Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) Inhibitors: Update

Systematic Review

December 2018

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Executive Summary

Background

Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors are monoclonal antibodies against the PCSK9 enzyme that interfere with the binding of the low-density lipoprotein (LDL) receptor, leading to higher LDL receptor expression in liver cells and lower plasma low-density lipoprotein cholesterol (LDL-C) levels. PCSK9 inhibitors are indicated for patients with hypercholesterolemia who do not achieve target serum levels of LDL-C despite treatment with lipid-lowering medications such as statins or ezetimibe. The U.S. Food and Drug Administration (FDA) approved 2 PCSK9 inhibitors (alirocumab [Praluent] and evolocumab [Repatha]) for the treatment of hypercholesterolemia in adults as an adjunct to diet and other lipid-lowering therapies.

PICO and Key Questions

This report is an update of a systematic review completed in 2015 for the Drug Effectiveness Review Project (DERP). The population this report focuses on is adults with familial or nonfamilial hypercholesterolemia who have not achieved recommended LDL-C serum levels despite lipid-lowering therapy. Eligible studies were randomized controlled trials (RCTs) and systematic reviews that assessed the comparative efficacy, effectiveness, and safety of alirocumab and evolocumab with each other and other active lipid-lowering therapies. Because of the dearth of evidence identified in the previous systematic review, we included placebo-controlled trials if the primary outcome was cardiovascular disease (CVD). Outcomes of interest were cardiovascular events, mortality, adverse events, and intermediate outcomes such as change in LDL-C and high-density lipoprotein (HDL-C) levels. The following are the key questions for this review:

1. What are the comparative benefits and harms of PCSK9 inhibitors in patients with familial hypercholesterolemia?
2. What are the comparative benefits and harms of PCSK9 inhibitors in patients who are intolerant to statins?
3. What are the comparative benefits and harms of PCSK9 inhibitors in patients with nonfamilial hypercholesterolemia who have not achieved target LDL-C levels?
4. What is the efficacy and effectiveness of PCSK9 inhibitor monotherapy or adjunct therapy with other lipid-lowering agents or other cardiovascular risk reduction methods (e.g., smoking cessation, diet)?
5. Do the comparative benefits and harms of PCSK9 inhibitors differ when used in different patient subgroups?

Methods

We describe our complete methods in Appendix A. Briefly, we searched Ovid MEDLINE, Cochrane Library, ClinicalTrials.gov, and several other websites to identify eligible studies. We rated the methodological quality of eligible RCTs or systematic reviews using standard

instruments adapted from national and international quality standards.[1-3] We rated the quality of the body of evidence for 6 outcomes (death because of CVD, cardiovascular events, change in LDL-C levels, incidence of overall adverse events, discontinuation because of adverse events, and serious adverse events) when possible, using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach.[4,5] We extracted data and effect estimates for relevant outcomes. If relevant effect measures were not reported, we used StatsDirect (version 3.1.20), Stata (version 14.2), and MEDCALC to calculate effect measures based on data provided in the study. We indicate values that we calculated with italics.

Key Findings

We included 13 RCTs (published in 16 articles) with data on more than 56,800 participants. We identified 8 RCTs in this update; 5 were from the original systematic review. In addition, we included 1 systematic review[6] and 2 pooled data analyses.[7,8] Three RCTs compared alirocumab to ezetimibe,[9-12] 2 RCTs compared alirocumab to ezetimibe plus statins,[13,14] and 1 RCT compared alirocumab to standard of care.[15] Four RCTs compared evolocumab to ezetimibe,[16-19] and 1 RCT[20] and 2 pooled data analyses compared evolocumab to standard of care.[7,8] We included 2 RCTs that compared alirocumab or evolocumab to a placebo-control group because the primary outcome was CVD.[21-24]

Benefits and Harms of PCSK9 Inhibitors in Patients With Heterozygous or Homozygous Familial Hypercholesterolemia (Key Question 1)

- We did not find any eligible studies on alirocumab.
- We did not find any eligible studies on patients with homozygous familial hypercholesterolemia.

Evolocumab vs. Standard of Care

- Compared to standard of care alone, evolocumab plus standard of care resulted in a statistically significant decrease in LDL-C levels after 48 weeks of treatment.
  - Mean percentage decrease -55.7% (95% confidence interval [CI] not reported [NR]; equivalent to a decrease of 36.0 mg/dl).
  - We rated the quality of the evidence as low (Table ES1).
- The risk of adverse events was statistically significantly lower for standard of care than evolocumab plus standard of care (*risk ratio [RR], 0.77; 95% CI, 0.63 to 0.92)*; nasopharyngitis (17.0% vs. 6.0%) and muscle events (10.0% vs. 4.6%) occurred more frequently in participants treated with evolocumab plus standard of care during 48 weeks of follow-up. We rated the quality of the evidence as low.
- We cannot draw meaningful conclusions about the comparative risks of serious adverse events (very low quality of evidence).

Table ES1. Summary of Findings (GRADE) for PCSK9 Inhibitors in Patients with Heterozygous Familial Hypercholesterolemia

Outcome	Number of Studies Sample Size (N)	Quality of the Evidence	Relationship and Treatment Effect	Rationale for Quality of the Evidence
Evolocumab Plus Standard of Care vs. Standard of Care				
LDL-C decrease at 48 weeks	1 pooled analysis of 2 RCTs[7] N = 440	Low	Evolocumab (140 mg or 420 mg) significantly reduced LDL-C compared to SOC Mean percentage decrease -55.7%; 95% CI, NR	Downgraded for very serious risk of bias
Overall adverse events at 48 weeks	1 pooled analysis of 2 RCTs[7] N = 440	Low	Significantly higher risk for adverse events for evolocumab + SOC than SOC RR, 0.77; 95% CI, 0.63 to 0.92	Downgraded for very serious risk of bias
Serious adverse events at 48 weeks	1 pooled analysis of 2 RCTs[7] N = 440	Very low	No relationship can be determined	Downgraded for very serious risk of bias

Abbreviations. CI: confidence interval; LDL-C: low-density lipoprotein-cholesterol; N: number of participants; NR: not reported; RCT: randomized controlled trial; RR: risk ratio; SOC: standard of care.

Benefits and Harms of PCSK9 Inhibitors in Patients Who Are Statin-Intolerant or Unable to Use Statins (Key Question 2)

Alirocumab vs. Ezetimibe

- Compared to ezetimibe, alirocumab resulted in a statistically significant greater decrease in LDL-C levels at 12 weeks.
  - Intention-to-treat analysis mean percentage change -30.4% (95% CI, -36.6% to -24.2%); equivalent to a decrease of 65.6 mg/dl based on an as-treated analysis.
  - We rated the quality of the evidence as moderate (Table ES2).
- The incidence of overall adverse events and serious adverse events in the alirocumab treatment group was similar to ezetimibe at 24 weeks. We graded the quality of evidence as moderate for risk of overall adverse events and low for risk of serious adverse events (1 RCT).
- The incidence of discontinuation of treatment because of adverse events at 24 weeks was lower in the alirocumab group than in the ezetimibe group (18.3% vs. 25.0%; *RR, 0.73 [95% CI, 0.45 to 1.18]*), but the finding was not statistically significantly different. We rated the quality of the evidence as low.
- We cannot draw meaningful conclusions about the comparative risks of cardiovascular events (very low quality of evidence).

Evolocumab vs. Ezetimibe (With Lipid-Lowering Background Therapy)

- Compared to ezetimibe, evolocumab resulted in a statistically significant greater decrease in LDL-C levels at 12 and 24 weeks.
  - The mean percentage change ranged from -35.9% (95% CI, -44.1% to -27.8%; equivalent to a decrease of *76.7 mg/dl*) to -38.1% (95% CI, -43.7% to -32.4%; equivalent to a decrease of 69.7 mg/dl) across 3 RCTs.
  - We rated the quality of the evidence as high (Table ES2).
- The incidence of adverse events and cardiovascular events at 12 and 24 weeks was similar between the evolocumab and ezetimibe groups. We rated the quality of the evidence as high for adverse events and low for cardiovascular events.
- The incidence of serious adverse events was similar in the evolocumab and ezetimibe treatment groups. We rated the quality of the evidence as low.
- The incidence of discontinuation due to adverse events was statistically significantly lower in the evolocumab treatment group than in the ezetimibe group.
  - *9.4% vs. 21.7%; RR, 0.43 (95% CI, 0.24 to 0.77).*
  - We rated the quality of the evidence as moderate.

Evolocumab Plus Ezetimibe vs. Ezetimibe (With Lipid-Lowering Background Therapy)

- Compared to ezetimibe, evolocumab plus ezetimibe resulted in a statistically significant greater decrease in LDL-C levels at 12 weeks
  - Mean percentage change -47.3% (95% CI, -53.7% to -40.8%); equivalent to a decrease of *95.6 mg/dl*.
  - We rated the quality of the evidence as low (Table ES2).
- The risk of adverse events was similar between treatment groups. We rated the quality of the evidence as low.
- We cannot draw meaningful conclusions about the comparative risks of discontinuation due to adverse events and serious adverse events (very low quality of evidence).

