN • Use of cholesterylester transfer protein inhibition treatment within 12 months prior to randomisation • Any prior use of PCSK9 inhibitor therapy

GLAGOV *(Continued)*

	• Consumption of any of the following drugs for more than 2 weeks in the last 3 months prior to LDL-C screening: systemic ciclosporin, systemic steroids, isotretinoin • History of malignancy (except non-melanoma skin cancers, cervical in situ carcinoma, breast ductal carcinoma in situ, or stage 1 prostate carcinoma) • Known major active infection, or major haematological, renal, metabolic, gastrointestinal, or endocrine dysfunction • Baseline IVUS did not meet IVUS core laboratory technical standards • Women could not be pregnant or breastfeeding. Premenopausal women must have been willing to use ≥ 1 highly effective method of birth control during treatment and for an additional 15 weeks after end of treatment
Interventions	**Background therapy:** statin **Randomised therapy:** evolocumab vs placebo. **Evolocumab dose:** 140 mg/2 week or to 420 mg/4 weeks. Resulting in a 2-week equivalent dose of 140–210 mg
Outcomes	
Notes	Funded by Amgen

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study did not describe this in detail. However, Amgen trials used interactive voice-response system which was likely used here as well.
Allocation concealment (selection bias)	Unclear risk	Not reported. However, Amgen trials used interactive voice-response system which was likely used here as well.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Described as double-blind. Quote: "Technicians blinded to the treatment status of the patient and the timing of each individual pullback will perform the analysis."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "The study includes adjudication of deaths and specific cardiovascular events potential endpoints (PEPs) by an independent Clinical Events Committee (CEC) and formal review of the accumulating data by an independent Data Monitoring Committee (DMC)."
Incomplete outcome data (attrition bias) All outcomes	High risk	124/970 participants excluded from the primary analysis.
Selective reporting (reporting bias)	Low risk	Reported the usual endpoints.
Other bias	Low risk	No concerns outside the assessed risk of bias domains.

ODYSSEY ALTERNATIVE

Study characteristics

ODYSSEY ALTERNATIVE *(Continued)*

Methods	**Type of RCT:** 1:1 parallel-group RCT, with stratification for CVD history **Settings:** outpatient care **Duration:** 24 weeks **Start and stop dates:** September 2012 and September 2016
Participants	**Number of participants:** 251 (excluding 63 participants in an atorvastatin rechallenge arm) **Number lost to follow-up:** 80 **Women:** 114 (45%) **Mean age (SD), years:** 63 (10) **History of CVD:** 115 (46%) **FH participants:** 38 (15%) Participants with primary hypercholesterolaemia and moderate, high, or very high CV risk, who were intolerant to statins 377 participants with a history of statin intolerance, and of moderate, high, or very high CV risk. Moderate CV risk defined as SCORE risk of ≥ 1% but < 5%; high risk defined as score risk ≥ 5%, or moderate chronic kidney disease, diabetes without target organ damage heFH; very high risk defined as history of documented CHD, ischaemic stroke, peripheral artery disease, TIA, abdominal aortic aneurysm, or carotid artery stent procedure, or carotid endarterectomy or carotid artery stent procedure, or renal artery stenosis or renal artery stent procedure or diabetes with target organ damage
Interventions	**Background therapy:** National Cholesterol Education Program Adult Treatment Panel III therapeutic lifestyle changes diet. Participants were allowed to continue to use bile acid, nicotinic acid, fenofibrate, or mega-3 acid **Randomised therapy:** alirocumab and placebo vs ezetimibe 10 mg daily or atorvastatin 20 mg and placebo **Alirocumab dose:** 24 weeks 75 mg every 2 weeks, with uptitration to 150 mg every 2 weeks at week 12. Resulting in a 2-week equivalent dose of 75–150 mg
Outcomes	MACE, all-cause mortality
Notes	• Atorvastatin arm was included as a rechallenge experiment. Main analysis focuses on alirocumab vs ezetimibe (151 participants) • LDL-C calculated using Friedewald formula • NCT01709513 • Funded by Sanofi and Regeneron

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described.
Allocation concealment (selection bias)	Low risk	Permuted-block design and central allocation.
Blinding of participants and personnel (performance bias)	Unclear risk	Placebo-controlled, participants self-administered. Unclear if staff were also blinded.

ODYSSEY ALTERNATIVE *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Lipid parameters assessed at central blinded laboratory.
Incomplete outcome data (attrition bias) All outcomes	High risk	36 (28.6%) participants in the alirocumab arm had missing lipid measurements compared with 44 (36.1%) in the ezetimibe arm. Potentially, these 'missing' participants simply did not make the required follow-up time (24 weeks) owing to late enrolment; without specific description of the reason for these lower numbers, some concern is warranted.
Selective reporting (reporting bias)	Low risk	Reported results showed agreement with ClinicalTrials.gov.
Other bias	Low risk	No concerns outside the assessed risk of bias domains.

ODYSSEY CHOICE I

Study characteristics	
Methods	**Type of RCT:** 1:2 parallel-group, double-blind, stratified RCT **Settings:** outpatient care **Duration:** 24 weeks **Start and stop dates:** October 2013 and May 2015
Participants	**Number of participants:** 803 **Number lost to follow-up:** NA **Women:** 341 (42%) **Mean age (SD), years:** 60 (10) **History of CVD:** NA **Participants with FH:** 45 (6%) Participants with poorly controlled hypercholesterolaemia and moderate CV risk with or without muscle-related statin intolerance, or with high CV risk receiving maximally tolerated dose. No definition of poorly controlled or moderate/high CV risk was provided.
Interventions	**Background therapy:** statin therapy **Randomised therapy:** alirocumab vs placebo. At 12 weeks, participants could switch to 150 mg every 2 weeks **Alirocumab dose:** 48 weeks 75 mg every 2 weeks or 300 mg every 4 weeks. Resulting in a 2-week equivalent dose of 75–150 mg. Treatment was allocated stratified on statin use or not
Outcomes	Adverse events, all-cause mortality
Notes	• All results based on an abstract • Results presented as alirocumab vs placebo • NCT01926782

ODYSSEY CHOICE I *(Continued)*

- Funded by Sanofi and Regeneron

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported.
Allocation concealment (selection bias)	Unclear risk	Not reported.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Placebo controlled trial.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Clinical events committee and blinded assessment using a central laboratory.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No details of missing data provided.
Selective reporting (reporting bias)	Low risk	Reported protocol-defined endpoints.
Other bias	Low risk	No concerns outside the assessed risk of bias domains.

ODYSSEY CHOICE II

Study characteristics

Methods	**Type of RCT:** 1:2 parallel group, double-blind RCT **Settings:** outpatient care **Duration:** 24 weeks **Start and stop dates:** December 2013 and June 2017
Participants	**Number of participants:** 233 **Number lost to follow-up:** NA **Women:** 103 (44%) **Mean age (SD):** 63 (10) **History of CVD:** NA **FH participants:** 29 (12%) Participants with primary hypercholesterolaemia (heFH or non-FH) with high CV risk with muscle-related statin intolerance, or moderate CV risk without muscle-related statin intolerance.
Interventions	**Background therapy:** ezetimibe, fenofibrate, or diet alone.

ODYSSEY CHOICE II *(Continued)*

	Randomised therapy: alirocumab vs placebo **Alirocumab dose:** 24 weeks of 75 mg every 2 weeks or 150 mg every 4 weeks. At 12 weeks, participants could switch to 150 mg every 2 weeks. Resulting in a 2-week equivalent dose of 75–150 mg.
Outcomes	All-cause mortality
Notes	• All results based on an abstract • Results presented as alirocumab vs placebo • NCT0203879 • Funded by Sanofi and Regeneron

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported.
Allocation concealment (selection bias)	Unclear risk	Not reported.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Placebo-blinded trial.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Clinical Events Committee.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No details provided on missing data.
Selective reporting (reporting bias)	Low risk	Reported protocol-defined endpoints.
Other bias	Low risk	No concerns outside the assessed risk of bias domains.

ODYSSEY COMBO I

Study characteristics

Methods	**Type of RCT:** 1:2 parallel-group, double-blind, stratified RCT **Settings:** outpatient care **Duration:** 52 weeks **Start and stop dates:** July 2012 and April 2014
Participants	**Number of participants:** 316 **Number lost to follow-up:** 30 **Women:** 108 (34%)

ODYSSEY COMBO I *(Continued)*

	Mean age (SD), years: 63 (9) **History of CVD:** 247 (78%) **FH participants:** 0 Participants with hypercholesterolaemia (LDL-C ≥ 70 mg/dL) and established CVD or LDL-C 100 mg/dL and CHD risk equivalents (e.g. chronic kidney disease) and on a maximally tolerated dose of statin, with possible addition of other LLTs
Interventions	**Background therapy:** both add-on to maximal tolerated dose of statin **Randomised therapy:** alirocumab vs placebo **Alirocumab dose:** 104 weeks of 75 mg every 2 weeks, with uptitration to 150 mg every 2 weeks at week 12 resulting in a 2-week equivalent dose of 75–150 mg
Outcomes	CVD, all-cause mortality
Notes	• LDL-C calculated using Friedewald formula, or if TGs > 400 mg/dL via beta quantification method • NCT01644175 • Funded by Sanofi and Regeneron

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Did not mention randomisation but presumably similar as COMBO II: used an interactive voice-response system.
Allocation concealment (selection bias)	Unclear risk	Did not describe allocation concealment.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Both blinded.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Clinical events committee and central laboratory.
Incomplete outcome data (attrition bias) All outcomes	High risk	20 (9.57%) participants in the alirocumab arm had missing lipid measurements compared with 10 (9.34%) in the comparator arm. Potentially, these 'missing' participants simply did not make the required follow-up time (24 weeks) owing to late enrolment; however, without specific description of the reasons for these lower numbers, some concern is warranted.
Selective reporting (reporting bias)	Low risk	Reported protocol-defined endpoints.
Other bias	Low risk	No concerns outside the assessed risk of bias domains.

ODYSSEY COMBO II

Study characteristics

ODYSSEY COMBO II *(Continued)*

Methods	**Type of RCT:** 2:1 parallel-group, double-blind, stratified, permuted-block RCT **Settings:** outpatient care **Duration:** 104 weeks **Start and stop dates:** August 2012 and July 2015
Participants	**Number of participants:** 720 **Number lost to follow-up:** 13 **Women:** 190 (26%) **Mean age (SD), years:** 62 (9) **History of CVD:** 649 (90%) **FH participants:** 0 Participants with hypercholesterolaemia (not defined) and established CHD or CHD risk equivalents (ischaemic stroke, peripheral artery disease, moderate chronic kidney disease, or diabetes mellitus plus ≥ 2 additional risk factors) and on a maximally tolerated dose of statin, without addition of other LLTs
Interventions	**Background therapy:** add-on to maximal tolerated dose of statin **Randomised therapy:** alirocumab and ezetimibe placebo vs ezetimibe 10 mg daily and placebo **Alirocumab:** 104 weeks of 75 mg every 2 weeks, with uptitration to 150 mg every 2 weeks at week 12, resulting in a 2-week equivalent dose of 75–150 mg
Outcomes	CVD, all-cause mortality
Notes	• LDL-C calculated using Friedewald formula, or if TGs exceeded 400 mg/dL via beta quantification method • NCT01644188 • Funded by Sanofi and Regeneron

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Used interactive voice-response system.
Allocation concealment (selection bias)	Low risk	Permuted blocks.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Both were blinded.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Clinical events committee and central laboratory.
Incomplete outcome data (attrition bias) All outcomes	Low risk	12 (2.51%) participants in the alirocumab arm had missing lipid measurements compared with 1 (0.41) in the comparator arm. Additionally, mixed-effects (ANCOVA) models were used.

ODYSSEY COMBO II *(Continued)*

Selective reporting (reporting bias)	Low risk	Reported protocol-defined endpoints.
Other bias	Low risk	No concerns outside the assessed risk of bias domains.

ODYSSEY DM-DYSLIPIDEMIA

Study characteristics	
Methods	**Type of RCT:** 1:2 parallel-group, open-label, stratified RCT **Settings:** outpatient care **Duration:** 24 weeks **Start and stop dates:** December 2015 and May 2018
Participants	**Number of participants:** 413 **Number lost to follow-up:** 4 **Women:** 197 (48%) **Mean age (SD), years:** 63.2 (9.1) **History of CVD:** 142 (34%) **FH participants:** NA People with T2DM and mixed dyslipidaemia at high CV risk with non-HDL-C not adequately controlled with maximally tolerated statin therapy. Inclusion criteria • Aged ≥ 18 years or legal age of majority at screening visit, whichever greater • Atherosclerotic CVD (including CHD, documented PAD or previous ischaemic stroke) or ≥ 1 additional CV risk factor, or a combination • Stable antihyperglycaemic treatment (including insulin) • Stable, maximally tolerated dose/regimen of statin for ≥ 4 weeks prior to screening without other LLT • Non-HDL-C ≥ 100 mg/dL (2.59 mmol/L) • TG ≥ 150 mg/dL and < 500 mg/dL • No weight variation > 5 kg within 3 months Exclusion criteria • HbA1c ≥ 9% • Use of any LLT (other than statin) or over-the-counter product/nutraceuticals known to impact lipids within 4 weeks prior to screening • BMI > 45 kg/m^2 • Alcohol consumption > 2 standard alcoholic drinks/day
Interventions	**Background therapy:** usual care (including maximally tolerated statins or non-statin therapies) **Randomised therapy:** alirocumab + usual care vs usual care only **Alirocumab dose:** 75–150 mg per 2 weeks
Outcomes	T2DM, all-cause mortality

ODYSSEY DM-DYSLIPIDEMIA *(Continued)*

Notes	Funded by Sanofi and Regeneron

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Centralised treatment allocation system (interactive voice- or web-response system, depending on the study site preference).
Allocation concealment (selection bias)	Low risk	Central allocation.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants not blinded.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Endpoint adjudication blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	4/413 participants lost to follow-up.
Selective reporting (reporting bias)	Low risk	Reported usual endpoints.
Other bias	Low risk	No concerns outside the assessed risk of bias domains.

ODYSSEY DM-INSULIN

Study characteristics

Methods	**Type of RCT:** 1:2 parallel-group, stratified RCT **Settings:** outpatient care **Duration:** 24 weeks **Start and stop dates:** October 2015 and May 2018
Participants	**Number of participants:** 517 **Number lost to follow-up:** 14 **Women:** 232 (45%) **Mean age (SD), years:** 63.7 (9.1) **History of CVD:** 193 (37%) **FH participants:** NA Study population comprised people with insulin-treated T2DM or type 1 diabetes and established atherosclerotic CVD or ≥ 1 additional CV risk factor (or a combination), who had LDL-C ≥ 1.8 mmol/L (≥ 70 mg/dL) despite stable maximally tolerated doses of statin with or without other LLTs. People with statin intolerance (therefore not taking statins) were also eligible for enrolment.

ODYSSEY DM-INSULIN *(Continued)*

Interventions	**Background therapy:** stable diet for glucose and lipid management, and received treatment for diabetes in accordance with local/regional SOC **Randomised therapy:** alirocumab vs placebo **Alirocumab dose:** 75–150 mg per 2 weeks
Outcomes	All-cause mortality
Notes	Funded by Sanofi and Regeneron

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "At randomization, treatment kit numbers were allocated according to a centralized treatment allocation system (either an interactive voice-response or web-response system, depending on the study site)."
Allocation concealment (selection bias)	Low risk	Placebo controlled.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Study participants, principal investigators and study-site personnel are blinded to all randomization assignments throughout the duration of the study."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Independent committee.
Incomplete outcome data (attrition bias) All outcomes	Low risk	14/517 participants lost to follow-up.
Selective reporting (reporting bias)	Low risk	Reported usual endpoints.
Other bias	Low risk	No concerns outside the assessed risk of bias domains.

ODYSSEY FH I

Study characteristics

Methods	**Type of RCT:** 2:1 parallel-group, double-blind, stratified RCT **Settings:** outpatient care **Duration:** 78 weeks **Start and stop dates:** July 2012 and December 2014
Participants	**Number of participants:** 486 **Number lost to follow-up:** 1 **Women:** 212 (44%)

ODYSSEY FH I *(Continued)*

	Mean age (SD), years: 52 (13) **History of CVD:** 225 (46%) **Participants with FH:** 485 (100%) Participants with heFH on a maximally tolerated dose of statin with LDL-C ≥ 70 mg/dL or ≥ 100 mg/dL, depending on CV risk
Interventions	**Background therapy:** add-on to maximal tolerated dose of statin and possible addition of other LLTs **Randomised therapy:** alirocumab vs placebo **Alirocumab dose:** 78 weeks of 75 mg every 2 weeks, with possible uptitration to 150 mg every 2 weeks at week 12. Resulting in a 2-week equivalent dose of 75–150 mg
Outcomes	CVD, adverse events, all-cause mortality
Notes	• LDL-C calculated using Friedewald formula, or if TGs > 400 mg/dL via beta quantification method • NCT01623155 • Funded by Sanofi and Regeneron

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Centralised interactive voice-response system or interactive web-response system.
Allocation concealment (selection bias)	Low risk	Central allocation.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Both blinded.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Endpoint adjudication was blinded and central laboratory.
Incomplete outcome data (attrition bias) All outcomes	Low risk	1 (0.31%) participant in the alirocumab arm had missing lipid measurements compared with 0 in the comparator arm. Additionally, mixed-effects (ANCOVA) models were used.
Selective reporting (reporting bias)	Low risk	Reported protocol-defined endpoints.
Other bias	Low risk	No concerns outside the assessed risk of bias domains.

ODYSSEY FH II

Study characteristics

Methods	**Type of RCT:** 2:1 parallel-group, double-blind, stratified RCT **Settings:** outpatient care

ODYSSEY FH II *(Continued)*

	Duration: 52 weeks **Start and stop dates:** December 2012 and January 2015
Participants	**Number of participants:** 249 **Number lost to follow-up:** 2 **Women:** 118 (47%) **Mean age (SD), years:** 53.2 (17.2) **History of CVD:** 89 (36%) **Participants with FH:** 249 (100%) Participants with heFH not adequately controlled with a maximally tolerated daily dose of statin with or without the other LMT, at a stable dose before the screening visit
Interventions	**Background therapy:** add-on to maximal tolerated dose of statin and possible addition of other LLTs **Randomised therapy:** alirocumab vs placebo **Alirocumab dose:** 78 weeks 75 mg every 2 weeks, with possible uptitration to 150 mg every 2 weeks at week 12. Resulting in a 2-week equivalent dose of 75–150 mg
Outcomes	CVD, adverse events, all-cause mortality
Notes	• LDL-C calculated using Friedewald formula, or if TGs > 400 mg/dL via beta quantification method • NCT01709500 • Subgroup analyses are provided for FH I and FH II combined • Funded by Sanofi and Regeneron

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Centralised interactive voice-response system or interactive web-response system.
Allocation concealment (selection bias)	Low risk	Central allocation.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Both blinded.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Endpoint adjudication was blinded and central laboratory.
Incomplete outcome data (attrition bias) All outcomes	Low risk	1 (0.60%) portion of the alirocumab arm had missing lipid measurements compared with 1 (1.22%) participant in the comparator arm. Additionally, mixed-effects (ANCOVA) models were used.
Selective reporting (reporting bias)	Low risk	Reported protocol-defined endpoints.
Other bias	Low risk	No concerns outside the assessed risk of bias domains.

ODYSSEY HIGH FH

Study characteristics	
Methods	**Type of RCT:** 2:1 parallel-group, double-blind, stratified RCT **Settings:** outpatient care **Duration:** 78 weeks **Start and stop dates:** December 2012 and January 2015
Participants	**Number of participants:** 107 **Number lost to follow-up:** 1 **Women:** NA **Mean age (SD), years:** NA **History of CVD:** 64 (60%) **Participants with FH:** 107 (100%) Participants with heFH on a maximally tolerated dose of statin with LDL-C ≥ 160 mg/dL
Interventions	**Background therapy:** both add-on to maximal tolerated dose of statin and possible addition of other LLTs **Randomised therapy:** alirocumab vs placebo **Alirocumab dose:** 78 weeks of 150 mg every 2 weeks
Outcomes	CVD, adverse events, all-cause mortality
Notes	• LDL-C calculated using Friedewald formula • Reported influenza • Subgroup analyses are provided for FH I and FH II combined • NCT01617655 • Funded by Sanofi and Regeneron

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Centralised interactive voice-response system or interactive web-response system.
Allocation concealment (selection bias)	Low risk	Central allocation.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Both blinded.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Endpoint adjudication was blinded and central laboratory.

ODYSSEY HIGH FH *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	1 (1.38%) participant in the alirocumab arm had missing lipid measurements compared with 0 in the comparator arm. Additionally, mixed-effects (ANCOVA) models were used.
Selective reporting (reporting bias)	Low risk	Reported protocol-defined endpoints.
Other bias	Low risk	No concerns outside the assessed risk of bias domains.

ODYSSEY JAPAN

Study characteristics	
Methods	**Type of RCT:** 2:1 parallel-group, double-blind, stratified RCT **Settings:** outpatient care **Duration:** 52 weeks **Start and stop dates:** March 2014 and September 2015
Participants	**Number of participants:** 216 **Number lost to follow-up:** 1 patient excluded from the primary analysis **Women:** 85 (39%) **Mean age (SD), years:** 60.8 (9.5) **History of CVD:** 216 (100%) **Participants with FH:** NA People with heFH, non-FH at high CV risk with coronary disease, or classified as category III were enrolled.
Interventions	**Background therapy:** statin and other LLT **Randomised therapy:** alirocumab vs placebo **Alirocumab dose:** 75 mg every 2 weeks
Outcomes	CVD, all-cause mortality
Notes	Funded by Sanofi and Regeneron

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported.
Allocation concealment (selection bias)	Unclear risk	Not reported.

ODYSSEY JAPAN *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Placebo controlled.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Endpoint committee.
Incomplete outcome data (attrition bias) All outcomes	Low risk	1 patient was excluded from the primary analysis.
Selective reporting (reporting bias)	Low risk	Reported protocol-endpoints.
Other bias	Low risk	No concerns outside the assessed risk of bias domains.

ODYSSEY KT

Study characteristics	
Methods	**Type of RCT:** 1:1 parallel-group, double-blind, stratified RCT **Settings:** outpatient care **Duration:** 24 weeks **Start and stop dates:** November 2014 and June 2017
Participants	**Number of participants:** 199 **Number lost to follow-up:** 0 **Women:** 35 (18%) **Mean age (SD), years:** 61.1 (9.7) **History of CVD:** 191 (96%) **Participants with FH:** 0 Study enrolled people aged ≥ 18 years with high CV risk who had inadequately controlled hypercholesterolaemia on maximally tolerated statin therapy at a stable dose for ≥ 4 weeks before screening.
Interventions	**Background therapy:** add-on to maximal tolerated statin dose **Randomised therapy:** alirocumab vs placebo **Alirocumab dose:** 75–150 mg every 2 weeks
Outcomes	CVD, all-cause mortality
Notes	Funded by Sanofi and Regeneron

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

ODYSSEY KT *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Not reported, most of the previous ODYSSEY trials described an automated procedure.
Allocation concealment (selection bias)	Unclear risk	Not reported, most of the previous ODYSSEY trials described a sufficient concealment procedure.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported, describes itself as double-blind.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported, most of the previous ODYSSEY trials had an independent adjudication committee.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up.
Selective reporting (reporting bias)	Low risk	Reported common endpoints.
Other bias	Low risk	No concerns outside the assessed risk of bias domains.

ODYSSEY Long Term

Study characteristics	
Methods	**Type of RCT:** 2:1 parallel-group, double-blind RCT with stratified randomisation **Settings:** outpatient care **Duration:** 78 weeks **Start and stop dates:** January 2012 and November 2014
Participants	**Number of participants:** 2341 **Number lost to follow-up:** 247 **Women:** 884 (38%) **Mean age (SD), years:** 63 (11) **History of CVD:** 1607 (68%) **Participants with FH:** 415 (18%) Participants with heFH or established CHD or CHD risk equivalent
Interventions	**Background therapy:** SOC **Randomised therapy:** alirocumab vs placebo for 78 weeks **Alirocumab dose:** 150 mg every 2 weeks
Outcomes	CVD, adverse events, all-cause mortality
Notes	• Blood samples were obtained after a 10-hour overnight fast

ODYSSEY Long Term *(Continued)*

- Total cholesterol, TGs, and HDL-C levels in serum were determined via CDC, National Heart Lung Blood Institute Lipid Standardization Program assays
- LDL-C calculated using Friedewald formula at all sampling points. LDL-C was also measured via ultracentrifugation and precipitation (beta-quantification) by the central laboratory at weeks 0, 12, 24, 52, and 78, and in cases where TG values were > 400 mg/dL
- ApoB, apolipoprotein A1, and lipoprotein(a) levels in serum were determined via immunonephelometry
- NCT01507831
- Funded by Sanofi and Regeneron

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Central computer-generated allocation system.
Allocation concealment (selection bias)	Low risk	Central computer-generated allocation system.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants and investigators were blinded with placebo identically packaged as alirocumab.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Biomarkers assessed at a central laboratory blinded for allocation. Clinical endpoints and adverse advents were similarly assessed in a blinded method.
Incomplete outcome data (attrition bias) All outcomes	High risk	ITT analysis excluded participants (167 (10.8%) in the intervention arm and 80 (10.1%) in the control arm) who missed LDL-C measurements during first 24 weeks. In total, 437 alirocumab participants did not complete study follow-up compared with 193 placebo participants. Categorical outcomes were analysed using an available-case analysis. Missing biomarker values were imputed using mixed models or multiple imputations.
Selective reporting (reporting bias)	Low risk	Reported protocol-defined endpoints.
Other bias	Low risk	No concerns outside the assessed risk of bias domains.

ODYSSEY MONO

Study characteristics

Methods	**Type of RCT:** 1:1 parallel-group, double-blind RCT **Settings:** outpatient care **Duration:** 24 weeks **Start and stop dates:** July 2012 and July 2013
Participants	**Number of participants:** 103 **Number lost to follow-up:** 0

ODYSSEY MONO *(Continued)*

	Women: 48 (47%) **Mean age (SD), years:** 60 (5) **History of CVD:** 103 (100%) **Participants with FH:** 0 Participants with 10-year risk of fatal CV events between 1% and < 5%
Interventions	**Background therapy:** National Cholesterol Education Program Adult Treatment Panel III therapeutic lifestyle changes diet **Randomised therapy:** alirocumab and placebo ezetimibe daily vs ezetimibe 10 mg daily plus alirocumab biweekly placebo **Alirocumab dose:** 24 weeks 75 mg every 2 weeks, at 12 weeks LDL-C-dependent uptitration occurred to 150 mg biweekly. Resulting in a 2-week equivalent dose of 75–150 mg
Outcomes	CVD, adverse events
Notes	• LDL-C calculated using Friedewald formula • NCT01644474 • Funded by Sanofi and Regeneron

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported.
Allocation concealment (selection bias)	Low risk	Permuted-block design.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants were blinded for treatment allocation and self-administered treatments.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Endpoint adjudication was blinded and central laboratory.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants were available at 24 weeks of follow-up.
Selective reporting (reporting bias)	Low risk	Reported protocol-defined endpoints.
Other bias	Low risk	No concerns outside the assessed risk of bias domains.