Table ES2. Summary of Findings (GRADE) for PCSK9 Inhibitors in Statin-Intolerant Patients

Outcome	Number of Studies Sample Size (N)	Quality of the Evidence	Relationship and Treatment Effect	Rationale for Quality of the Evidence
Alirocumab vs. Ezetimibe in Statin-Intolerant Patients				
Cardiovascular events (composite outcome) at 24 weeks	1 RCT[11] N = 250	Very low	No relationship can be determined	Downgraded for risk of bias and very serious imprecision

Outcome	Number of Studies Sample Size (N)	Quality of the Evidence	Relationship and Treatment Effect	Rationale for Quality of the Evidence
LDL-C decrease at 24 weeks	1 RCT[11] N = 250	Moderate	Statistically significant greater reduction of LDL-C with alirocumab than ezetimibe -30.4%; 95% CI, -36.6% to -24.2%	Downgraded for imprecision
Overall adverse events at 24 weeks	1 RCT[11] N = 250	Moderate	Similar risks for adverse events between alirocumab and ezetimibe *RR, 1.02; 95% CI, 0.91 to 1.15*	Downgraded for imprecision
Discontinuation because of adverse events at 24 weeks	1 RCT[11] N = 250	Low	Numerically lower risk for discontinuation because of adverse events alirocumab than ezetimibe *RR, 0.73; 95% CI, 0.45 to 1.18*	Downgraded for very serious imprecision
Serious adverse events at 24 weeks	1 RCT[11] N = 250	Low	Similar risks for serious adverse events *RR, 1.18; 95% CI, 0.53 to 2.63*	Downgraded for very serious imprecision
Evolocumab vs. Ezetimibe in Statin-Intolerant Patients				
Cardiovascular events (composite outcome) at 12 and 24 weeks	3 RCTs[17-19] N = 590	Low	Similar risks for cardiovascular events Range: *RR, 0.67; 95% CI, 0.15 to 2.92; to RR, 3.00; 95% CI, 0.13 to 71.0*	Downgraded for very serious imprecision
LDL-C decrease at 12 and 24 weeks	3 RCTs[17-19] N = 590	High	Statistically significant greater reduction of LDL-C with evolocumab than ezetimibe Range: -35.9%; 95% CI, -44.1% to -27.8%; to -38.1%; 95% CI, -43.7% to -32.4%;	Not downgraded for any domain
Overall adverse events at 12 and 24 weeks	3 RCTs[17-19] N = 590	High	Similar risks for adverse events with evolocumab and ezetimibe Range: *RR, 0.90; 95% CI, 0.73 to 1.10; to RR, 0.95; 95% CI, 0.62 to 1.44*	Not downgraded for any domain
Discontinuation because of adverse events at 12 and 24 weeks	3 RCTs[17-19] N = 590	Moderate	Statistically significant lower risk for discontinuation because of adverse events with evolocumab than ezetimibe Range: *RR, 0.30; 95% CI, 0.18 to 0.50; to RR, 0.65; 95% CI, 0.33 to 1.29*	Downgraded for imprecision

Outcome	Number of Studies Sample Size (N)	Quality of the Evidence	Relationship and Treatment Effect	Rationale for Quality of the Evidence
Serious adverse events at 12 and 24 weeks	3 RCTs[17-19] N = 590	Low	Similar risks for serious adverse events with evolocumab and ezetimibe *Range: RR, 0.45; 95% CI, 0.19 to 1.07 to RR, 3.00; 95% CI, 0.13 to 71.00*	Downgraded for very serious imprecision
Evolocumab Plus Ezetimibe vs. Ezetimibe in Statin-Intolerant Patients				
LDL-C decrease at 12 weeks	1 RCT[19] N = 64	Low	Statistically significant greater reduction of LDL-C with evolocumab than ezetimibe -47.3%; 95% CI, -53.7% to -40.8%	Downgraded for very serious imprecision
Overall adverse events at 12 weeks	1 RCT[19] N = 64	Low	Similar risks for adverse events with evolocumab and ezetimibe *RR, 1.12; 95% CI, 0.77 to 1.65*	Downgraded for risk of bias and imprecision
Discontinuation because of adverse events at 12 weeks	1 RCT[19] N = 64	Very low	No relationship can be determined	Downgraded for risk of bias and very serious imprecisions
Serious adverse events at 12 weeks	1 RCT[19] N = 64	Very low	No relationship can be determined	Downgraded for risk of bias and very serious imprecisions

Abbreviations. CI: confidence interval; LDL-C: low-density lipoprotein-cholesterol; N: number of participants; NR: not reported; RCT: randomized controlled trial; RR: risk ratio.

Benefits and Harms of PCSK9 Inhibitors in Patients With Nonfamilial Hypercholesterolemia Who Do Not Achieve Target Levels (Key Question 3)

Alirocumab vs. Other Lipid-Lowering Regimens

- Compared to ezetimibe plus baseline statin, or compared to 1 of 3 statin regimens (original statin only, doubling the dose of original statin, or switching to another statin), alirocumab resulted in a statistically significant decrease in LDL-C levels after 24 weeks of treatment.
  - The mean percentage change ranged from -23.6% (95% CI, -30.2% to -17.0%; equivalent to a decrease of *30.2 mg/dl*) when compared to ezetimibe with an original statin dose to -49.2% (95% CI, -55.3% to -43.1%; *P* < .0001; equivalent to a decrease of *61.4 mg/dl*) when compared to ezetimibe with a doubling of the statin dose.
  - We rated the quality of the evidence as high (Table ES3).

- The overall risk of adverse events was similar among participants receiving alirocumab and those receiving ezetimibe plus different statin regimens. We rated the quality of the evidence as high.
- Because of low event rates, we cannot draw any meaningful conclusions about the comparative incidence of cardiovascular events (very low quality of evidence).

Alirocumab vs. Standard of Care

- Compared to standard of care, alirocumab in participants with type 2 diabetes mellitus and mixed dyslipidemia on maximally tolerated doses of statins resulted in a statistically significant decrease in LDL-C levels after 24 weeks of treatment.
  - Mean percentage change -43.0% (95% CI, NR; *P* < .0001; equivalent to -*33.2 mg/dl*).
  - We rated the quality of the evidence as moderate (Table ES3).
- The overall risk of adverse events was similar among participants receiving alirocumab and those receiving standard of care. We rated the quality of the evidence as moderate.

Alirocumab vs. Placebo (With Statin and/or Ezetimibe Background Therapy)

- Compared to a placebo, alirocumab resulted in a statistically significant reduction (9.5% vs. 11.1%; hazard ratio [HR], 0.85 [95% CI, 0.78 to 0.93]) in the incidence of a composite cardiovascular event outcome that included death from coronary heart disease, nonfatal myocardial infarction, fatal or nonfatal ischemic stroke, or unstable angina requiring hospitalization. We rated the quality of the evidence as high (Table ES3).
- Overall mortality was statistically significantly lower in the alirocumab group than the placebo group (3.5% vs. 4.1%; HR, 0.85 [95% CI, 0.73 to 0.99]); death from cardiovascular causes, however, was not statistically significantly different between treatment groups (2.5% vs. 2.9%; HR 0.88 [95% CI, 0.74 to 1.05]). We rated the quality of evidence for death because of cardiovascular events as moderate (Table ES3).

Evolocumab vs. Ezetimibe (With Statin Background Therapy)

- Compared to ezetimibe, evolocumab in participants on high-intensity or moderate-intensity statins resulted in a statistically significant decrease in LDL-C levels after 10 to 12 weeks of treatment.
  - Mean percentage change -43.8% (95% CI, -52.1% to -35.6%, equivalent to a decrease of *38.8 mg/dl*) for participants on high-intensity statins and -43.5% (95% CI, -49.7% to -37.3%, equivalent to a decrease of *55.0 mg/dl*) for participants on moderate-intensity statins).
  - We rated the quality of the evidence as moderate (Table ES3).
- The overall incidence of adverse events was similar among participants receiving evolocumab and those receiving ezetimibe. We rated the quality of the evidence as high.

Evolocumab vs. Placebo (With Statin and/or Ezetimibe Background Therapy)

- Compared to a placebo, evolocumab resulted in a statistically significant reduction (9.8% vs. 11.3%; HR, 0.85 [95% CI, 0.79 to 0.92]) in the incidence of a composite cardiovascular event outcome that included cardiovascular death, myocardial infarction, stroke, hospitalization for

unstable angina, or coronary revascularization. We rated the quality of the evidence as high (Table ES3).