ODYSSEY OPTIONS I

Study characteristics

ODYSSEY OPTIONS I *(Continued)*

Methods	**Type of RCT:** 2:1 parallel-group, double-blind, stratified, permuted-block designed RCT **Settings:** outpatient care **Duration:** 24 weeks **Start and stop dates:** NA
Participants	**Number of participants:** 355 **Number lost to follow-up:** 10 **Women:** 124 (35%) **Mean age (SD), years:** 63 (10) **History of CVD:** 200 (56%) **FH participants:** 31 (9%) Participants with history of CVD and LDL-C levels ≥ 70 mg/dL, or CVD risk factors and LDL-C ≥ 100 mg/dL
Interventions	**Background therapy:** 24 weeks 20 mg or 40 mg of baseline atorvastatin and National Cholesterol Education Program Adult Treatment Panel III **Randomised therapy:** alirocumab vs ezetimibe 10 mg/day, or atorvastatin 20 mg or 40 mg, or atorvastatin 40 mg regimen only, switch to rosuvastatin 40 mg **Alirocumab dose:** 75 mg every 2 weeks, with uptitration to 150 mg at week 12. Resulting in a 2-week equivalent dose of 75–150 mg Resulting in 7 groups • atorvastatin 20 mg plus alirocumab 75 mg every 2 weeks • atorvastatin 20 mg plus ezetimibe 10 mg every day • atorvastatin 20 mg plus atorvastatin 20 mg every day • atorvastatin 40 mg plus alirocumab 75 mg every 2 weeks • atorvastatin 40 mg plus ezetimibe 10 mg every day • atorvastatin 40 mg plus atorvastatin 40 mg every day • rosuvastatin 40 mg All blinded with placebo alirocumab and over-encapsulated tables for ezetimibe, atorvastatin, and rosuvastatin
Outcomes	CVD, adverse events, all-cause mortality
Notes	• Unless otherwise specified, comparisons are made of alirocumab therapy vs pooled other therapies • Fasting blood samples were collected in the morning • LDL-C calculated using Friedewald formula • Lipoprotein(a) was analysed using an immunoradiometric assay on the Siemens BNII • NCT01730040 • Funded by Sanofi and Regeneron
Risk of bias	

Bias	Authors' judgement	Support for judgement

ODYSSEY OPTIONS I *(Continued)*

Random sequence generation (selection bias)	Low risk	Centralised interactive voice-response system or interactive web-response system.
Allocation concealment (selection bias)	Low risk	Permuted-block design and central allocation.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Both blinded.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Endpoint adjudication was blinded and central laboratory.
Incomplete outcome data (attrition bias) All outcomes	Low risk	4 (3.85%) participants in the alirocumab arm had missing lipids measurements compared with 6 (2.39%) in the comparator arm. Additionally, mixed-effects (ANCOVA) models were used.
Selective reporting (reporting bias)	Low risk	Reported protocol-defined endpoints.
Other bias	Low risk	No concerns outside the assessed risk of bias domains.

ODYSSEY OPTIONS II

Study characteristics	
Methods	**Type of RCT:** double-blind, placebo-controlled, parallel-group RCT **Settings:** outpatient care **Duration:** 24 weeks **Start and stop dates:** NA
Participants	**Number of participants:** 305 **Number lost to follow-up:** 7 **Women:** 118 (39%) **Mean age (SD), years:** 61 (10) **History of CVD:** 177 (58%) **Participants with FH:** 41 (13%) Participants with history of CVD and LDL-C levels ≥ 70 mg/dL, or CVD risk factors and LDL-C ≥ 100 mg/dL
Interventions	**Background therapy:** participants received 24 weeks baseline rosuvastatin 10 mg or 20 mg and National Cholesterol Education Program Adult Treatment Panel III **Randomised therapy:** alirocumab vs add-on ezetimibe 10 mg/day, or additional rosuvastatin 10 mg or 20 mg **Alirocumab dose:** add-on of 75 mg every 2 weeks, with uptitration to 150 mg at week 12. Resulting in a 2-week equivalent dose of 75–150 mg

ODYSSEY OPTIONS II *(Continued)*

	Resulting in 6 groups • rosuvastatin 10 mg plus alirocumab 75 mg every 2 weeks • rosuvastatin 10 mg plus ezetimibe 10 mg every day • rosuvastatin 10 mg plus rosuvastatin 10 mg every day • rosuvastatin 20 mg plus alirocumab 75 mg every 2 weeks • rosuvastatin 20 mg plus ezetimibe every day • rosuvastatin 20 mg plus rosuvastatin 20 mg every day All blinded with placebo alirocumab and overencapsulated tables for ezetimibe, rosuvastatin
Outcomes	CVD, any adverse events, all-cause mortality
Notes	• Unless otherwise specified, comparisons were made of alirocumab therapy vs pooled other therapies • Fasting blood samples were collected in the morning • LDL-C calculated using Friedewald formula • Lipoprotein(a) was analysed using an immunoradiometric assay on the Siemens BNII • NCT01730053 • Funded by Sanofi and Regeneron

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Centralised interactive voice-response system or interactive web-response system.
Allocation concealment (selection bias)	Low risk	Permuted-block design and central allocation.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Both blinded.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Endpoint adjudication was blinded and central laboratory.
Incomplete outcome data (attrition bias) All outcomes	Low risk	2 (1.94%) participants in the alirocumab arm had missing lipid measurements compared with 5 (2.48%) in the comparator arms. Additionally, mixed-effects (ANCOVA) models were used.
Selective reporting (reporting bias)	Low risk	Reported protocol-defined endpoints.
Other bias	Low risk	No concerns outside the assessed risk of bias domains.

ODYSSEY OUTCOMES

Study characteristics

Methods	**Type of RCT:** 1:1 double-blind, stratified, placebo-controlled, parallel-group RCT (with run-in phase) **Settings:** outpatient care

ODYSSEY OUTCOMES *(Continued)*

	Duration: median follow-up 2.8 years **Start and stop dates:** August 2012 and January 2018
Participants	**Number of participants:** 18,924 **Number lost to follow-up:** 86 **Women:** 4762 (25%) **Mean age (SD), years:** 59 (9) **History of CVD:** 0 **Participants with FH:** NA People aged ≥ 40 years had been hospitalised with an acute coronary syndrome (myocardial infarction or unstable angina) 1–12 months before randomisation, and had LDL-C ≥ 70 mg/dL (1.8 mmol/L), non-HDL-C ≥ 100 mg/dL, or ApoB level ≥ 80 mg/dL
Interventions	**Background therapy:** minimum of 2 weeks of stable treatment with atorvastatin 40–80 mg once daily, rosuvastatin 20–40 mg once daily, or maximum tolerated dose of 1 of these statins (including no statin in the case of documented unacceptable adverse effects) **Randomised therapy:** alirocumab vs placebo **Alirocumab dose:** 75 mg every 2 weeks followed by blinded, lipid-guided adjustment.
Outcomes	CVD, defined as a composite of: death from CHD, non-fatal myocardial infarction, unstable angina requiring hospitalisation, and ischaemia-driven coronary revascularisation
Notes	Funded by Sanofi and Regeneron

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Centralised treatment allocation system. Quote: "the Interactive Voice Response System (IVRS) and the Interactive Web Response System (IWRS) depending on the choice of the site."
Allocation concealment (selection bias)	Low risk	Placebo controlled.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "The trial-group assignments and lipid levels during the trial were concealed from the patients and investigators."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Independent Clinical Events Committee
Incomplete outcome data (attrition bias) All outcomes	Low risk	86/18,924 participants lost to follow-up.
Selective reporting (reporting bias)	Low risk	Reported protocol-defined endpoints.

ODYSSEY OUTCOMES *(Continued)*

Other bias	Low risk	No concerns outside the assessed risk of bias domains.

OSLER-1

Study characteristics	
Methods	**Type of RCT:** 1:2 parallel-group, open-label stratified trial **Settings:** outpatient care **Duration:** 52 weeks **Start and stop dates:** October 2011 and July 2018 (including single-arm extension)
Participants	**Number of participants:** 1104 **Number lost to follow-up:** 169 **Women:** 610 (55%) **Mean age (SD), years:** 56 (12) **History of CVD:** 210 (19%) **FH participants:** 414 (38%) Participants with and without a history of CVD or FH; all were previously enrolled in phase 2 PCSK9 inhibitor trials and completed these trials without serious adverse events
Interventions	**Background therapy:** SOC **Randomised therapy:** evolocumab vs SOC for 52 weeks **Evolocumab dose:** 420 mg every 4 weeks, resulting in a 2-week equivalent dose of 210 mg
Outcomes	CVD, adverse events, all-cause mortality
Notes	• Plasma lipids, ApoA1, ApoB, and lipoprotein(a) were measured after a fast ≥ 9 hours • LDL-C values based on the preparative ultracentrifugation method • Lipoprotein(a) assay type: Polymedco Cortlandt Manor, NY, on the Olympus Analyzer • NCT01439880 • Funded by Amgen

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomisation performed centrally using an interactive voice-response or web-response system.
Allocation concealment (selection bias)	Low risk	Central allocation.
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding. Lack of blinding will likely cause a change in adherence or in participants regarding SOC/lifestyle (or both) that may have influenced outcomes.

OSLER-1 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	High risk	Outcomes such as adverse events may be biased owing to detection bias.
Incomplete outcome data (attrition bias) All outcomes	High risk	At week 52, 73/368 (19.83%) of SOC arm dropped out, and 96/736 (13.04%) of intervention arm dropped out. No mention of how missing data were handled.
Selective reporting (reporting bias)	Low risk	Reported protocol-defined endpoints.
Other bias	Low risk	No concerns outside the assessed risk of bias domains.

OSLER-2

Study characteristics	
Methods	**Type of RCT:** 1:2 parallel-group, open-label stratified trial **Settings:** outpatient care **Duration:** 2 years **Start and stop dates:** April 2014 and June 2018 (including single-arm extension)
Participants	**Number of participants:** 3681 **Number lost to follow-up:** 169 **Women:** 1736 (47%) **Mean age (SD), years:** 59 (11) **History of CVD:** NA **FH participants:** NA Participants with and without a history of CVD or FH; all were previously enrolled in phase 2 PCSK9 inhibitor trials and completed these trials without serious adverse events
Interventions	**Background therapy:** SOC **Randomised therapy:** evolocumab vs SOC **Evolocumab dose:** 420 mg every 4 weeks or 140 mg every 2 weeks
Outcomes	CVD, adverse events, all-cause mortality
Notes	Funded by Amgen

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was performed centrally using an interactive voice-response or web-response system.

OSLER-2 *(Continued)*

Allocation concealment (selection bias)	Low risk	Central allocation.
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding.
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear.
Selective reporting (reporting bias)	Low risk	Traditional endpoints.
Other bias	Low risk	No concerns outside the assessed risk of bias domains.

Sugizaki 2019

Study characteristics	
Methods	**Type of RCT:** 1:1 parallel-group trial **Settings:** outpatient care **Duration:** NA **Start and stop dates:** NA
Participants	**Number of participants:** 24 **Number lost to follow-up:** NA **Women:** NA **Mean age (SD), years:** NA **History of CVD:** NA **FH participants:** NA People with thin-cap fibroatheroma
Interventions	**Background therapy:** SOC **Randomised therapy:** alirocumab vs rosuvastatin 10 mg/day **Evolocumab dose:** 75 mg/2 weeks
Outcomes	Did not report on outcomes relevant for this study.
Notes	Only available in abstract form.
Risk of bias	

Sugizaki 2019 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Only available in abstract form; insufficient detail on randomisation method.
Allocation concealment (selection bias)	Unclear risk	Only available in abstract form; insufficient detail on randomisation method.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Judged on the abstract, it seems the study did not use placebo to conceal allocated treatment.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Only available in abstract form; insufficient detail on blinding method.
Incomplete outcome data (attrition bias) All outcomes	Low risk	The scatter dots plot of 36 measurements added up to 24 (to total number of allocated participants).
Selective reporting (reporting bias)	High risk	The abstract only reported on plaque-related outcomes. Full report might report more.
Other bias	Low risk	No concerns outside the assessed risk of bias domains.

ANCOVA: analysis of covariance; ApoB: apolipoprotein B; BMI: body mass index; CABG: coronary artery bypass graft; CDC: Centers for Disease Control and Prevention; CHD: coronary heart disease; CV: cardiovascular; CVD: cardiovascular disease; FH: familial hypercholesterolaemia; HbA1c: glycosylated haemoglobin; HDL-C: high-density lipoprotein cholesterol; heFH: heterozygous familial hypercholesterolaemia; hs-CRP: high-sensitivity C-reactive protein; ITT: intention-to-treat; IVUS: intravascular ultrasound; LDL-C: low-density lipoprotein cholesterol; LLT: lipid-lowering therapy; LMT: lipid modifying treatments; PAD: peripheral artery disease; MACE: major adverse cardiac events; NA: not available; NYHA: New York Heart Association; RCT: randomised controlled trial; SD: standard deviation; SOC: standard of care; T2DM: type 2 diabetes mellitus; TG: triglycerides; TSH: thyroid-stimulating hormone; TIA: transient ischaemic attack; ULN: upper limit of normal.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
ANITSCHKOW	Follow-up time too short.
Ballantyne 2015	Terminated PCSK9 monoclonal antibodies.
Baruch 2013	Follow-up time too short.
Cho 2014	Follow-up time too short.
Desai 2014	Follow-up time too short.
Dias 2012	Follow-up time too short.
Dufour 2012	Meta-analysis without separate results.
EBBINGHAUS	Subset of the included FOURIER trial.