Table ES3. Summary of Findings (GRADE) for PCSK9 Inhibitors in Patients Who Did Not Achieve Target Levels

Outcome	Number of Studies Sample Size (N)	Quality of the Evidence	Relationship and Treatment Effect	Rationale for Quality of the Evidence
Alirocumab vs. Ezetimibe Plus Other Lipid-Lowering Therapies in Patients With Nonfamilial Hypercholesterolemia Not Achieving Target Levels				
Cardiovascular events at 52 weeks and from the time of the last dose plus 70 days	2 RCTs[12,13] N = 1,075	Very low	No relationship can be determined	Downgraded for risk of bias and very serious imprecision
LDL-C decrease at 24 weeks	3 RCTs[12-14] N = 1,380	High	Statistically significant greater reduction of LDL-C with alirocumab as an add-on to statin therapy compared to ezetimibe as an add-on to statin therapy Range: -23.6% (95% CI, -30.2% to -17.0%) to -49.2% (95% CI, -55.3% to -43.1%); *P* < .0001	Not downgraded for any domain
Overall adverse events at 52 weeks and from the time of the last dose plus 70 days	3 RCTs[12-14] N = 1,380	High	Similar risks for adverse events between alirocumab plus statin and ezetimibe plus statin Range: RR, 1.02 (95% CI, 0.83 to 1.24) to 1.06 (95% CI, 0.95 to 1.18)	Not downgraded for any domain
Discontinuation because of adverse events at 52 weeks and from the time of the last dose plus 70 days	3 RCTs[12-14] N = 1,380	Low	Similar risks for discontinuation because of adverse events between alirocumab plus statin and ezetimibe plus statin Range: RR, 1.70 (95% CI, 0.51 to 5.63) to 0.61 (95% CI, 0.21 to 1.81)	Downgraded for very serious imprecision
Serious adverse events at 52 weeks and from the time	3 RCTs[12-14] N = 1,380	Moderate	Similar risks for serious adverse events between alirocumab plus statin and ezetimibe plus statin	Downgraded for imprecision

Outcome	Number of Studies Sample Size (N)	Quality of the Evidence	Relationship and Treatment Effect	Rationale for Quality of the Evidence
of the last dose plus 70 days			Range: RR, 0.55 (95% CI, 0.17 to 1.84) to 0.74 (95% CI, 0.27 to 2.04)	
Alirocumab vs. Standard of Care In Patients With Nonfamilial Hypercholesterolemia Not Achieving Target Levels				
LDL-C decrease at 24 weeks	1 RCT[15] N = 413	Moderate	Statistically significant greater reduction of LDL-C with alirocumab compared to SOC -43.0%; 95% CI, NR	Downgraded for imprecision
Overall adverse events at 24 weeks	1 RCT[15] N = 413	Moderate	Similar risks for adverse events between alirocumab and SOC RR, 1.03; 95% CI, 0.89 to 1.19	Downgraded for imprecision
Discontinuation because of adverse events at 24 weeks	1 RCT[15] N = 413	Low	Similar risks for discontinuation because of adverse events between alirocumab SOC 3.6% vs. 4.0%	Downgraded for very serious imprecision
Serious adverse event at 24 weeks	1 RCT[15] N = 413	Low	Similar risks for serious adverse events between alirocumab and SOC 9.5% vs. 8.8%	Downgraded for very serious imprecision
Alirocumab vs. Placebo in Patients With Nonfamilial Hypercholesterolemia Not Achieving Target Levels				
Cardiovascular events (composite outcome) at a median of 34 months	1 RCT[24] N = 18,924	High	Statistically significant reduction in cardiovascular risk with alirocumab compared to placebo HR 0.85; 95% CI, 0.78 to 0.93 9.5% vs. 11.1%	Not downgraded for any domain
Death from cardiovascular causes at a median of 34 months	1 RCT[24] N = 18,924	Moderate	Similar risks for death from cardiovascular causes between alirocumab and placebo 2.5% vs. 2.9%	Downgraded for imprecision
Evolocumab vs. Ezetimibe (With Statin Background Therapy) in Patients With Nonfamilial Hypercholesterolemia Not Achieving Target Levels				
Cardio-vascular events at the mean of weeks 10 and 12	1 RCT[16] N = 1,899	Very low	No relationship can be determined	Downgraded for indirectness and very serious imprecision

Outcome	Number of Studies Sample Size (N)	Quality of the Evidence	Relationship and Treatment Effect	Rationale for Quality of the Evidence
LDL-C decrease at the mean of weeks 10 and 12	1 RCT[16] N =1,899	Moderate	Statistically significant greater reduction of LDL-C with evolocumab compared to ezetimibe -43.8%; 95% CI, -52.1% to -35.6%	Downgraded for risk of bias
Overall adverse events at the mean of weeks 10 and 12	1 RCT[16] N = 1,899	High	Similar risks for adverse events between alirocumab and standard of care RR, 0.9; 95% CI, 0.76 to 1.08	Not downgraded for any domain
Discontinuation because of adverse events at the mean of weeks 10 and 12	1 RCT[16] N = 1,899	Low	Similar risks for discontinuation because of adverse events between alirocumab and standard of care 1.9% vs. 1.8%	Downgraded for very serious imprecision
Serious adverse events at the mean of weeks 10 and 12	1 RCT[16] N = 1,899	Low	Similar risks for serious adverse events between alirocumab and standard of care 2.1% vs. 0.9%	Downgraded for very serious imprecision
Evolocumab vs. Placebo in Patients With Nonfamilial Hypercholesterolemia Not Achieving Target Levels				
Cardiovascular events (composite outcome) at a median of 26 months	1 RCT[21-23] N = 27,564	High	Statistically significant reduction in cardiovascular risk with evolocumab compared to placebo HR 0.85; 95% CI, 0.79 to 0.92 9.8% vs. 11.3%	Not downgraded for any domain

Abbreviations. CI: confidence interval; HR: hazard ratio; LDL-C: low-density lipoprotein-cholesterol; NR: not reported; RCT: randomized controlled trial; SOC: standard of care; RR: risk ratio

Efficacy and Effectiveness of PCSK9 Inhibitors as Monotherapy or Adjunct Therapy with Other Lipid-Lowering Agents or Cardiovascular Risk Reduction Methods (Key Question 4)

Evolocumab Plus Standard of Care vs. Standard of Care in a Mixed Population of Familial and Nonfamilial Hypercholesterolemia

- Compared to standard of care alone, evolocumab plus standard of care resulted in a statistically significant decrease in LDL-C levels.
    - Mean percentage change -58.4% (95% CI, NR; equivalent to a decrease of 70.5 mg/dl) and cardiovascular events (HR, 0.47; 95% CI, 0.28 to 0.78) after 48 weeks of treatment.

- We rated the quality of the evidence as low for the decrease in LDL-C levels and for cardiovascular events (Table ES4).
- The incidence of adverse events was statistically significantly higher for evolocumab plus standard of care than standard of care alone at 48 weeks (69.2% vs. 64.8%; *RR, 1.07* [*95% CI, 1.02 to 1.12*]). We rated the quality of the evidence as moderate.
- The incidence of serious adverse events was similar between treatment groups. We rated the quality of the evidence as low.
- We cannot draw any meaningful conclusions about the comparative incidence of death resulting from cardiovascular events (very low quality of evidence).

Alirocumab vs. Ezetimibe as First-Line Therapies in a Population Without Lipid-Lowering Therapy

- Compared to ezetimibe, alirocumab led to a statistically significant greater reduction in LDL-C levels.
  - Mean percentage change -31.6% (95% CI, -40.2% to -23.0).
  - We rated the quality of the evidence as low (Table ES4).
- Fewer participants receiving alirocumab than participants receiving ezetimibe experienced adverse events, although the difference was not statistically significant.
  - 69.2% vs. 78.4%; RR, 0.88 (95% CI, 0.70 to 1.11).
  - We rated the quality of the evidence as low.
- We cannot draw any meaningful conclusions about the comparative incidence of adverse events leading to discontinuation or serious adverse events (very low-quality evidence).

Table ES4. Summary of Findings (GRADE) for PCSK9 Inhibitors in Mixed Populations with Hypercholesterolemia

Outcome	Number of Studies Sample Size (N)	Quality of the Evidence	Relationship and Treatment Effect	Rationale for Quality of the Evidence
Evolocumab Plus Standard of Care vs. Standard of Care in Mixed Populations With Hypercholesteremia				
Death from cardiovascular events at 48 weeks	Pooled analysis of 2 RCTs[8,20] N = 4,465	Very low	No relationship can be determined	Downgraded for risk of bias and very serious imprecision
Cardiovascular events (composite outcome) at 48 weeks	Pooled analysis of 2 RCTs[8,20] N = 4,465	Low	Significantly lower risk for evolocumab + SOC than SOC HR, 0.47; 95% CI, 0.28 to 0.78)	Downgraded for risk of bias and imprecision
LDL-C decrease at 48 weeks	Pooled analysis of 2 RCTs[8,20] N = 4,465	Low	Significantly greater reduction for evolocumab + SOC than SOC -58.4%; 95% CI, NR	Downgraded for serious risk of bias

Outcome	Number of Studies Sample Size (N)	Quality of the Evidence	Relationship and Treatment Effect	Rationale for Quality of the Evidence
Overall adverse events at 48 weeks	Pooled analysis of 2 RCTs[8,20] N = 4,465	Moderate	Significantly higher risk for evolocumab + SOC than SOC RR, 1.07; 95% CI, 1.02 to 1.12	Downgraded for risk of bias
Serious adverse events at 48 weeks	Pooled analysis of 2 RCTs[8,20] N = 4,465	Low	Similar risks between treatment groups 7.3% vs. 8.6%	Downgraded for risk of bias and imprecision
Alirocumab vs. Ezetimibe for First -Line Therapy				
LDL-C decrease at 24 weeks	1 RCT[9,10] N = 103	Low	Statistically significant greater reduction of LDL-C with alirocumab than ezetimibe -31.6%; 95% CI, NR	Downgraded for very serious imprecision
Overall adverse events at 24 weeks	1 RCT[9,10] N = 103	Low	Numerically higher risk for adverse events for ezetimibe than alirocumab RR, 0.88; 95% CI, 0.70 to 1.11	Downgraded for very serious imprecision
Discontinuation because of treatment-emergent adverse events at 24 weeks	1 RCT[9,10] N = 103	Very low	No relationship can be determined	Downgraded for risk of bias and very serious imprecision
Patients with any serious adverse events at 24 weeks	1 RCT[9,10] N = 103	Very low	No relationship can be determined	Downgraded for risk of bias and very serious imprecision

Abbreviations. CI: confidence interval; LDL-C: low-density lipoprotein-cholesterol; N: number of participants; NR: not reported; RCT: randomized controlled trial; SOC: standard of care; RR: risk ratio

Subgroup Differences in Efficacy and Adverse Events (Key Question 5)

- Participants with diabetes experienced a similar statistically significant reduction in cardiovascular events at 26 months when treated with evolocumab (HR, 0.83; 95% CI, 0.75 to 0.93) as participants without diabetes (HR, 0.87; 95% CI, 0.79 to 0.96). We rated the quality of evidence as high (Table ES5).
- Men and women achieved similar LDL-C level reductions at 24 weeks when treated with alirocumab compared with ezetimibe (mean percentage change in men -32.9% [95% CI, -41.2% to -24.5%] vs. mean percentage change in women -27.3% [95% CI, -36.5% to -18.1%; P = .83]). We rated the quality of evidence as moderate.

Table ES5. Summary of Findings (GRADE) for Subgroup Differences in Efficacy and Adverse Events

Outcome	Number of Studies Sample Size (N)	Quality of the Evidence	Relationship and Treatment Effect	Rationale for Quality of the Evidence
Evolocumab vs. Placebo in Participants With Nonfamilial Hypercholesterolemia Not Achieving Target Levels: Diabetes and No Diabetes				
Cardiovascular events at 26 months	1 RCT[21-23] N = 27,564	High	Similar reductions in cardiovascular events for participants with and without diabetes mellitus Diabetes: HR, 0.83; 95% CI, 0.75 to 0.93 No diabetes: HR, 0.87; 95% CI, 0.79 to 0.96	Not downgraded for any domain
Alirocumab vs. Ezetimibe in Statin-Intolerant Participants: Men and Women				
LDL-C decrease	1 RCT[11] N = 314	Moderate	Similar reductions in LDL-C for men and women Men: -32.9%; 95% CI, -41.2% to -24.5% Women: -27.3%; 95% CI, -36.5% to -18.1%	Downgraded for imprecision

Abbreviations. CI: confidence interval; HR: hazard ratio; LDL-C: low-density lipoprotein-cholesterol; N: number of participants; NR: not reported; RCT: randomized controlled trial.

Ongoing Studies

- We identified 9 ongoing or recently completed but not yet published studies of PCSK9 inhibitors, many of which do not provide a head-to-head comparison or are open label: 2 studies for alirocumab and 7 studies for evolocumab.
- The planned follow-up duration ranges from 12 to 36 weeks for studies evaluating an intermediate primary endpoint, such as change in LDL-C level. For studies with cardiovascular event or safety primary endpoints, the planned follow-up periods range from 1.5 to 5 years.

Conclusions

The evidence showed that PCSK9 inhibitors were more effective than other lipid-lowering therapies at reducing LDL-C serum levels in various populations with familial or nonfamilial hypercholesterolemia. In particular, participants with statin intolerance experienced substantial reductions of LDL-C levels. The incidences of adverse events, discontinuations because of adverse events, or serious adverse events were, in general, similar between participants who received PCSK9 inhibitors and participants who received other lipid-lowering treatments.

These findings confirm the results of the original systematic review. This update provides additional evidence for populations with nonfamilial hypercholesterolemia, for example, on alirocumab for the treatment of statin-intolerant patients. In addition, the update presents findings of 2 trials that had large sample sizes to help determine the influence of a PCSK9

inhibitor on cardiovascular risks (composite of cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, or coronary revascularization).

In these studies, participants treated with alirocumab or evolocumab experienced statistically significant reductions in cardiovascular risks compared to participants in the placebo groups with statin background therapy during the 34- and 26-month follow-up periods. However, the absolute risk reductions of the incidence of cardiovascular events were small in both trials. The incidence of all-cause mortality was statistically significantly lower for alirocumab than a placebo after 34 months but not significantly different between evolocumab and a placebo after 26 months.

Although the evidence is limited to draw meaningful conclusions about the influence of PCSK9 inhibitors on mortality, the available evidence indicates that PCSK9 inhibitors are an effective treatment option for patients with familial or nonfamilial hypercholesterolemia who do not achieve target LDL-C levels. To date, it is still unclear at what level of cardiovascular risk (based on the Atherosclerotic Cardiovascular Disease Risk Algorithm of the American College of Cardiology/American Heart Association) PCSK9 inhibitors should be initiated. In addition, most studies had follow-up periods of only 12 to 24 weeks. The long-term benefits and harms of PCSK9 inhibitors remain unclear.

List of Brand Names and Generic Drugs

Table 1 describes current PCSK9 inhibitors and their FDA approval status.

Table 1. List of PCSK9 inhibitors

Generic Drug (Alternative Names)	Manufacturer	Dose	Frequency	Form	FDA Status
Alirocumab (Praluent)	Sanofi S.A.	75–150 mg	Biweekly	Subcutaneous injection	Approved July 24, 2015
		300 mg	Monthly		
Evolocumab (Repatha)	Amgen Inc.	140 mg	Biweekly	Subcutaneous injection	Approved August 27, 2015
		420 mg	Monthly		

Abbreviations. FDA: U.S. Food and Drug Administration; PCSK9: proprotein convertase subtilisin/kexin type 9.

Background

Cardiovascular disease (CVD) continues to be a major cause of morbidity and mortality in the U.S.[25] Among other risk factors, high serum cholesterol is a main target for treatment in populations at risk for CVD because of the well-established association between hypercholesterolemia and CVD.[6,26] Statins and ezetimibe have demonstrated effectiveness in reducing the risk of cardiovascular events by lowering low-density lipoprotein cholesterol (LDL-C) levels.[6,26] Despite treatment with maximum doses of statins or ezetimibe, some patients do not achieve recommended target levels of serum LDL-C. Particularly, patients with familial hypercholesterolemia or patients who are intolerant of these drugs might benefit from additional reductions in LDL-C afforded by alternative treatment options.[6]

In addition to statins and ezetimibe, LDL-C levels may be further reduced by targeting the proprotein convertase subtilisin/kexin type 9 (PCSK9) enzyme produced by the liver.[27] PCSK9 inhibitors are monoclonal antibodies against the PCSK9 enzyme that interfere with the binding of the LDL receptor, leading to higher LDL receptor expression in liver cells and lower plasma LDL-C levels.[27] Based largely on short-term trials, 2 PCSK9 inhibitors received FDA approval in 2015 (Table 1) and are being used for patients with statin intolerance, patients with familial hypercholesterolemia, and patients unable to lower their LDL-C to an adequate level.[28-30] A third PCSK9 inhibitor (bococizumab) under development by Pfizer Inc. was discontinued in 2016 in part because of attenuating reductions in LDL-C levels and increases in immunogenicity over time.[31]

State Medicaid program administrators are interested in an update of the evidence on the use of PCSK9 inhibitors to reduce LDL-C and the risk of cardiovascular events in difficult-to-treat patients. Additionally, they are interested in whether PCSK9 inhibitors are sufficient as a

monotherapy or an adjunct therapy with other lipid-lowering agents to reduce cardiovascular risk; or whether other risk reduction methods, such as smoking cessation, are necessary.

PICO

Populations

- Patients with heterozygous and homozygous familial hypercholesterolemia
- Patients with hypercholesterolemia who are unable to use statins because of intolerance or for any other reasons
- Patients with nonfamilial hypercholesterolemia who have not achieved LDL-C < 100 mg/dl or < 70 mg/dl with standard therapy (e.g., statins)

Comparators

- Head-to-head comparisons of included interventions
- Active pharmacological treatments (e.g., statins), including trials of add-on therapy that provide comparative data on an included drug versus another active treatment
- Placebo, if CVD outcomes are included

Outcomes

- Health events and survival
  - Coronary heart disease
  - Nonfatal myocardial infarction
  - Stroke
  - Need for revascularization
  - Mortality (coronary heart disease and all-cause)
- Intermediate outcomes
  - LDL-C decrease
  - Ability to raise high-density lipoprotein cholesterol (HDL-C)
- Overall adverse events
- Withdrawals (i.e., discontinuations) due to adverse events
- Serious adverse events
- Specific adverse events
  - Injection site reactions
  - Allergic reactions
  - Gastrointestinal disturbance
  - Glucose intolerance
  - (Serious) hypocholesterolemia
  - Incidence of diabetes
  - Increased liver enzymes
  - Muscle-related events
  - Neurocognitive dysfunction
  - Nasopharyngitis
  - Adverse events with a 5-percentage point or more difference between study groups

Study Designs

- RCTs
- Systematic reviews (with or without a meta-analysis)

Key Questions

1. What are the comparative benefits and harms of PCSK9 inhibitors in patients with heterozygous and homozygous familial hypercholesterolemia?
2. What are the comparative benefits and harms of PCSK9 inhibitors in patients with hypercholesterolemia who are unable to use statins because of intolerance or for any other reasons?
3. What are the comparative benefits and harms of PCSK9 inhibitors in patients with nonfamilial hypercholesterolemia who have not achieved LDL-C < 100 mg/dl or < 70 mg/dl with their current lipid-lowering regimen (e.g., statin with or without ezetimibe)?
4. What is the efficacy and effectiveness of PCSK9 inhibitor monotherapy or adjunct therapy with other lipid-lowering agents (e.g., statin with or without ezetimibe) or other cardiovascular risk reduction methods (e.g., smoking cessation, diet) on cardiovascular risk in patients with hypercholesterolemia?
5. Do the comparative benefits and harms of PCSK9 inhibitors differ when used in different patient subgroups based on demographics (e.g., age), socioeconomic status, other medications, or comorbidities?