Study	Reason for exclusion
EQUATOR	Terminated PCSK9 monoclonal antibodies.
Gaudet 2012	Meta-analysis of 3 studies without separate results.
Gaudet 2013	Meta-analysis of 3 studies without separate results.
Gumbiner 2012	Follow-up time too short.
Habibinejad 2016	No relevant data.
HAUSER-RCT	Enrolled children.
Hopkins 2013	Follow-up time too short.
Jones 2015	Meta-analysis of 4 studies without separate results.
Kastelein 2015	Follow-up time too short.
Kawashiri 2012	No randomisation to PCSK9 inhibitor.
Mabuchi 2015	No empirical results.
Maxwell 2012	No empirical results.
Mearns 2014	No empirical results.
Pordy 2013	Dose-response modelling.
Raal 2014a	Meta-analysis without separate results.
Raal 2014b	Follow-up time too short.
Shaywitz 2012	Follow-up time too short.
SPIRE 1/2	Terminated PCSK9 monoclonal antibodies.
SPIRE biomarker trials	Terminated PCSK9 monoclonal antibodies.
Stawowy 2014	Follow-up time too short.
Stein 2012	This reference published on a subset of the data included in OSLER-1.
Stein 2013	Follow-up time too short.
Swergold 2010	Follow-up time too short.
Swergold 2011	Follow-up time too short.
TAUSSIG	Enrolled children.
Wan 2013	Follow-up time too short.

Characteristics of ongoing studies *[ordered by study ID]*

ALTAIR

Study name	ALTAIR
Methods	Phase IV, open-label, randomised, parallel-group, single-centre study
Participants	Japanese adults hospitalised for PCI and having suboptimal control of LDL-C levels (> 70 mg/dL) despite statin therapy.
Interventions	Alirocumab 75 mg every 2 weeks added to rosuvastatin 10 mg/day Rosuvastatin 10 mg/day, with initiation or dose adjustment (or both) of non-statin lipid-lowering to achieve an LDL-C target of < 70 mg/dL
Outcomes	
Starting date	NA
Contact information	NA
Notes	

EVOLVD

Study name	Cholesterol lowering with EVOLocumab to prevent cardiac allograft vasculopathy in de-novo heart transplant recipients (EVOLVD)
Methods	Parallel arm RCT
Participants	De novo heart transplant recipients
Interventions	Evolocumab Placebo
Outcomes	
Starting date	November 2018
Contact information	
Notes	

NCT02833844

Study name	Double-blind, randomised, placebo-controlled, multicentre study to evaluate safety, tolerability, and efficacy on LDL-C of evolocumab (AMG 145) in subjects with HIV and with hyperlipidaemia or mixed dyslipidaemia, or both
Methods	Parallel RCT
Participants	HIV-positive participants with hyperlipidaemia or mixed dyslipidaemia (timeframe: week 24)

NCT02833844 *(Continued)*

Interventions	Evolocumab Placebo
Outcomes	Percent change from baseline in LDL-C
Starting date	June 2016
Contact information	
Notes	Amgen

UMIN000034592

Study name	NA
Methods	NA
Participants	NA
Interventions	NA
Outcomes	NA
Starting date	26 October 2018
Contact information	
Notes	upload.umin.ac.jp/cgi-open-bin/ctr_e/ctr_view.cgi?recptno=R000039437 Comparative clinical study of alilocumab (Praluent) and evorocumab (Repatha) for dyslipidaemia

LDL-C: low-density lipoprotein cholesterol; NA: not available; PCI: percutaneous coronary intervention; RCT: randomised controlled trial.

DATA AND ANALYSES

Comparison 1. Alirocumab versus placebo

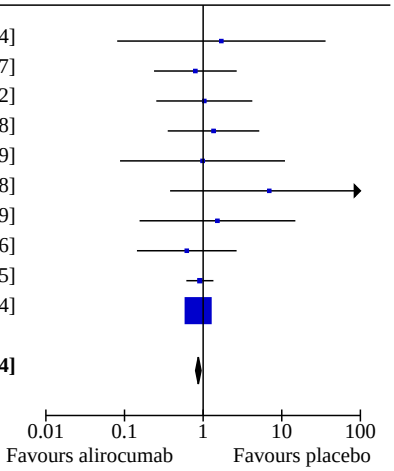
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Any cardiovascular disease	10	23868	Odds Ratio (IV, Fixed, 95% CI)	0.87 [0.80, 0.94]
1.2 All-cause mortality	12	24797	Odds Ratio (IV, Fixed, 95% CI)	0.83 [0.72, 0.96]
1.3 Any myocardial infarction	9	23352	Odds Ratio (IV, Fixed, 95% CI)	0.86 [0.79, 0.94]
1.4 Any stroke	8	22835	Odds Ratio (IV, Fixed, 95% CI)	0.73 [0.58, 0.91]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.5 Influenza	11	23964	Odds Ratio (IV, Fixed, 95% CI)	1.09 [0.83, 1.42]
1.6 Type 2 diabetes mellitus	6	22306	Odds Ratio (IV, Fixed, 95% CI)	0.96 [0.86, 1.07]
1.7 Any cancer	6	3806	Odds Ratio (IV, Fixed, 95% CI)	0.88 [0.61, 1.26]
1.8 Hypertension	10	24347	Odds Ratio (IV, Fixed, 95% CI)	0.92 [0.72, 1.18]

Analysis 1.1. Comparison 1: Alirocumab versus placebo, Outcome 1: Any cardiovascular disease

	Alirocumab		Placebo			Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
ODYSSEY CHOICE II	2	173	0	58	0.1%	1.71 [0.08 , 36.04]	
ODYSSEY CHOICE I	8	573	4	229	0.4%	0.80 [0.24 , 2.67]	
ODYSSEY COMBO I	6	207	3	107	0.3%	1.03 [0.25 , 4.22]	
ODYSSEY FH I	8	323	3	163	0.3%	1.35 [0.35 , 5.18]	
ODYSSEY FH II	2	167	1	82	0.1%	0.98 [0.09 , 10.99]	
ODYSSEY HIGH FH	6	72	0	35	0.1%	6.94 [0.38 , 126.78]	
ODYSSEY JAPAN	3	143	1	72	0.1%	1.52 [0.16 , 14.89]	
ODYSSEY KT	3	97	5	102	0.3%	0.62 [0.14 , 2.66]	
ODYSSEY Long Term	72	1553	40	788	3.9%	0.91 [0.61 , 1.35]	
ODYSSEY OUTCOMES	1301	9462	1474	9462	94.4%	0.86 [0.80 , 0.94]	
Total (95% CI)		**12770**		**11098**	**100.0%**	**0.87 [0.80 , 0.94]**	
Total events:	1411		1531				

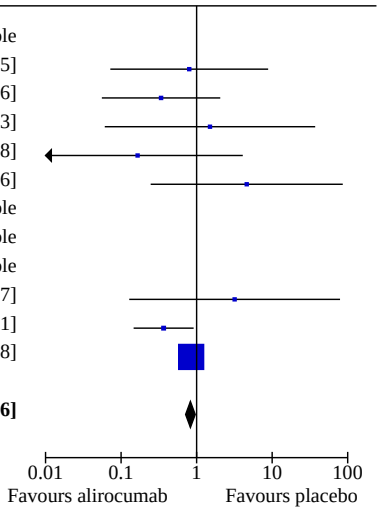
Heterogeneity: Chi² = 3.17, df = 9 (P = 0.96); I² = 0%
Test for overall effect: Z = 3.52 (P = 0.0004)
Test for subgroup differences: Not applicable



Analysis 1.2. Comparison 1: Alirocumab versus placebo, Outcome 2: All-cause mortality

Study or Subgroup	Alirocumab Events	Alirocumab Total	Placebo Events	Placebo Total	Weight	Odds Ratio IV, Fixed, 95% CI
ODYSSEY CHOICE II	0	173	0	58		Not estimable
ODYSSEY CHOICE I	2	573	1	229	0.4%	0.80 [0.07 , 8.85]
ODYSSEY COMBO I	2	207	3	107	0.6%	0.34 [0.06 , 2.06]
ODYSSEY DM-DYSLIPIDEMIA	1	275	0	137	0.2%	1.50 [0.06 , 37.13]
ODYSSEY DM-INSULIN	0	345	1	172	0.2%	0.17 [0.01 , 4.08]
ODYSSEY FH I	4	323	0	163	0.2%	4.61 [0.25 , 86.06]
ODYSSEY FH II	0	167	0	82		Not estimable
ODYSSEY HIGH FH	0	72	0	35		Not estimable
ODYSSEY JAPAN	0	143	0	72		Not estimable
ODYSSEY KT	1	97	0	102	0.2%	3.19 [0.13 , 79.17]
ODYSSEY Long Term	8	1553	11	788	2.5%	0.37 [0.15 , 0.91]
ODYSSEY OUTCOMES	334	9462	392	9462	95.6%	0.85 [0.73 , 0.98]
Total (95% CI)		**13390**		**11407**	**100.0%**	**0.83 [0.72 , 0.96]**
Total events:	352		408			

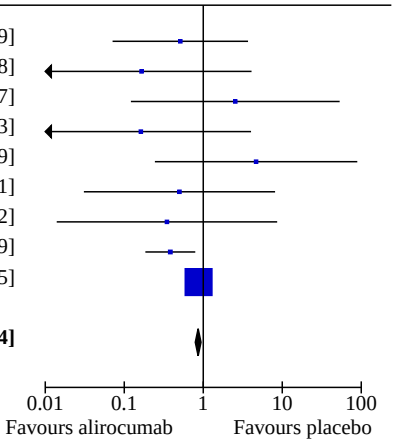
Heterogeneity: Chi² = 7.19, df = 7 (P = 0.41); I² = 3%
Test for overall effect: Z = 2.55 (P = 0.01)
Test for subgroup differences: Not applicable



Analysis 1.3. Comparison 1: Alirocumab versus placebo, Outcome 3: Any myocardial infarction

Study or Subgroup	Alirocumab Events	Alirocumab Total	Placebo Events	Placebo Total	Weight	Odds Ratio IV, Fixed, 95% CI
ODYSSEY COMBO I	2	207	2	107	0.2%	0.51 [0.07 , 3.69]
ODYSSEY DM-INSULIN	0	345	1	172	0.1%	0.17 [0.01 , 4.08]
ODYSSEY FH I	2	323	0	163	0.1%	2.54 [0.12 , 53.27]
ODYSSEY FH II	0	167	1	82	0.1%	0.16 [0.01 , 4.03]
ODYSSEY HIGH FH	4	72	0	35	0.1%	4.66 [0.24 , 89.09]
ODYSSEY JAPAN	1	143	1	72	0.1%	0.50 [0.03 , 8.11]
ODYSSEY KT	0	97	1	102	0.1%	0.35 [0.01 , 8.62]
ODYSSEY Long Term	13	1553	17	788	1.3%	0.38 [0.19 , 0.79]
ODYSSEY OUTCOMES	1199	9462	1349	9462	98.1%	0.87 [0.80 , 0.95]
Total (95% CI)		**12369**		**10983**	**100.0%**	**0.86 [0.79 , 0.94]**
Total events:	1221		1372			

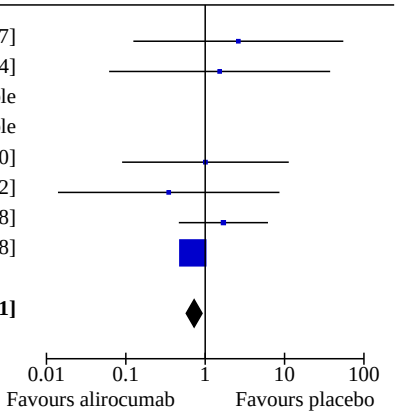
Heterogeneity: Chi² = 9.39, df = 8 (P = 0.31); I² = 15%
Test for overall effect: Z = 3.53 (P = 0.0004)
Test for subgroup differences: Not applicable



Analysis 1.4. Comparison 1: Alirocumab versus placebo, Outcome 4: Any stroke

Study or Subgroup	Alirocumab Events	Alirocumab Total	Placebo Events	Placebo Total	Weight	Odds Ratio IV, Fixed, 95% CI
ODYSSEY COMBO I	2	207	0	107	0.6%	2.62 [0.12 , 54.97]
ODYSSEY FH I	1	323	0	163	0.5%	1.52 [0.06 , 37.54]
ODYSSEY FH II	0	167	0	82		Not estimable
ODYSSEY HIGH FH	0	72	0	35		Not estimable
ODYSSEY JAPAN	2	143	1	72	0.9%	1.01 [0.09 , 11.30]
ODYSSEY KT	0	97	1	102	0.5%	0.35 [0.01 , 8.62]
ODYSSEY Long Term	10	1553	3	788	3.1%	1.70 [0.47 , 6.18]
ODYSSEY OUTCOMES	120	9462	171	9462	94.4%	0.70 [0.55 , 0.88]
Total (95% CI)		**12024**		**10811**	**100.0%**	**0.73 [0.58 , 0.91]**
Total events:	135		176			