Methods

We describe our complete methods in Appendix A. Briefly, we searched Ovid MEDLINE, Cochrane Library, ClinicalTrials.gov, and several other websites to identify eligible studies. We rated the methodological quality of eligible RCTs or systematic reviews using standard instruments adapted from national and international quality standards.[1-3] We rated the quality of the body of evidence for 6 outcomes (death because of CVD, cardiovascular events, change in LDL-C levels, incidence of overall adverse events, discontinuation because of adverse events, and serious adverse events) when possible, using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach.[4,5] We extracted data and effect estimates for relevant outcomes. If relevant effect measures were not reported, we used StatsDirect (version 3.1.20), Stata (version 14.2), and MEDCALC to calculate effect measures based on data provided in the study. We indicate values that we calculated with italics.

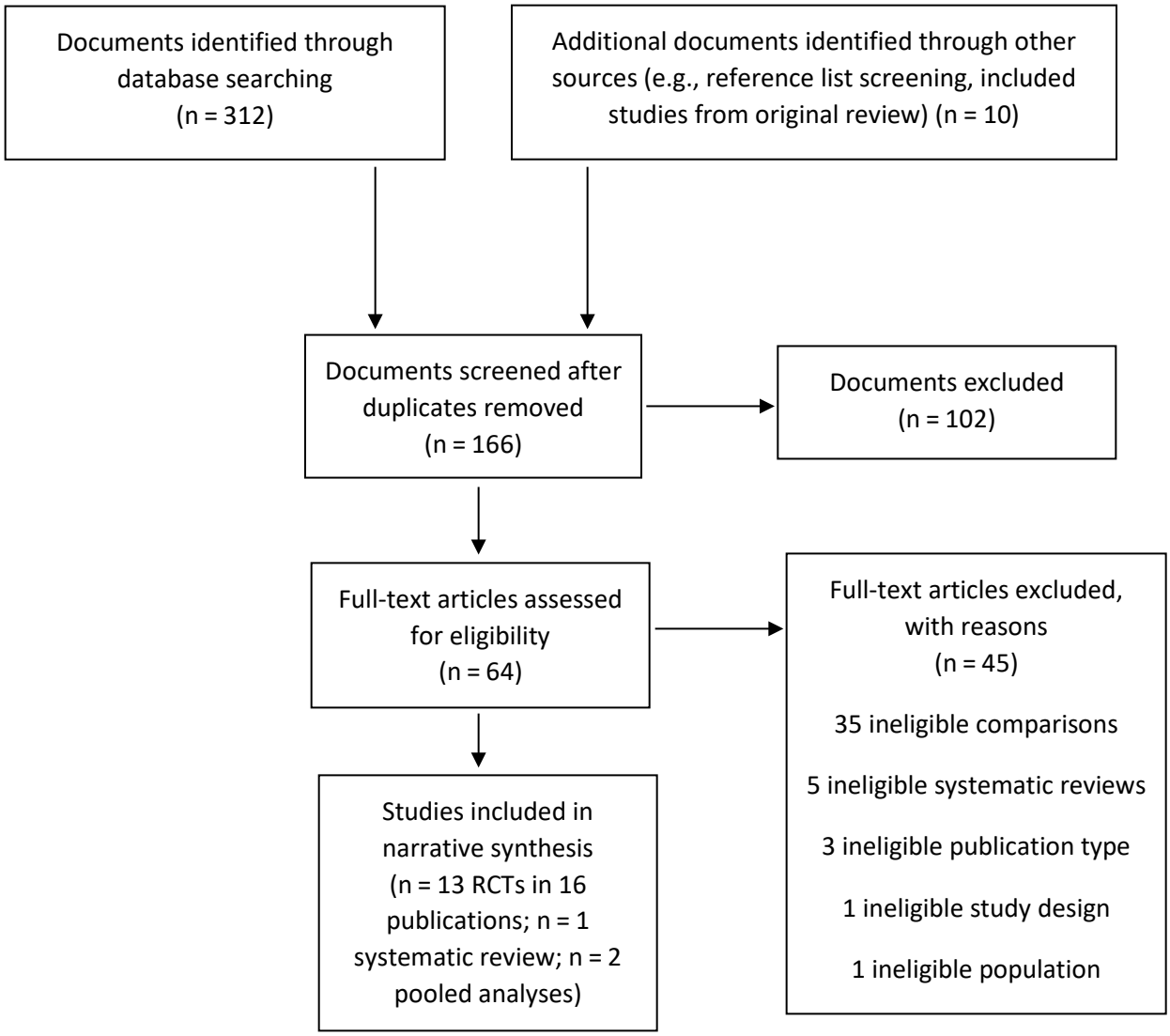
Findings

We included 13 RCTs with data on more than 56,800 participants. Of these 13 studies, 8 RCTs are new to this update. In addition, we included 1 systematic review[6] and 2 pooled data analysis.[7,8] Three RCTs compared alirocumab to ezetimibe,[9-12] 2 RCTs compared alirocumab to ezetimibe plus statins,[13,14] and 1 RCT compared alirocumab with standard of care.[15] In addition,

we included 1 RCT that compared alirocumab to a placebo control group because the primary outcome was CVD.[24]

Figure 1 is the PRISMA diagram of the literature review.

Figure 1. PRISMA Diagram



Four RCTs compared evolocumab to ezetimibe,[16-19] and 1 RCT[20] and 2 pooled data analyses compared evolocumab to standard of care.[7,8] In addition, we included 1 RCT that compared evolocumab to a placebo control group because the primary outcome was CVD.[21-23]Nine RCTs were short-term (up to 24 weeks), 1 was medium-term (up to 1 year), and 2 were long-term follow-up studies.

Pharmaceutical manufacturers sponsored all trials and the 2 pooled data analyses included in this review. The included systematic review did not receive any external funding. We rated the methodological quality of 2 trials as good, of 10 trials as fair, and of 1 trial as poor; we rated the quality of the systematic review as good and the quality of the 2 pooled analyses as poor.

The remaining sections are organized by populations (Key Questions 1 to 4). Within each section, we summarize the evidence on benefits and harms of PCSK9 inhibitors for the respective population and, if available, present findings on subgroups of interest within each section (Key Question 5). At the end of the section, we summarize results of the systematic review[6] and describe ongoing studies.

Detailed evidence tables are in Appendix Tables B1 (study characteristics), B2 (efficacy outcomes), and B3 (adverse event outcomes). Appendix C lists the bibliography of excluded studies, and Appendix D lists the bibliography of included studies.

Patients With Heterozygous Familial Hypercholesterolemia

Table 2 summarizes the findings (GRADE) for the primary research evidence for patients with heterozygous familial hypercholesterolemia. The evidence is limited to evolocumab plus standard of care compared to standard of care alone (see Appendix C for details). Because of serious methodological limitations, we rated the quality of the evidence as low for LDL-C decrease and risk of adverse events. Because of additional serious imprecision, we rated the quality of evidence as very low for serious adverse events.

Table 2. Summary of Findings (GRADE) for PCSK9 Inhibitors for Heterozygous Familial Hypercholesterolemia

Outcome	Quality of the Evidence	Relationship	Rationale
Alirocumab			
No eligible evidence			
Evolocumab Plus Standard of Care vs. Standard of Care			
LDL-C decrease at 48 weeks (1 pooled analysis of 2 RCTs)[7]	Low	Significantly greater reduction with evolocumab + SOC compared to SOC	Downgraded for very serious risk of bias
Overall risk of adverse events at 48 weeks (1 pooled analysis of 2 RCTs)[7]	Low	Significantly higher incidence with evolocumab + SOC compared to SOC	Downgraded for very serious risk of bias
Serious adverse events at 48 weeks (1 pooled analysis of 2 RCTs)[7]	Very low	No relationship can be determined	Downgraded for very serious risk of bias and imprecision

Note. Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach used. Abbreviations. LDL-C: low-density lipoprotein-cholesterol; SOC: standard of care.

Table 3 summarizes the study characteristics, primary study endpoint findings, serious adverse events, and discontinuations because of adverse events for the pooled analysis comparing evolocumab plus standard of care with standard of care alone in this population.[7] We assessed this study as poor methodological quality because of lack of intention-to-treat analysis, lack of blinding, potential funding bias, and the fact that the statistical analysis compared follow-up data to baseline data that were not collected at the time of randomization. Detailed evidence tables are in Appendix Tables B1 (study characteristics), B2 (efficacy outcomes), and B3 (adverse event outcomes).

Table 3. Summary of Evidence: RCTs of PCSK9 Inhibitors for Heterozygous Familial Hypercholesterolemia

Study; Registration Number; Trial Name	Dose, Frequency, and N Randomized	Primary Study Endpoint; Difference From Comparator	N (%) With at Least 1 Serious Adverse Event	N (%) With Adverse Event(s) Leading to Discontinuation
Alirocumab				
No eligible evidence				
Evolocumab Plus Standard of Care vs. Standard of Care				
Hovingh et al., 2017[7] NCT01439880 NCT01854918 Pooled analysis of OSLER data	140 mg SC Q2W or 420 mg SC + SOC = 289 SOC = 151 Total N = 440	Mean percentage change in LDL-C at 48 weeks vs. placebo[a]: 140 mg SC Q2W or 420 mg SC Q4W + SOC: *-56%* (CI NR); *P* = NR	140 mg SC Q2W or 420 mg SC Q4W + SOC: 21 (7.3) SOC: 13 (8.6)	140 mg SC Q2W or 420 mg SC Q4W + SOC: 0 (0) SOC: NR

Notes. [a] Compared to baseline from the RUTHERFORD (Reduction of LDL-C with PCSK9 Inhibition in Heterozygous Familial Hypercholesterolemia Disorder) parent studies. Abbreviations. LDL-C: low-density lipoprotein-cholesterol; NR: not reported; OSLER: Open-label Study of Long-term Evaluation against LDL-C; Q2W: dose delivered every 2 weeks; SC: subcutaneous; SOC: standard of care.

Alirocumab

We did not find any eligible studies evaluating alirocumab in patients with heterozygous familial hypercholesterolemia.

Evolocumab Plus Standard of Care vs. Standard of Care

Study Characteristics

A pooled data analysis by Hovingh et al.[7] of subgroups from 2 open-label RCTs assessed the long-term efficacy of evolocumab plus standard of care compared to standard of care alone during 48 weeks of follow-up. This study pooled data of 440 participants who had completed the RUTHERFORD (Reduction of LDL-C with PCSK9 Inhibition in Heterozygous Familial Hypercholesterolemia Disorder) trials[32] and participated in the OSLER (Open-label Study of

Long-term Evaluation against LDL-C) program.[8] OSLER consisted of 2 open-label RCTs that enrolled patients who had completed 1 of 5 phase 2 trials (OSLER-1) or 1 of 7 phase 3 trials (OSLER-2) of evolocumab. In OSLER, participants were rerandomized to open-label evolocumab treatment (140 mg every 2 weeks or 420 mg every 4 weeks) plus standard of care or standard of care alone. Standard of care was based on local guidelines for the treatment of LDL-C.[8] The original RUTHERFORD trials included patients with heterozygous familial hypercholesterolemia who did not reach target LDL-C levels (< 100 mg/dl) despite cholesterol-lowering therapy.[32] Hovingh et al. pooled data of participants from the RUTHERFORD trials who were part of OSLER-1 and OSLER-2.[7] At the start of the RUTHERFORD trials, the mean LDL-C was *72.1mg/dl*; 28% of participants had coronary artery disease.[7]

We rated this study as poor methodological quality because of lack of intention-to-treat analysis, lack of blinding, and potential for funding bias. Also, statistical analyses compared changes in LDL-C levels to baseline values of the original RUTHERFORD studies (not to baseline levels at the time of rerandomization).

Findings

Compared to baseline values in the RUTHERFORD trials, participants treated with evolocumab plus standard of care had greater changes in LDL-C after 48 weeks than participants on standard of care treatment (difference in mean percentage change from baseline -55.7% [equivalent to a decrease of 36.0 mg/dl; 95% CI, NR] see Table 3).[7] Participants treated with evolocumab plus standard of care also had greater changes in HDL-C levels; the difference in mean percentage increase in HDL-C levels from baseline was 8% [95% CI, NR]).[7] The study did not report any other efficacy outcomes of interest.

During 48 weeks of open-label treatment, authors reported a significantly higher risk of adverse events for participants treated with evolocumab plus standard of care compared to participants receiving standard of care (79.9% vs. 66.9%; *RR, 1.30; 95% CI, 1.09 to 1.59*).[7] Nasopharyngitis (17.0% vs. 6.0%) and muscle events (10.0% vs. 4.6%) occurred more frequently in participants treated with evolocumab plus standard of care compared to participants treated with standard of care alone during 48 weeks of follow-up.[7] However, the incidence of serious adverse events was similar (7.3% vs. 8.6%; see Table 3).[7]

Patients With Homozygous Familial Hypercholesterolemia

We did not find any eligible studies evaluating evolocumab in patients with homozygous familial hypercholesterolemia.

Patients Who Are Statin-Intolerant or Unable to Use Statins

Table 4 provides the Summary of Findings (GRADE) for the primary research evidence for patients with hypercholesterolemia who are statin-intolerant or unable to use statins. The

evidence is limited to alirocumab compared to ezetimibe, evolocumab compared to ezetimibe, and evolocumab plus ezetimibe compared to ezetimibe alone.

Table 4. Summary of Findings (GRADE) for PCSK9 Inhibitors in Statin-Intolerant Patients

Outcome	Quality of the Evidence	Relationship	Rationale
Alirocumab vs. Ezetimibe			
Cardiovascular events at 24 weeks (1 RCT)[11]	Very low	Not statistically significant but numerically greater incidence of cardiovascular events with alirocumab compared to ezetimibe	Downgraded for risk of bias and very serious imprecision
LDL-C decrease (1 RCT) at 24 weeks[11]	Moderate	Statistically significant greater reduction with alirocumab compared to ezetimibe	Downgraded for imprecision
Overall risk of adverse events at 24 weeks (1 study)[11]	Moderate	Similar incidence	Downgraded for imprecision
Discontinuation because of adverse events at 24 weeks (1 RCT)[11]	Low	Not statistically significant but numerically lower incidence for discontinuation because of adverse events for alirocumab compared to ezetimibe	Downgraded for very serious imprecision
Serious adverse events at 24 weeks (1 RCT)[11]	Low	Similar incidence	Downgraded for very serious imprecision
Evolocumab vs. Ezetimibe			
Cardiovascular events at 12 and 24 weeks (3 RCTs)[17-19]	Low	Similar incidence	Downgraded for very serious imprecision
LDL-C decrease at 12 and 24 weeks (3 RCTs)[17-19]	High	Statistically significant greater reduction with evolocumab compared to ezetimibe	Not downgraded for any domain
Overall incidence adverse events at 12 and 24 weeks (3 RCTs)[17-19]	High	Similar incidence	Not downgraded for any domain

Outcome	Quality of the Evidence	Relationship	Rationale
Discontinuation because of adverse events at 12 and 24 weeks (3 RCTs)[17-19]	Moderate	Statistically significant lower incidence with evolocumab compared to ezetimibe	Downgraded for imprecision
Serious adverse events at 12 and 24 weeks (3 RCTs)[17-19]	Low	Similar incidence	Downgraded for very serious imprecision
Evolocumab Plus Ezetimibe vs. Ezetimibe			
LDL-C decrease at 12 weeks (1 RCT)[19]	Low	Statistically significant greater reduction with evolocumab compared to ezetimibe	Downgraded for very serious imprecision
Overall adverse events at 12 weeks (1 RCT)[19]	Low	Similar incidence	Downgraded for risk of bias and imprecision
Discontinuation because of adverse events at 12 weeks (1 RCT)[19]	Very low	No relationship can be determined	Downgraded for risk of bias and very serious imprecision
Serious adverse events at 12 weeks (1 RCT)[19]	Very low	No relationship can be determined	Downgraded for risk of bias and very serious imprecision

Notes. Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach used. Abbreviations. RCT: randomized controlled trial.

We rated the quality of the evidence as moderate, because of imprecision, for LDL-C decrease and the overall risk of adverse events for alirocumab compared with ezetimibe. Because of very serious imprecision, we graded the quality of evidence as low for serious adverse events and discontinuation due to adverse events. Because of very serious imprecision and risk of bias, we rated the quality of evidence as very low for cardiovascular events.

For the comparison of evolocumab with ezetimibe, we rated the quality of the evidence as high for LDL-C decrease and overall risk of adverse events. Because of very serious imprecision, we rated the quality of evidence as very low for cardiovascular events and serious adverse events. For discontinuation due to adverse events, we rated the quality of evidence as moderate because of imprecision.

For the comparison of evolocumab plus ezetimibe to ezetimibe alone, we rated the quality of the evidence as low for LDL-C decrease because of very serious imprecision. Because of imprecision and risk of bias from lack of blinding, we graded the quality of evidence as low for overall risk of adverse events, and very low for serious adverse events and discontinuation due to adverse events.

Table 5 summarizes the study characteristics, primary study endpoint findings, serious adverse events, and discontinuations because of adverse events for alirocumab or evolocumab monotherapy and evolocumab plus ezetimibe compared to ezetimibe in patients with statin intolerance. We assessed the 4 studies as fair methodological quality for efficacy and adverse events outcomes because of potential funding bias. Detailed evidence tables are in Appendix Tables B1 (study characteristics), B2 (efficacy outcomes), and B3 (adverse event outcomes).