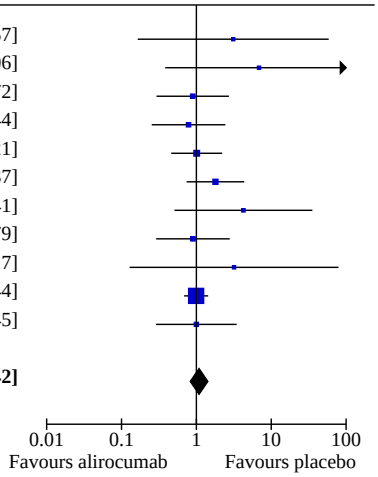
Heterogeneity: Chi² = 2.92, df = 5 (P = 0.71); I² = 0%
Test for overall effect: Z = 2.75 (P = 0.006)
Test for subgroup differences: Not applicable



Analysis 1.5. Comparison 1: Alirocumab versus placebo, Outcome 5: Influenza

Study or Subgroup	Alirocumab Events	Alirocumab Total	Placebo Events	Placebo Total	Weight	Odds Ratio IV, Fixed, 95% CI
ODYSSEY CHOICE II	4	173	0	58	0.8%	3.11 [0.16 , 58.57]
ODYSSEY COMBO I	6	209	0	107	0.9%	6.87 [0.38 , 123.06]
ODYSSEY DM-DYSLIPIDEMIA	9	275	5	137	5.9%	0.89 [0.29 , 2.72]
ODYSSEY DM-INSULIN	8	344	5	170	5.7%	0.79 [0.25 , 2.44]
ODYSSEY FH I	20	323	10	163	11.8%	1.01 [0.46 , 2.21]
ODYSSEY FH II	24	167	7	82	9.2%	1.80 [0.74 , 4.37]
ODYSSEY HIGH FH	8	72	1	35	1.6%	4.25 [0.51 , 35.41]
ODYSSEY JAPAN	9	143	5	72	5.7%	0.90 [0.29 , 2.79]
ODYSSEY KT	1	97	0	102	0.7%	3.19 [0.13 , 79.17]
ODYSSEY Long Term	88	1553	45	788	53.0%	0.99 [0.69 , 1.44]
ODYSSEY OUTCOMES	5	9451	5	9443	4.7%	1.00 [0.29 , 3.45]
Total (95% CI)		**12807**		**11157**	**100.0%**	**1.09 [0.83 , 1.42]**
Total events:	182		83			

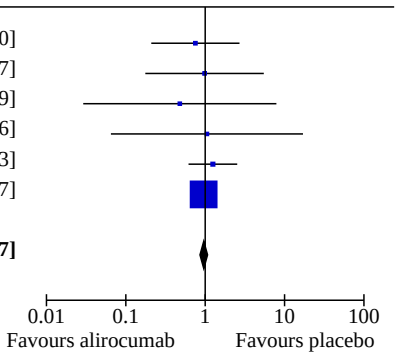
Heterogeneity: Chi² = 6.14, df = 10 (P = 0.80); I² = 0%
Test for overall effect: Z = 0.60 (P = 0.55)
Test for subgroup differences: Not applicable



Analysis 1.6. Comparison 1: Alirocumab versus placebo, Outcome 6: Type 2 diabetes mellitus

Study or Subgroup	Alirocumab Events	Alirocumab Total	Placebo Events	Placebo Total	Weight	Odds Ratio IV, Fixed, 95% CI
ODYSSEY FH I	6	323	4	163	0.7%	0.75 [0.21 , 2.70]
ODYSSEY FH II	4	167	2	82	0.4%	0.98 [0.18 , 5.47]
ODYSSEY HIGH FH	1	72	1	35	0.2%	0.48 [0.03 , 7.89]
ODYSSEY KT	1	97	1	102	0.2%	1.05 [0.06 , 17.06]
ODYSSEY Long Term	27	1553	11	788	2.4%	1.25 [0.62 , 2.53]
ODYSSEY OUTCOMES	648	9462	676	9462	96.1%	0.96 [0.85 , 1.07]
Total (95% CI)		**11674**		**10632**	**100.0%**	**0.96 [0.86 , 1.07]**
Total events:	687		695			

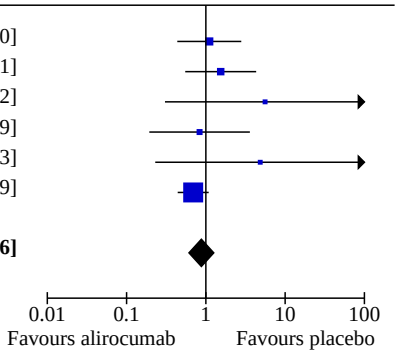
Heterogeneity: Chi² = 0.92, df = 5 (P = 0.97); I² = 0%
Test for overall effect: Z = 0.74 (P = 0.46)
Test for subgroup differences: Not applicable



Analysis 1.7. Comparison 1: Alirocumab versus placebo, Outcome 7: Any cancer

Study or Subgroup	Alirocumab Events	Alirocumab Total	Placebo Events	Placebo Total	Weight	Odds Ratio IV, Fixed, 95% CI
ODYSSEY COMBO I	15	209	7	107	15.0%	1.10 [0.44 , 2.80]
ODYSSEY FH I	15	323	5	163	12.2%	1.54 [0.55 , 4.31]
ODYSSEY FH II	5	167	0	82	1.5%	5.58 [0.31 , 102.22]
ODYSSEY JAPAN	5	143	3	72	6.1%	0.83 [0.19 , 3.59]
ODYSSEY KT	2	102	0	97	1.4%	4.85 [0.23 , 102.33]
ODYSSEY Long Term	47	1553	34	788	63.9%	0.69 [0.44 , 1.09]
Total (95% CI)		**2497**		**1309**	**100.0%**	**0.88 [0.61 , 1.26]**
Total events:	89		49			

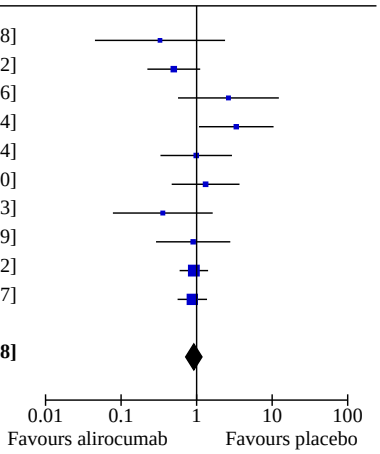
Heterogeneity: Chi² = 5.22, df = 5 (P = 0.39); I² = 4%
Test for overall effect: Z = 0.71 (P = 0.48)
Test for subgroup differences: Not applicable



Analysis 1.8. Comparison 1: Alirocumab versus placebo, Outcome 8: Hypertension

Study or Subgroup	Alirocumab Events	Alirocumab Total	Placebo Events	Placebo Total	Weight	Odds Ratio IV, Fixed, 95% CI
ODYSSEY CHOICE II	2	173	2	58	1.6%	0.33 [0.05 , 2.38]
ODYSSEY CHOICE I	14	573	11	230	9.5%	0.50 [0.22 , 1.12]
ODYSSEY COMBO I	10	209	2	107	2.6%	2.64 [0.57 , 12.26]
ODYSSEY DM-DYSLIPIDEMIA	8	137	5	275	4.8%	3.35 [1.07 , 10.44]
ODYSSEY DM-INSULIN	10	344	5	170	5.2%	0.99 [0.33 , 2.94]
ODYSSEY FH I	10	209	6	163	5.8%	1.31 [0.47 , 3.70]
ODYSSEY FH II	3	167	4	82	2.7%	0.36 [0.08 , 1.63]
ODYSSEY JAPAN	9	143	5	72	4.8%	0.90 [0.29 , 2.79]
ODYSSEY Long Term	60	1553	33	788	32.7%	0.92 [0.60 , 1.42]
ODYSSEY OUTCOMES	36	9451	41	9443	30.5%	0.88 [0.56 , 1.37]
Total (95% CI)		**12959**		**11388**	**100.0%**	**0.92 [0.72 , 1.18]**
Total events:	162		114			

Heterogeneity: Chi² = 12.04, df = 9 (P = 0.21); I² = 25%
Test for overall effect: Z = 0.68 (P = 0.50)
Test for subgroup differences: Not applicable



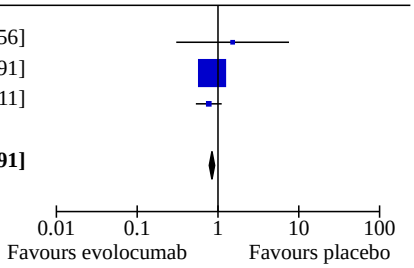
Comparison 2. Evolocumab versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Any cardiovascular disease	3	29432	Odds Ratio (IV, Fixed, 95% CI)	0.84 [0.78, 0.91]
2.2 All-cause mortality	3	29432	Odds Ratio (IV, Fixed, 95% CI)	1.04 [0.91, 1.19]
2.3 Any myocardial infarction	3	29432	Odds Ratio (IV, Fixed, 95% CI)	0.72 [0.64, 0.82]
2.4 Any stroke	2	28531	Odds Ratio (IV, Fixed, 95% CI)	0.79 [0.65, 0.94]
2.5 Influenza	1	901	Odds Ratio (IV, Fixed, 95% CI)	1.21 [0.69, 2.11]
2.6 Type 2 diabetes mellitus	3	29433	Odds Ratio (IV, Fixed, 95% CI)	1.05 [0.94, 1.17]

Analysis 2.1. Comparison 2: Evolocumab versus placebo, Outcome 1: Any cardiovascular disease

Study or Subgroup	Evolocumab Events	Evolocumab Total	Placebo Events	Placebo Total	Weight	Odds Ratio IV, Fixed, 95% CI
Descartes	6	599	2	302	0.2%	1.52 [0.30 , 7.56]
FOURIER	1344	13784	1563	13779	95.6%	0.84 [0.78 , 0.91]
GLAGOV	59	484	74	484	4.2%	0.77 [0.53 , 1.11]
Total (95% CI)		**14867**		**14565**	**100.0%**	**0.84 [0.78 , 0.91]**
Total events:	1409		1639			

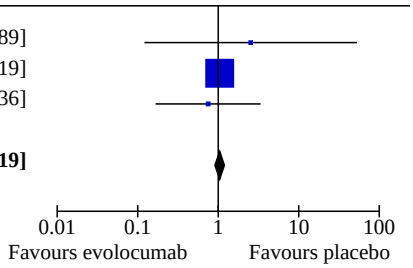
Heterogeneity: Chi² = 0.75, df = 2 (P = 0.69); I² = 0%
Test for overall effect: Z = 4.47 (P < 0.00001)
Test for subgroup differences: Not applicable



Analysis 2.2. Comparison 2: Evolocumab versus placebo, Outcome 2: All-cause mortality

Study or Subgroup	Evolocumab Events	Evolocumab Total	Placebo Events	Placebo Total	Weight	Odds Ratio IV, Fixed, 95% CI
Descartes	2	599	0	302	0.2%	2.53 [0.12 , 52.89]
FOURIER	444	13784	426	13779	99.0%	1.04 [0.91 , 1.19]
GLAGOV	3	484	4	484	0.8%	0.75 [0.17 , 3.36]
Total (95% CI)		**14867**		**14565**	**100.0%**	**1.04 [0.91 , 1.19]**
Total events:	449		430			

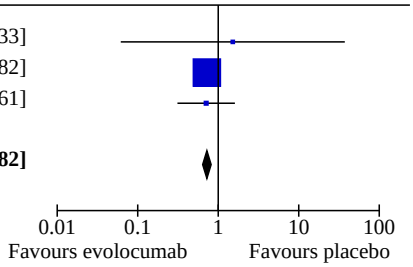
Heterogeneity: Chi² = 0.51, df = 2 (P = 0.77); I² = 0%
Test for overall effect: Z = 0.60 (P = 0.55)
Test for subgroup differences: Not applicable



Analysis 2.3. Comparison 2: Evolocumab versus placebo, Outcome 3: Any myocardial infarction

Study or Subgroup	Evolocumab Events	Evolocumab Total	Placebo Events	Placebo Total	Weight	Odds Ratio IV, Fixed, 95% CI
Descartes	1	599	0	302	0.1%	1.52 [0.06 , 37.33]
FOURIER	468	13784	639	13779	97.7%	0.72 [0.64 , 0.82]
GLAGOV	10	484	14	484	2.1%	0.71 [0.31 , 1.61]
Total (95% CI)		**14867**		**14565**	**100.0%**	**0.72 [0.64 , 0.82]**
Total events:	479		653			

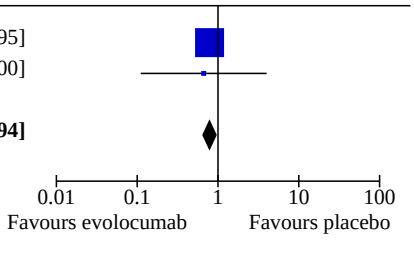
Heterogeneity: Chi² = 0.21, df = 2 (P = 0.90); I² = 0%
Test for overall effect: Z = 5.28 (P < 0.00001)
Test for subgroup differences: Not applicable



Analysis 2.4. Comparison 2: Evolocumab versus placebo, Outcome 4: Any stroke

Study or Subgroup	Evolocumab Events	Evolocumab Total	Placebo Events	Placebo Total	Weight	Odds Ratio IV, Fixed, 95% CI
FOURIER	207	13784	262	13779	99.0%	0.79 [0.65 , 0.95]
GLAGOV	2	484	3	484	1.0%	0.67 [0.11 , 4.00]
Total (95% CI)		**14268**		**14263**	**100.0%**	**0.79 [0.65 , 0.94]**
Total events:	209		265			

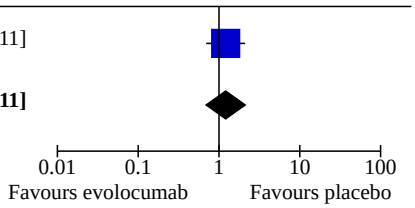
Heterogeneity: Chi² = 0.03, df = 1 (P = 0.86); I² = 0%
Test for overall effect: Z = 2.59 (P = 0.010)
Test for subgroup differences: Not applicable



Analysis 2.5. Comparison 2: Evolocumab versus placebo, Outcome 5: Influenza

Study or Subgroup	Evolocumab Events	Evolocumab Total	Placebo Events	Placebo Total	Weight	Odds Ratio IV, Fixed, 95% CI
Descartes	45	599	19	302	100.0%	1.21 [0.69 , 2.11]
Total (95% CI)		**599**		**302**	**100.0%**	**1.21 [0.69 , 2.11]**
Total events:	45		19			

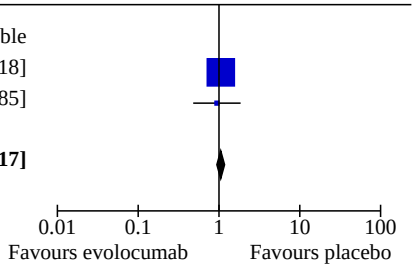
Heterogeneity: Not applicable
Test for overall effect: Z = 0.67 (P = 0.50)
Test for subgroup differences: Not applicable



Analysis 2.6. Comparison 2: Evolocumab versus placebo, Outcome 6: Type 2 diabetes mellitus

Study or Subgroup	Evolocumab Events	Evolocumab Total	Placebo Events	Placebo Total	Weight	Odds Ratio IV, Fixed, 95% CI
Descartes	0	599	0	302		Not estimable
FOURIER	677	13784	644	13780	97.4%	1.05 [0.94 , 1.18]
GLAGOV	17	484	18	484	2.6%	0.94 [0.48 , 1.85]
Total (95% CI)		**14867**		**14566**	**100.0%**	**1.05 [0.94 , 1.17]**
Total events:	694		662			

Heterogeneity: $Chi^2 = 0.10$, df = 1 (P = 0.75); $I^2 = 0\%$
Test for overall effect: Z = 0.89 (P = 0.38)
Test for subgroup differences: Not applicable



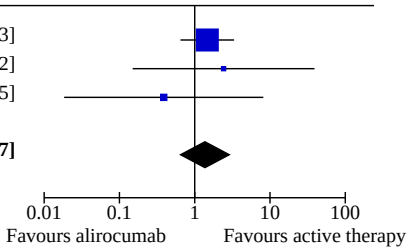
Comparison 3. Alirocumab versus active therapy

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Any cardiovascular disease	3	1379	Odds Ratio (M-H, Fixed, 95% CI)	1.37 [0.65, 2.87]
3.2 All-cause mortality	5	1733	Odds Ratio (IV, Fixed, 95% CI)	0.51 [0.18, 1.40]
3.3 Any myocardial infarction	5	1734	Odds Ratio (IV, Fixed, 95% CI)	1.45 [0.64, 3.28]
3.4 Any stroke	5	1734	Odds Ratio (M-H, Fixed, 95% CI)	0.85 [0.13, 5.61]
3.5 Influenza	4	1483	Odds Ratio (M-H, Fixed, 95% CI)	1.72 [0.91, 3.25]
3.6 Type 2 diabetes mellitus	2	660	Odds Ratio (IV, Fixed, 95% CI)	0.28 [0.05, 1.55]
3.7 Any cancer	1	720	Odds Ratio (M-H, Fixed, 95% CI)	1.08 [0.43, 2.69]
3.8 Hypertension	4	1630	Odds Ratio (IV, Fixed, 95% CI)	1.01 [0.57, 1.79]

Analysis 3.1. Comparison 3: Alirocumab versus active therapy, Outcome 1: Any cardiovascular disease

Study or Subgroup	Alirocumab Events	Alirocumab Total	Active therapy Events	Active therapy Total	Weight	Odds Ratio M-H, Fixed, 95% CI
ODYSSEY COMBO II	23	479	8	241	81.7%	1.47 [0.65 , 3.33]
ODYSSEY OPTIONS I	1	104	1	250	4.7%	2.42 [0.15 , 39.02]
ODYSSEY OPTIONS II	0	103	2	202	13.6%	0.39 [0.02 , 8.15]
Total (95% CI)		**686**		**693**	**100.0%**	**1.37 [0.65 , 2.87]**
Total events:	24		11			

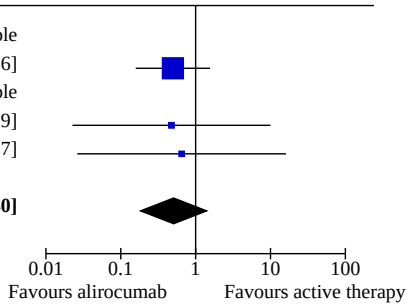
Heterogeneity: Chi² = 0.85, df = 2 (P = 0.65); I² = 0%
Test for overall effect: Z = 0.82 (P = 0.41)
Test for subgroup differences: Not applicable



Analysis 3.2. Comparison 3: Alirocumab versus active therapy, Outcome 2: All-cause mortality

Study or Subgroup	Alirocumab Events	Alirocumab Total	Active therapy Events	Active therapy Total	Weight	Odds Ratio IV, Fixed, 95% CI
ODYSSEY ALTERNATIVE	0	126	0	125		Not estimable
ODYSSEY COMBO II	6	479	6	241	78.9%	0.50 [0.16 , 1.56]
ODYSSEY MONO	0	52	0	51		Not estimable
ODYSSEY OPTIONS I	0	104	2	250	11.1%	0.48 [0.02 , 9.99]
ODYSSEY OPTIONS II	0	103	1	202	10.0%	0.65 [0.03 , 16.07]
Total (95% CI)		**864**		**869**	**100.0%**	**0.51 [0.18 , 1.40]**
Total events:	6		9			

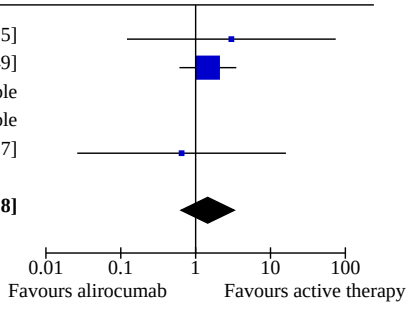
Heterogeneity: Chi² = 0.03, df = 2 (P = 0.99); I² = 0%
Test for overall effect: Z = 1.31 (P = 0.19)
Test for subgroup differences: Not applicable



Analysis 3.3. Comparison 3: Alirocumab versus active therapy, Outcome 3: Any myocardial infarction

Study or Subgroup	Alirocumab Events	Alirocumab Total	Active therapy Events	Active therapy Total	Weight	Odds Ratio IV, Fixed, 95% CI
ODYSSEY ALTERNATIVE	1	126	0	125	6.5%	3.00 [0.12 , 74.35]
ODYSSEY COMBO II	20	479	7	241	87.1%	1.46 [0.61 , 3.49]
ODYSSEY MONO	0	52	0	51		Not estimable
ODYSSEY OPTIONS I	0	104	0	251		Not estimable
ODYSSEY OPTIONS II	0	103	1	202	6.5%	0.65 [0.03 , 16.07]
Total (95% CI)		**864**		**870**	**100.0%**	**1.45 [0.64 , 3.28]**
Total events:	21		8			

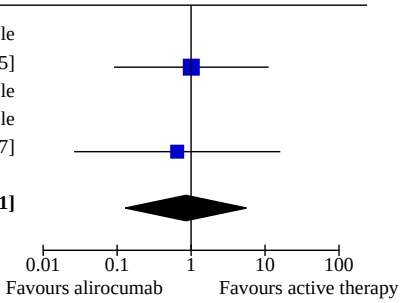
Heterogeneity: Chi² = 0.44, df = 2 (P = 0.80); I² = 0%
Test for overall effect: Z = 0.89 (P = 0.37)
Test for subgroup differences: Not applicable



Analysis 3.4. Comparison 3: Alirocumab versus active therapy, Outcome 4: Any stroke

Study or Subgroup	Alirocumab Events	Alirocumab Total	Active therapy Events	Active therapy Total	Weight	Odds Ratio M-H, Fixed, 95% CI
ODYSSEY ALTERNATIVE	0	126	0	125		Not estimable
ODYSSEY COMBO II	2	479	1	241	56.7%	1.01 [0.09 , 11.15]
ODYSSEY MONO	0	52	0	51		Not estimable
ODYSSEY OPTIONS I	0	104	0	251		Not estimable
ODYSSEY OPTIONS II	0	103	1	202	43.3%	0.65 [0.03 , 16.07]
Total (95% CI)		**864**		**870**	**100.0%**	**0.85 [0.13 , 5.61]**
Total events:	2		2			

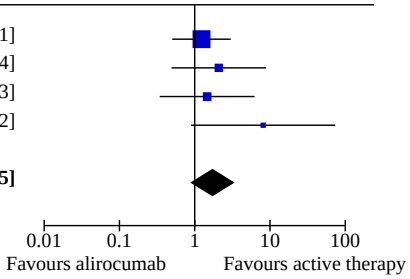
Heterogeneity: Chi² = 0.05, df = 1 (P = 0.83); I² = 0%
Test for overall effect: Z = 0.17 (P = 0.87)
Test for subgroup differences: Not applicable



Analysis 3.5. Comparison 3: Alirocumab versus active therapy, Outcome 5: Influenza

Study or Subgroup	Alirocumab Events	Alirocumab Total	Active therapy Events	Active therapy Total	Weight	Odds Ratio M-H, Fixed, 95% CI
ODYSSEY COMBO II	17	479	7	241	59.3%	1.23 [0.50 , 3.01]
ODYSSEY MONO	6	52	3	51	17.7%	2.09 [0.49 , 8.84]
ODYSSEY OPTIONS I	3	104	5	251	18.8%	1.46 [0.34 , 6.23]
ODYSSEY OPTIONS II	4	103	1	202	4.3%	8.12 [0.90 , 73.62]
Total (95% CI)		**738**		**745**	**100.0%**	**1.72 [0.91 , 3.25]**
Total events:	30		16			

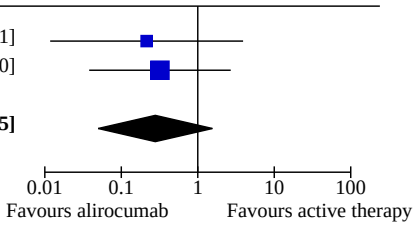
Heterogeneity: Chi² = 2.56, df = 3 (P = 0.46); I² = 0%
Test for overall effect: Z = 1.67 (P = 0.09)
Test for subgroup differences: Not applicable



Analysis 3.6. Comparison 3: Alirocumab versus active therapy, Outcome 6: Type 2 diabetes mellitus

Study or Subgroup	Alirocumab Events	Alirocumab Total	Active therapy Events	Active therapy Total	Weight	Odds Ratio IV, Fixed, 95% CI
ODYSSEY OPTIONS I	0	104	5	251	35.0%	0.21 [0.01 , 3.91]
ODYSSEY OPTIONS II	1	103	6	202	65.0%	0.32 [0.04 , 2.70]
Total (95% CI)		**207**		**453**	**100.0%**	**0.28 [0.05 , 1.55]**
Total events:	1		11			

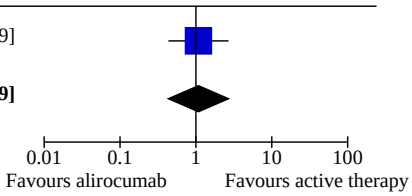
Heterogeneity: Chi² = 0.05, df = 1 (P = 0.83); I² = 0%
Test for overall effect: Z = 1.46 (P = 0.14)
Test for subgroup differences: Not applicable



Analysis 3.7. Comparison 3: Alirocumab versus active therapy, Outcome 7: Any cancer

Study or Subgroup	Alirocumab Events	Alirocumab Total	Active therapy Events	Active therapy Total	Weight	Odds Ratio M-H, Fixed, 95% CI
ODYSSEY COMBO II	15	479	7	241	100.0%	1.08 [0.43 , 2.69]
Total (95% CI)		**479**		**241**	**100.0%**	**1.08 [0.43 , 2.69]**
Total events:	15		7			

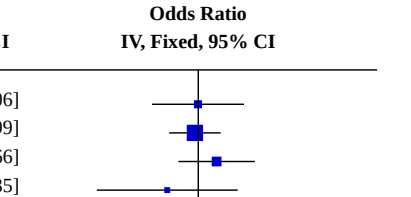
Heterogeneity: Not applicable
Test for overall effect: Z = 0.17 (P = 0.87)
Test for subgroup differences: Not applicable



Analysis 3.8. Comparison 3: Alirocumab versus active therapy, Outcome 8: Hypertension

Study or Subgroup	Alirocumab Events	Alirocumab Total	Active therapy Events	Active therapy Total	Weight	Odds Ratio IV, Fixed, 95% CI
ODYSSEY ALTERNATIVE	4	126	4	125	16.5%	0.99 [0.24 , 4.06]
ODYSSEY COMBO II	18	479	10	241	52.6%	0.90 [0.41 , 1.99]
ODYSSEY OPTIONS I	5	104	7	250	23.9%	1.75 [0.54 , 5.66]
ODYSSEY OPTIONS II	1	103	5	202	7.0%	0.39 [0.04 , 3.35]
Total (95% CI)		**812**		**818**	**100.0%**	**1.01 [0.57 , 1.79]**
Total events:	28		26			

Heterogeneity: $Chi^2 = 1.69$, df = 3 (P = 0.64); $I^2 = 0\%$
Test for overall effect: Z = 0.04 (P = 0.97)
Test for subgroup differences: Not applicable