Table 5. Summary of Evidence: RCTs of PCSK9 Inhibitors for Statin-Intolerant Patients

Study; Registration Number; Trial Name	Dose, Frequency, and N Randomized	Primary Study Endpoint; Difference From Comparator (95% CI)	N (%) With at Least 1 Serious Adverse Event	N (%) With Adverse Event Leading to Discontinuation
Alirocumab vs. Ezetimibe				
Moriarty et al., 2015[11] NCT01709513 ODYSSEY ALTERNATIVE	75 to 150 mg SC Q2W = 126 Ezetimibe 10 mg oral daily = 125 Total N = 250[a]	Mean percentage change in LDL-C from baseline at 24 weeks: -30.4% (-36.6% to -24.2%; *P* < .0001)	Alirocumab: 12 (9.5) Ezetimibe: 10 (8.1)	Alirocumab: 23 (18.3) Ezetimibe: 31 (25.0)
Evolocumab vs. Ezetimibe				
Sullivan et al., 2012[19] NCT01375764 GAUSS	420 mg SC = 32 420 mg SC + ezetimibe 10 mg oral daily = 31 Ezetimibe 10 mg oral daily = 33 Total N = 96[b]	Mean percentage change in LDL-C from baseline at 12 weeks[a]: 420 mg: -35.9% (-44.1% to -27.8%); *P* < .001 420 mg + ezetimibe: -47.3% (-53.7% to -40.8%); *P* < .001	420 mg[ab]: 1 (3.1) 420 mg[b] + ezetimibe: 0 (0) Ezetimibe: 0 (0)	420 mg[b]: 1 (3.1) 420 mg + ezetimibe: 1 (3.1) Ezetimibe: 2 (6.3)
Stroes et al., 2014[18] NCT01763905 GAUSS-2	140 mg SC Q2W + placebo oral daily = 103 Ezetimibe 10 mg oral daily + placebo SC Q2W = 51 420 mg SC Q4W + placebo oral daily = 102 Ezetimibe 10 mg oral daily + placebo SC = 51 Total N = 307	Mean percentage change from baseline in LDL-C reduction at the mean weeks 10 and 12 vs. ezetimibe + placebo SC: 140 mg SC Q2W + placebo oral: -36.9% (-42.3% to -31.6%); *P* < .001 420 mg SC + placebo oral: -38.7% (-43.1% to -34.3%); *P* < .001 Mean percentage change from baseline in LDL-C reduction at 12 weeks vs. ezetimibe + placebo SC:	140 mg SC Q2W + placebo daily: 5 (5) Ezetimibe 10 mg oral daily + placebo SC Q2W: 1 (2) 420 mg SC + placebo daily: 1 (1) Ezetimibe 10 mg oral daily + placebo SC: 3 (6)	140 mg SC Q2W + placebo daily: 6 (6) Ezetimibe 10 mg oral daily + placebo SC Q2W: 4 (8) 420 mg SC + placebo daily: 11 (11) Ezetimibe 10 mg oral daily + placebo SC: 9 (18)

Study; Registration Number; Trial Name	Dose, Frequency, and N Randomized	Primary Study Endpoint; Difference From Comparator (95% CI)	N (%) With at Least 1 Serious Adverse Event	N (%) With Adverse Event Leading to Discontinuation
		140 mg SC Q2W: -38.1% (-43.7% to -32.4%); *P* < .001 420 mg SC: -37.6% (-42.2% to -32.9%); *P* < .001		
Nissen et al., 2016[17] NCT01984424 GAUSS-3	420 mg SC Q4W + placebo oral daily = 145 Ezetimibe 10 mg oral daily + placebo SC = 73 Total N = 218	Mean percentage change from baseline in LDL-C reduction at the mean for 22 and 24 weeks vs. ezetimibe + placebo SC: 420 mg SC Q4W + oral placebo: -37.8% (-42.3% to -33.3%); *P* < .001) Mean percentage change from baseline in LDL-C reduction at 24 weeks vs. ezetimibe + placebo SC: 420 mg SC Q4W + placebo oral: -36.1% (-41.1% to -31.1); *P* < .001)	420 mg SC + oral placebo daily: 9 (6.2) Ezetimibe 10 mg oral daily + placebo SC: 10 (13.7)	Discontinued oral drug treatment: 420 mg SC Q4W + oral placebo daily: 23 (15.9) Ezetimibe 10 mg oral daily + placebo SC: 14 (19.2) Discontinued SC drug treatment: 420 mg SC Q4W + oral placebo daily: 7 (4.8) Ezetimibe 10 mg oral daily + placebo SC: 4 (5.5)

Note. [a] Total N for trial was 314, but atorvastatin arm (N = 63) not included here because it is a statin re-challenge arm with no efficacy comparisons made with alirocumab or ezetimibe arms; [b] Findings for FDA-approved doses only. Abbreviations. GAUSS: Goal Achievement after Utilizing an anti-PCSK9 antibody in Statin Intolerant Subjects; LDL-C: low-density lipoprotein-cholesterol; ODYSSEY ALTERNATIVE: Efficacy and safety of alirocumab vs. ezetimibe in statin-intolerant patients, with a statin rechallenge arm: the ODYSSEY ALTERNATIVE randomized trial; Q2W: dose delivered every 2 weeks; Q4W: dose delivered every 4 weeks; SC: subcutaneous.

Alirocumab vs. Ezetimibe

Study Characteristics

One RCT by Moriarty et al. (ODYSSEY ALTERNATIVE)[11] of fair methodological quality assessed the efficacy of alirocumab compared to ezetimibe in 314 participants with primary hypercholesterolemia and statin intolerance.[11] After a 4-week single-blind placebo run-in phase, this study randomized participants from multiple sites in Europe and North America to either alirocumab 75 mg every 2 weeks (increased to 150 mg at week 12, depending on week 8 LDL-C

values), ezetimibe 10 mg, or atorvastatin 20 mg.[11] Investigators excluded participants who developed muscle symptoms during the placebo run-in period prior to randomization.[11] Eligible participants were at moderate to very high cardiovascular risk (see Appendix B for more detail).[11] At screening, patients at moderate or high cardiovascular risk were eligible if they had an LCL-C level ≥ 100 mg/dl, and patients at very high risk were eligible if they had an LCL-C level ≥ 70 mg/dl [11] All participants were unable to tolerate 2 or more statins, including 1 at the lowest approved starting dose.[11] Almost half of the participants in each treatment arm were at very high cardiovascular risk (ranging from 50% to 58% over 10 years).[11] Depending on the treatment arm, 43% to 51% had coronary heart disease.[11] Overall, 14% of participants had a history of myocardial infarction.[11] The primary endpoint of the study was the percentage change in LDL-C serum concentration from baseline to 24 weeks for alirocumab compared to ezetimibe.[11] The manufacturer of alirocumab funded the included study.

Findings

At 24 weeks, participants treated with alirocumab 75 mg to 150 mg every 2 weeks had statistically significant greater reductions of LDL-C levels than participants in the ezetimibe group (difference in mean percentage change from baseline, intention-to-treat analysis: -30.4% [95% CI, -36.6% to -24.2%; *P* < .0001]; on-treatment analysis: -35.1% [95% CI, -40.7% to -29.5%; *P* < .0001; equivalent to a decrease of *65.6 mg/dl*; Table 5).[11] Participants receiving alirocumab and ezetimibe had similar increases in HDL-C levels (mean percentage change from baseline 7.7% [95% CI, NR] vs. 6.8% [95% CI, NR]).[11] The percentage of participants with adjudicated cardiovascular events was greater in the alirocumab group than in the ezetimibe group (3.2% vs. 0.8%); however, the number of events was small (5 in total), and this difference was not statistically significant.[11] The study did not report on any other efficacy outcomes of interest.

For overall adverse events within 24 weeks, incidences were similar in the alirocumab group and the ezetimibe group (82.5% vs. 80.6%; *RR, 1.02* [*95% CI, 0.91 to 1.15*]). The incidence of serious adverse events (9.5% vs. 8.1%*; RR, 1.18* [*95% CI, 0.53 to 2.63*]) was also similar between treatment groups (see Table 5).[11] The percentage of discontinuations because of adverse events was lower in the alirocumab group than in the ezetimibe group (18.3% vs. 25.0%; *RR, 0.73* [*95% CI, 0.45 to 1.18*]), but this difference did not reach statistical significance (see Table 5).[11] Likewise, the incidence of skeletal muscle-related adverse events was numerically but not statistically significantly lower in participants treated with alirocumab compared to those receiving ezetimibe (32.5% vs. 41.1%; HR, 0.71 [95% CI, 0.47 to 1.06]; *P* = .10).[11] This study also examined differences in levels of LDL-C between men and women. At 24 weeks, the mean percentage change from baseline was similar between men and women (-32.9% [95% CI, -41.2% to -24.5%] vs. -27.3% [95% CI, -36.5% to -18.1%]; *P* = .83).[11]

Evolocumab

Study Characteristics

Three RCTs (GAUSS [Goal Achievement after Utilizing an anti-PCSK9 antibody in Statin Intolerant Subjects],[19] GAUSS-2,[18] and GAUSS-3[17]) evaluated the comparative efficacy of evolocumab and ezetimibe in participants with statin intolerance (see Appendix B). Sullivan et al.[19] also evaluated the comparative efficacy of evolocumab combined with ezetimibe and ezetimibe monotherapy.