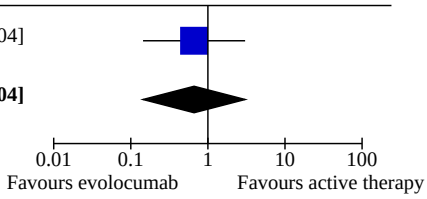
Comparison 4. Evolocumab versus active therapy

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 Any cardiovascular disease	1	218	Odds Ratio (IV, Fixed, 95% CI)	0.66 [0.14, 3.04]
4.2 All-cause mortality	3	5223	Odds Ratio (IV, Fixed, 95% CI)	0.43 [0.14, 1.30]
4.3 Any myocardial infarction	3	5003	Odds Ratio (IV, Fixed, 95% CI)	0.66 [0.23, 1.85]
4.4 Influenza	3	5223	Odds Ratio (IV, Fixed, 95% CI)	1.22 [0.88, 1.70]
4.5 Type 2 diabetes mellitus	2	5005	Odds Ratio (M-H, Fixed, 95% CI)	3.52 [0.18, 68.33]
4.6 Hypertension	2	5005	Odds Ratio (IV, Fixed, 95% CI)	1.51 [0.06, 37.04]

Analysis 4.1. Comparison 4: Evolocumab versus active therapy, Outcome 1: Any cardiovascular disease

Study or Subgroup	Evolocumab Events	Evolocumab Total	Active therapy Events	Active therapy Total	Weight	Odds Ratio IV, Fixed, 95% CI
GAUSS-3	4	145	3	73	100.0%	0.66 [0.14 , 3.04]
Total (95% CI)		**145**		**73**	**100.0%**	**0.66 [0.14 , 3.04]**
Total events:	4		3			

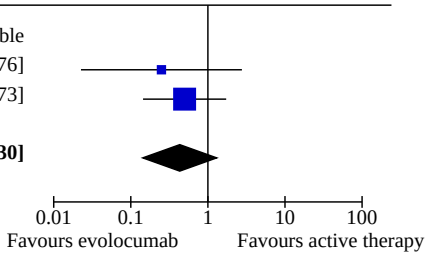
Heterogeneity: Not applicable
Test for overall effect: Z = 0.53 (P = 0.60)
Test for subgroup differences: Not applicable



Analysis 4.2. Comparison 4: Evolocumab versus active therapy, Outcome 2: All-cause mortality

Study or Subgroup	Evolocumab Events	Evolocumab Total	Active therapy Events	Active therapy Total	Weight	Odds Ratio IV, Fixed, 95% CI
GAUSS-3	0	145	0	73		Not estimable
OSLER-1	1	882	2	442	21.1%	0.25 [0.02 , 2.76]
OSLER-2	5	2454	5	1227	78.9%	0.50 [0.14 , 1.73]
Total (95% CI)		**3481**		**1742**	**100.0%**	**0.43 [0.14 , 1.30]**
Total events:	6		7			

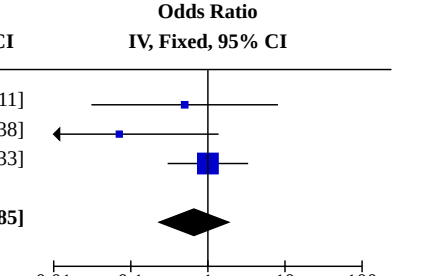
Heterogeneity: Chi² = 0.25, df = 1 (P = 0.62); I² = 0%
Test for overall effect: Z = 1.49 (P = 0.14)
Test for subgroup differences: Not applicable



Analysis 4.3. Comparison 4: Evolocumab versus active therapy, Outcome 3: Any myocardial infarction

Study or Subgroup	Evolocumab Events	Evolocumab Total	Active therapy Events	Active therapy Total	Weight	Odds Ratio IV, Fixed, 95% CI
GAUSS-3	1	145	1	73	13.8%	0.50 [0.03 , 8.11]
OSLER-1	0	736	3	368	12.2%	0.07 [0.00 , 1.38]
OSLER-2	8	2454	4	1227	74.0%	1.00 [0.30 , 3.33]
Total (95% CI)		**3335**		**1668**	**100.0%**	**0.66 [0.23 , 1.85]**
Total events:	9		8			

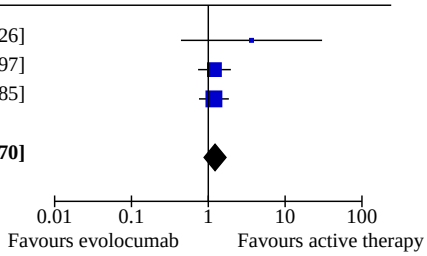
Heterogeneity: Chi² = 2.67, df = 2 (P = 0.26); I² = 25%
Test for overall effect: Z = 0.79 (P = 0.43)
Test for subgroup differences: Not applicable



Analysis 4.4. Comparison 4: Evolocumab versus active therapy, Outcome 4: Influenza

Study or Subgroup	Evolocumab Events	Evolocumab Total	Active therapy Events	Active therapy Total	Weight	Odds Ratio IV, Fixed, 95% CI
GAUSS-3	7	145	1	73	2.4%	3.65 [0.44 , 30.26]
OSLER-1	57	882	24	442	44.3%	1.20 [0.74 , 1.97]
OSLER-2	66	2454	28	1227	53.3%	1.18 [0.76 , 1.85]
Total (95% CI)		**3481**		**1742**	**100.0%**	**1.22 [0.88 , 1.70]**
Total events:	130		53			

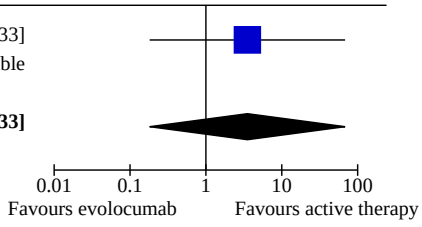
Heterogeneity: Chi² = 1.05, df = 2 (P = 0.59); I² = 0%
Test for overall effect: Z = 1.22 (P = 0.22)
Test for subgroup differences: Not applicable



Analysis 4.5. Comparison 4: Evolocumab versus active therapy, Outcome 5: Type 2 diabetes mellitus

Study or Subgroup	Evolocumab Events	Evolocumab Total	Active therapy Events	Active therapy Total	Weight	Odds Ratio M-H, Fixed, 95% CI
OSLER-1	3	882	0	442	100.0%	3.52 [0.18 , 68.33]
OSLER-2	0	2454	0	1227		Not estimable
Total (95% CI)		**3336**		**1669**	**100.0%**	**3.52 [0.18 , 68.33]**
Total events:	3		0			

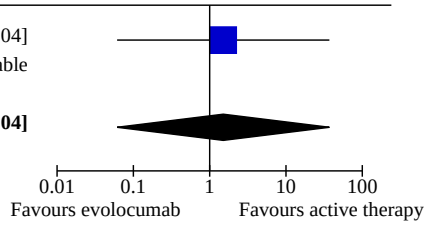
Heterogeneity: Not applicable
Test for overall effect: Z = 0.83 (P = 0.41)
Test for subgroup differences: Not applicable



Analysis 4.6. Comparison 4: Evolocumab versus active therapy, Outcome 6: Hypertension

Study or Subgroup	Evolocumab Events	Evolocumab Total	Active therapy Events	Active therapy Total	Weight	Odds Ratio IV, Fixed, 95% CI
OSLER-1	1	882	0	442	100.0%	1.51 [0.06 , 37.04]
OSLER-2	0	2454	0	1227		Not estimable
Total (95% CI)		**3336**		**1669**	**100.0%**	**1.51 [0.06 , 37.04]**
Total events:	1		0			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.25 (P = 0.80)
Test for subgroup differences: Not applicable



ADDITIONAL TABLES

Table 1. Summary results – alirocumab compared with placebo

Outcome	Number of studies	Intervention		Comparison		Fixed-effectOR (95% CI)	Fixed-effect RD (95% CI)
		Events	Available participants	Events	Available participants		
Any CVD	10	1411	12,770	1531	11,098	0.87 (0.80 to 0.94)	–0.02 (–0.02 to –0.01)
All-cause mortality	12	352	13,390	408	11,407	0.83 (0.72 to 0.96)	–0.01 (–0.01 to –0.001)
Any MI	9	1221	12,369	1372	10,983	0.86 (0.79 to 0.94)	–0.02 (–0.02 to –0.01)
Any stroke	8	135	12,024	173	10,811	0.73 (0.58 to 0.91)	–0.004 (–0.007 to –0.001)
Influenza	11	182	12,807	83	11,157	1.09 (0.83 to 1.42)	0.01 (–0.01 to 0.02)
Type 2 diabetes mellitus	6	687	11,674	695	10,632	0.96 (0.86 to 1.07)	–0.002 (–0.009 to 0.004)
Any cancer	6	88	2,497	49	1,309	0.88 (0.61 to 1.26)	–0.003 (–0.02 to 0.01)
Hypertension	10	162	12,959	114	11,388	0.92 (0.72 to 1.18)	–0.003 (–0.01 to 0.01)

CI: confidence interval; CVD: cardiovascular disease; MI: myocardial infarction; OR: odds ratio; RD: risk difference.

Table 2. Summary results – evolocumab compared with placebo

Outcome	Number of studies	Intervention		Comparison		Fixed-effect OR (95% CI)	Fixed-effect RD (95% CI)
		Events	Available participants	Events	Available participants		
Any CVD	3	1409	14,867	1639	14,565	0.84 (0.78 to 0.91)	–0.016 (–0.023 to –0.009)
All-cause mortality	3	449	14,867	430	14,565	1.04 (0.91 to 1.19)	0.001 (–0.003 to 0.005)
Any MI	3	479	14,867	653	14,565	0.72 (0.64 to 0.82)	–0.012 (–0.016 to –0.008)
Any stroke	2	209	14,268	265	14,263	0.79 (0.65 to 0.94)	–0.004 (–0.007 to –0.001)

Table 2. Summary results – evolocumab compared with placebo *(Continued)*

Influenza	1	45	599	19	302	1.21 (0.69 to 2.11)	0.012 (–0.026 to 0.045)
Type 2 diabetes mellitus	3	694	14,867	662	14,566	1.05 (0.94 to 1.17)	0.003 (–0.004 to 0.011)
Any cancer	0	—	—	—	—	Not reported	Not reported
Hypertension	0	—	—	—	—	Not reported	Not reported

CI: confidence interval; CVD: cardiovascular disease; MI: myocardial infarction; OR: odds ratio; RD: risk difference.

Table 3. Summary results – alirocumab compared with alternative lipid-lowering treatments

Outcome	Number of studies	Intervention		Comparison		Fixed-effect OR (95% CI)	Fixed-effect RD (95% CI)
		Events	Available participants	Events	Available participants		
Any CVD	3	24	686	11	693	1.37 (0.65 to 2.87)	0.009 (–0.008 to 0.027)
All-cause mortality	5	6	864	9	869	0.51 (0.18 to 1.40)	–0.006 (–0.015 to 0.003)
Any MI	5	21	864	8	870	1.45 (0.64 to 3.28)	0.007 (–0.006 to 0.020)
Any stroke	5	2	864	2	870	0.85 (0.13 to 5.61)	0.000 (–0.005 to 0.005)
Influenza	4	30	738	16	745	1.72 (0.91 to 3.25)	0.017 (–0.001 to 0.036)
Type 2 diabetes mellitus	2	1	207	11	453	0.28 (0.05 to 1.55)	–0.019 (–0.041 to 0.002)
Any cancer	1	15	479	7	241	1.08 (0.43 to 2.69)	0.002 (–0.030 to 0.027)
Hypertension	4	28	812	26	818	1.01 (0.57 to 1.79)	0.003 (–0.015 to 0.020)

CI: confidence interval; CVD: cardiovascular disease; MI: myocardial infarction; OR: odds ratio; RD: risk difference.

Table 4. Summary results – evolocumab compared with alternative lipid-lowering treatments

Outcome	Number of studies	Intervention		Comparison		Fixed-effect OR (95% CI)	Fixed-effect RD (95% CI)
		Events	Available participants	Events	Available participants		
Any CVD	1	4	145	3	73	0.66 (0.14 to 3.04)	–0.01 (–0.07 to 0.04)
All-cause mortality	3	6	3481	7	1742	0.43 (0.14 to 1.30)	–0.00 (–0.01 to 0.01)
Any MI	3	9	3335	8	1668	0.66 (0.23 to 1.85)	–0.00 (–0.00 to 0.00)
Any stroke	2	0	2599	0	1300	NA	NA
Influenza	3	130	3481	53	1742	1.22 (0.88 to 1.70)	0.01 (–0.00 to 0.02)
Type 2 diabetes mellitus	2	3	3336	0	1669	3.52 (0.18 to 68.33)	0.001 (–0.001 to 0.002)
Any cancer	—	—	—	—	—	NA	NA
Hypertension	2	1	3336	0	1669	1.51 (0.06 to 37.04)	0.00 (–0.00 to 0.01)

CI: confidence interval; CVD: cardiovascular disease; MI: myocardial infarction; NA: not available; OR: odds ratio; RD: risk difference.

APPENDICES

Appendix 1. Search strategies

MEDLINE search strategy

1. exp antibodies, monoclonal/
2. monoclonal antibod*.tw.
3. MAB*.tw.
4. evolocumab.tw.
5. amg 145.tw.
6. amg145.tw.
7. alirocumab.tw.
8. regn 727.tw.
9. regn727.tw.
10. sar 236553.tw.
11. sar236553.tw.
12. 1D05-IgG2.tw.
13. LGT209.tw.
14. RG7652.tw.
15. Bococizumab.tw.
16. "pf 04950615".tw.
17. pf04950615.tw.
18. rn 316.tw.
19. rn316.tw.
20. or/1-19
21. exp Proprotein Convertases/
22. proprotein convertase*.tw.
23. pro-protein convertase*.tw.
24. pcsk9.tw.
25. serine proteinase*.tw.
26. or/21-25
27. exp Cardiovascular Diseases/
28. cardio*.tw.
29. cardia*.tw.
30. heart*.tw.
31. coronary*.tw.
32. angina*.tw.
33. ventric*.tw.
34. myocard*.tw.
35. pericard*.tw.
36. isch?em*.tw.
37. emboli*.tw.
38. arrhythmi*.tw.
39. thrombo*.tw.
40. atrial fibrillat*.tw.
41. tachycardi*.tw.
42. endocardi*.tw.
43. (sick adj sinus).tw.
44. exp Stroke/
45. (stroke or stokes).tw.
46. cerebrovasc*.tw.
47. cerebral vascular.tw.
48. apoplexy.tw.
49. (brain adj2 accident*).tw.
50. ((brain* or cerebral or lacunar) adj2 infarct*).tw.
51. exp Hyperlipidemias/
52. hyperlipid*.tw.
53. hyperlip?emia*.tw.
54. hypercholesterol*.tw.
55. hypercholester?emia*.tw.

56. hyperlipoprotein?emia*.tw.
57. hypertriglycerid?emia*.tw.
58. exp Arteriosclerosis/
59. exp Cholesterol/
60. cholesterol.tw.
61. "coronary risk factor* ".tw.
62. exp Cognition/
63. exp dementia/
64. cognitive function*.tw.
65. dementia.tw.
66. alzheimer*.tw.
67. or/27-66
68. 20 and 26 and 67
69. randomized controlled trial.pt.
70. controlled clinical trial.pt.
71. randomized.ab.
72. placebo.ab.
73. drug therapy.fs.
74. randomly.ab.
75. trial.ab.
76. groups.ab.
77. 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76
78. exp animals/ not humans.sh.
79. 77 not 78
80. 68 and 79
81. limit 80 to yr="2005 -Current"

CENTRAL search strategy

#1 MeSH descriptor: [Antibodies, Monoclonal] explode all trees

#2 monoclonal next antibod*

#3 MAB*

#4 evolocumab

#5 "amg 145" or amg145

#6 alirocumab

#7 "regn 727" or regn727 or "sar 236553" or sar236553 or 1D05-IgG2 or LGT209 or RG7652

#8 Bococizumab

#9 "pf 04950615" or pf04950615 or "rn 316" or rn316

#10 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9

#11 MeSH descriptor: [Proprotein Convertases] explode all trees

#12 proprotein next convertase*

#13 pro-protein next convertase*

#14 pcsk9

#15 serine next proteinase*

#16 #11 or #12 or #13 or #14 or #15

#17 MeSH descriptor: [Cardiovascular Diseases] explode all trees

#18 cardio*

#19 cardia*

#20 heart*

#21 coronary*

#22 angina*

#23 ventric*

#24 myocard*

#25 pericard*

#26 isch?em*

#27 emboli*

#28 arrhythmi*

#29 thrombo*

#30 atrial next fibrillat*

#31 tachycardi*

#32 endocardi*

#33 (sick next sinus)

#34 MeSH descriptor: [Stroke] explode all trees

#35 (stroke or stokes)

#36 cerebrovasc*

#37 cerebral next vascular

#38 apoplexy

#39 (brain near/2 accident*)

#40 ((brain* or cerebral or lacunar) near/2 infarct*)

#41 MeSH descriptor: [Hyperlipidemias] explode all trees

#42 hyperlipid*

#43 hyperlip?emia*

#44 hypercholesterol*

#45 hypercholester?emia*

#46 hyperlipoprotein?emia*

#47 hypertriglycerid?emia*

#48 MeSH descriptor: [Arteriosclerosis] explode all trees

#49 MeSH descriptor: [Cholesterol] explode all trees

#50 cholesterol

#51 "coronary risk factor*"

#52 MeSH descriptor: [Cognition] explode all trees

#53 MeSH descriptor: [Dementia] explode all trees

#54 cognitive next function*

#55 dementia

#56 alzheimer*

#57 #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40 or #41 or #42 or #43 or #44 or #45 or #46 or #47 or #48 or #49 or #50 or #51 or #52 or #53 or #54 or #55 or #56

#58 #10 and #16 and #57 Publication Year from 2005 to 2019

Embase search strategy

1. exp monoclonal antibody/

2. monoclonal antibod*.tw.

3. MAB*.tw.

4. evolocumab.tw.

5. amg 145.tw.

6. amg145.tw.

7. alirocumab.tw.

8. regn 727.tw.

9. regn727.tw.

10. sar 236553.tw.

11. sar236553.tw.

12. 1D05-IgG2.tw.

13. LGT209.tw.

14. RG7652.tw.

15. Bococizumab.tw.

16. "pf 04950615".tw.

17. pf04950615.tw.

18. rn 316.tw.

19. rn316.tw.

20. or/1-19

21. exp serine proteinase/

22. proprotein convertase*.tw.

23. pro-protein convertase*.tw.

24. serine proteinase*.tw.

25. pcsk9.tw.

26. or/21-25

27. exp cardiovascular disease/

28. cardio*.tw.

29. cardia*.tw.

30. heart*.tw.

31. coronary*.tw.

32. angina*.tw.

33. ventric*.tw.

34. myocard*.tw.

35. pericard*.tw.

36. isch?em*.tw.

37. emboli*.tw.

38. arrhythmi*.tw.

39. thrombo*.tw.

40. atrial fibrillat*.tw.

41. tachycardi*.tw.

42. endocardi*.tw.

43. (sick adj sinus).tw.

44. exp cerebrovascular disease/

45. (stroke or stokes).tw.

46. cerebrovasc*.tw.

47. cerebral vascular.tw.

48. apoplexy.tw.

49. (brain adj2 accident*).tw.

50. ((brain* or cerebral or lacunar) adj2 infarct*).tw.

51. exp hyperlipidemia/

52. hyperlipid*.tw.

53. hyperlip?emia*.tw.

54. hypercholesterol*.tw.

55. hypercholester?emia*.tw.

56. hyperlipoprotein?emia*.tw.

57. hypertriglycerid?emia*.tw.

58. exp Arteriosclerosis/

59. exp Cholesterol/

60. cholesterol.tw.

61. "coronary risk factor*".tw.

62. exp cognition/

63. exp dementia/

64. cognitive function*.tw.

65. dementia.tw.

66. alzheimer*.tw.

67. or/27-66

68. 20 and 26 and 67

69. random$.tw.

70. factorial$.tw.

71. crossover$.tw.

72. cross over$.tw.

73. cross-over$.tw.

74. placebo$.tw.

75. (doubl$ adj blind$).tw.

76. (singl$ adj blind$).tw.

77. assign$.tw.

78. allocat$.tw.

79. volunteer$.tw.

80. crossover procedure/

81. double blind procedure/

82. randomized controlled trial/

83. single blind procedure/

84. 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83

85. (animal/ or nonhuman/) not human/

86. 84 not 85

87. 68 and 86

88. limit 87 to embase

89. limit 88 to yr="2005 -Current"

Web of Science search strategy

12 #11 AND #10

11 TS=((random* or blind* or allocat* or assign* or trial* or placebo* or crossover* or cross-over*))

10 #9 AND #8 AND #7

9 TS=("proprotein convertase*" or "pro-protein convertase*" or pcsk9 or "serine proteinase*")

8 TS=("monoclonal antibod*" or MAB* or evolocumab or "amg 145" or amg145 or alirocumab or "regn 727" or regn727 or "sar 236553" or sar236553 or 1D05-IgG2 or LGT209 or RG7652 or Bococizumab or "pf 04950615" or pf04950615 or "rn 316" or rn316)

7 #6 OR #5 OR #4 OR #3 OR #2 OR #1

6 TS=("cognitive function*" or dementia or alzheimer*)

5 TS=(cardio* OR cardia* OR heart* OR coronary* OR angina* OR ventric* OR myocard*)

4 TS=(pericard* OR isch?em* OR emboli* OR arrhythmi* OR thrombo*)

3 TS=("atrial fibrillat*" OR tachycardi* OR endocardi*)

2 TS=(stroke OR stokes OR cerebrovasc* OR cerebral OR apoplexy OR (brain SAME accident*) OR (brain SAME infarct*))

1 TS=(hyperlipid* OR hyperlip?emia* OR hypercholesterol* OR hypercholester?emia* OR hyperlipoprotein?emia* OR hypertriglycerid?emia*)

Clinical trials registers search terms

PCSK9 OR alirocumab OR evolocumab

WHAT'S NEW

Date	Event	Description
17 December 2020	Amended	Minor edits to abstract

HISTORY

Protocol first published: Issue 6, 2015
Review first published: Issue 4, 2017

Date	Event	Description
20 August 2020	New citation required and conclusions have changed	Results and conclusion stratified per compound (alirocumab and evolocumab) and comparison (active treatment or placebo), finding higher certainty of evidence for placebo comparisons than against active treatment. After removing trials evaluating the terminated compound bococizumab (three) and RG7652 (one), 23 RCTs were included.
20 August 2020	New search has been performed	Evidence up to date to 2 December 2019.

CONTRIBUTIONS OF AUTHORS

AFS drafted the protocol, the full review, and conducted all analyses.

AFS, JPLC, LSP, JPC screened hits and extracted data.

JPLC, LSP, JTW, JPO, AH, and JPC provided guidance during critical revision of the manuscript.

DECLARATIONS OF INTEREST

AFS has received unrelated funding from Servier for the development of a genetically guided drug target validation platform. Servier does not produce a PCSK9 monoclonal antibody drug.

JPLC: none.

LSP: none.

JTW: none.

JPO: none.

AH is a member of the organisation committee of The Genetics of Subsequent Coronary Heart Disease Consortium and the Heart failure Molecular Epidemiology for Therapeutic Targets Consortium (HERMES) each comprising over 20 member cohorts. A number of Pharma companies have provided direct and in-kind support for these initiatives, but AH is not a direct recipient of any of these funds.

JPC: none.

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- No sources of support supplied

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- BHF, UK

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- NIHR, UK

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We note the following deviations from the protocol.

First review (Schmidt 2017)

- We intended to present a 'Risk of bias' figure depicting risk of bias per item, weighted for how much an individual randomised controlled trial contributed to the overall effect estimate of PCSK9 inhibitors on low-density lipoprotein cholesterol (LDL-C). However, some studies did not report on LDL-C, or did not report it at the same time point, making it impossible to present such a figure.
- Owing to the small number of events off all-cause mortality and the cardiovascular disease (CVD) endpoints, we decided against using the usual inverse variance method of pooling, which may result in biased estimates. Instead, we pooled clinical events by reconstructing individual participant data based on cell frequencies, and analysed these data using a mixed-effect generalised linear regression model with a random intercept (fixed-effect) (Bradburn 2007; Sweeting 2004).
- We meta-analysed biomarker results despite considerable heterogeneity in continuous endpoints, this contrary to the protocol statement that no meta-analysis would be performed if heterogeneity was larger than 50%. We decided to combine results because estimates were universally on one side of the neutral effect.
- Owing to the small number of events, we performed all subgroup analyses for LDL-C instead of CVD. Similarly, subgroups explored were slightly different from those described in the protocol as the result of available data.
- We intended to extract data for continuous endpoints as mean percentage change from baseline, or as the difference at the end of follow-up. However, the latter was unavailable in most studies, and we focused on the former.
- Instead of data on cognitive function, we decided (post hoc) to extract data on neurological events.

This update

- Because of the robustness of the evidence, we dropped the biomarker outcomes.
- We refocused clinical outcomes on a core set, including CVD and its separate elements (provided sufficient data), all-cause mortality, influenza, hypertension, cancer diagnoses, and type 2 diabetes. We retained quality of life (despite having no data) for future exploration.
- We presented results by compound (alirocumab and evolocumab) and control group (placebo or active treatment), where terminated monoclonal antibodies (bococizumab and RG7652) were dropped from the review.
- Due to the above-mentioned reordering and removal of studies, sample size decreased for most outcomes to such an extent that subgroup analyses were no longer informative.
- Due to the unavailability of subgroup specific reports, these analyses could not be performed for clinical endpoints.

- The 2017 version of the review reported on possible heterogeneity by dosage, finding none. However, many trials changed the dosage over the run-time of the trial making such an analysis (and especially its interpretation) problematic, as such the current review does not perform a similar stratification.
- There was very little variation in observed risk of bias and percentage of missingness precluding stratified analyses to assess sensitivity.
- We added myocardial infarction and any stroke to the 'Summary of findings' tables.
- Due to performing analyses using Review Manager 5 instead of R, we no longer present random-effects estimates.
- John-Paul L Carter has joined the author team.

INDEX TERMS

Medical Subject Headings (MeSH)

Antibodies, Monoclonal, Humanized [*therapeutic use]; Anticholesteremic Agents [therapeutic use]; Cardiovascular Diseases [*prevention & control]; Cause of Death; Cholesterol, LDL [*blood]; Cholinergic Antagonists [therapeutic use]; Ezetimibe [therapeutic use]; Hydroxymethylglutaryl-CoA Reductase Inhibitors [therapeutic use]; Myocardial Infarction [epidemiology]; *PCSK9 Inhibitors; Primary Prevention [methods]; Proprotein Convertase 9 [immunology]; Randomized Controlled Trials as Topic; Secondary Prevention [methods]; Stroke [epidemiology]; Time Factors

MeSH check words

Humans; Middle Aged