We rated all 3 multicenter, multinational studies as fair methodological quality because of potential funding bias and unclear method of randomization and concealment. The manufacturer of evolocumab funded all GAUSS trials.

In addition, we identified 1 unpublished RCT (GAUSS-4, NCT02634580)[33] that was completed at the end of 2017. The study was conducted at 30 centers in Japan and enrolled participants who were hypercholesterolemic and statin-intolerant.[33] Investigators randomized 61 participants to 4 groups: evolocumab 140 mg every 2 weeks and oral placebo daily, evolocumab 420 mg every 4 weeks and oral placebo daily, ezetimibe 10 mg with subcutaneous placebo every 2 weeks, and the same combination every 4 weeks.[33]

The phase 2 GAUSS study[19] by Sullivan et al. randomized 160 participants with a history of muscle-related adverse effects with at least 1 statin to different doses of evolocumab (280 mg, 350 mg, 420 mg), evolocumab 420 mg plus ezetimibe 10 mg, and ezetimibe 10 mg plus a subcutaneous placebo. The administration of ezetimibe was not blinded.[19] Overall, the mean baseline LDL-C level was 193 mg/dl, 17% of participants had a history of coronary artery disease, and 50% of participants were at high or moderately high risk for cardiovascular disease according to National Cholesterol Education Program categories.[19] This study was conducted at multiple sites in North America, Australia, and Europe and followed participants for 12 weeks.[19] The primary endpoint was the percentage change in LDL-C from baseline to 12 weeks.[19]

The subsequent phase 3 GAUSS-2 study by Stroes et al.[18] compared evolocumab 140 mg every 2 weeks or 420 mg every 4 weeks to ezetimibe 10 mg plus a subcutaneous placebo every 2 or every 4 weeks in 307 participants with intolerance to at least 2 statins (see Appendix B). Eligible participants did not tolerate any dose or dose increase above the smallest tablet strength because of muscle-related adverse effects.[18] Study participants did not meet LDL-C treatment goals according to the National Cholesterol Education Program.[18] The percentage of participants in the high-risk category ranged from 50% to 63%.[18] Overall, at baseline the mean LDL-C level was 193 mg/dl; 33% of participants received lipid-lowering therapy and 18% received low-dose statins.[18] The co-primary endpoints were the percentage change in LDL-C levels from baseline to weeks 10 and 12 (mean level), and to week 12.[18]

The GAUSS-3 study (phase 3) by Nissen et al.[17] enrolled participants with uncontrolled LDL-C levels and a history of statin intolerance defined as intolerance to atorvastatin 10 mg and any other statin at any dose, or intolerance to 3 or more statins (1 statin at the lowest starting

average daily dose and any 2 other statins at any dose) due to skeletal muscle-related symptoms (see Appendix B). An initial statin rechallenge with atorvastatin 20 mg or placebo crossover identified participants with statin-related muscle symptoms.[17] Subsequently, this study randomized 218 participants with confirmed statin intolerance to evolocumab 420 mg every 4 weeks plus an oral placebo (N = 145) or ezetimibe 10 mg daily plus a subcutaneous placebo (N = 73).[17] At baseline, the mean LDL-C level was 219.9 mg/dl and was similar between groups.[17] Depending on the treatment arm, 33.1% to 28.8% had coronary artery disease.[17] Two or more cardiovascular risk factors were present in almost half of the participants in each group.[17] The co-primary endpoints were the percentage change in LDL-C levels from baseline to week 22 and up to week 24 .[17]

Findings

In this section, we report results of FDA-approved doses only.

Evolocumab vs. Ezetimibe (With Lipid-Lowering Background Therapy)

The phase 2 GAUSS trial by Sullivan et al.[19] reported statistically significant greater reductions in LDL-C levels at 12 weeks for participants treated with evolocumab 420 mg every 4 weeks compared to ezetimibe 10 mg (difference in mean percentage change from baseline: -35.9% [95% CI, -44.1% to -27.8%; *P* < .001]; equivalent to a decrease of *76.7 mg/dl*; see Table 5). No deaths or cardiovascular or cerebrovascular events occurred in any treatment arm.[19]

Efficacy results from the phase 3 GAUSS-2 trial[18] were consistent with findings from the other GAUSS trials. At 12 weeks, the difference in mean percentage change in LDL-C levels from baseline was -37.6 % (95% CI, -42.2% to -32.9%; *P* < .001; equivalent to a decrease of 68.8 mg/dl) for participants treated with evolocumab 420 mg every 4 weeks compared to participants who received ezetimibe; the difference for participants treated with 140 mg every 2 weeks was -38.1% (95% CI, -43.7% to -32.4%; *P* < .001; equivalent to a decrease of 69.7 mg/dl) compared to participants treated with ezetimibe (see Table 5).[18]

The GAUSS-3 trial followed participants for 24 weeks.[17] Overall, statistically significant reductions in LDL-C levels were maintained through week 24 (see Table 5). For example, reductions in LDL-C levels for participants treated with evolocumab 420 mg every 4 weeks were statistically significantly greater than reductions in participants who received ezetimibe 10 mg (difference in mean percentage change from baseline -36.1% [95% CI, -41.1% to -31.1%; *P* < .001]; equivalent to a decrease of 71.7 mg/dl; see Table 5).[17]

The unpublished GAUSS-4 RCT [33] reported greater reductions of LDL-C for participants treated with evolocumab than participants treated with ezetimibe at 12 weeks (difference in mean percentage change from baseline -40.1% [95% CI, -48.68% to -31.60%; *P* < .001]).

GAUSS and GAUSS-2 reported similar incidence of adverse events with evolocumab 420 mg and ezetimibe 10 mg (GAUSS: 56.3% vs. 59.4%; *RR, 0.95 [95% CI, 0.62 to 1.44*][19]; GAUSS-2, pooled groups: 66% vs. 73%, *RR, 0.91 [95% CI, 0.78 to 1.06*]).[18] The incidence of serious adverse events

was also similar between treatment groups (*GAUSS-2* pooled groups: 3% vs. 4%*; RR, 0.75 [95% CI, 0.22 to 2.59*]) (see Table 5).[18] In the GAUSS and GAUSS-2 trials, the number of participants who discontinued treatment because of adverse events was not statistically significantly different (e.g., GAUSS-2 pooled groups: 8% vs. 13%, *RR, 0.65 [95% CI, 0.33 to 1.29*]) (see Table 5).[18,19] In the GAUSS-2 study, the incidence of most specific adverse events was similar between the evolocumab and ezetimibe groups; however, muscle-related adverse events were statistically significantly less common in the evolocumab groups than in the ezetimibe groups (12% vs. 23%; *RR, 0.54 [95% CI, 0.32 to 0.90*]).[18]

During the 24-week follow-up period of GAUSS-3, the incidence of adverse events, discontinuations because of adverse events, and serious adverse events remained similar (see Table 5).[17] The percentage of participants who experienced muscle-related adverse events was lower in the evolocumab group than the ezetimibe group (20.7% vs. 28.8%; *RR, 0.72 [95% CI, 0.44 to 1.16*]).[17]

Evolocumab plus Ezetimibe vs. Ezetimibe (With Statin Lipid-Lowering Background Therapy)

The GAUSS trial also included a combination arm of evolocumab 420 mg every 4 weeks plus ezetimibe 10 mg.[19] Compared to ezetimibe 10 mg monotherapy, participants in the combination arm had statistically significant greater reductions in LDL-C levels at 12 weeks (difference in mean percentage change from baseline -47.3% [95% CI, -53.7% to -40.8%; $P < .001$]; equivalent to a decrease of *95.6 mg/dl*; see Table 5).[19]

The incidence of adverse events was similar with the combination of evolocumab 420 mg plus ezetimibe and ezetimibe 10 mg monotherapy (66.7% vs. 59.4%; *RR, 1.12 [95% CI, 0.77 to 1.65*]).[19] The incidence of serious adverse events and discontinuation because of adverse events were also similar and are presented in Table 5. However, because of the small number of events, we were not able to draw any meaningful conclusions for these outcomes.

Patients With Nonfamilial Hypercholesterolemia Not Achieving Target Levels

Table 6 summarizes the findings (GRADE) for the primary research evidence for patients with nonfamilial hypercholesterolemia who did not achieve target levels despite statin therapy (see Appendix B for details).

Table 6. Summary of Findings (GRADE) for RCTs of PCSK9 Inhibitors for Patients Not Achieving Target Levels

Outcome	Quality of the Evidence	Relationship	Rationale
Alirocumab vs. Other Lipid-Lowering Regimens			
Cardiovascular events at 52 weeks and from the time of the last dose plus 70 days (2 RCTs)[12,13]	Very low	No relationship can be determined	Downgraded for risk of bias and very serious imprecision
LDL-C decrease at 24 weeks (3 RCTs)[12-14]	High	Statistically significant greater reduction in LDL-C with alirocumab as an add-on to statin therapy compared to ezetimibe as an add-on to statin therapy	Not downgraded for any domain
Overall adverse events at 52 weeks and from the time of the last dose plus 70 days (3 RCTs) [12-14]	High	Similar incidence	Not downgraded for any domain
Discontinuation because of adverse events at 52 weeks and from the time of the last dose plus 70 days (3 RCTs)[12-14]	Low	Similar incidence	Downgraded for very serious imprecision
Serious adverse events at 52 weeks and from the time of the last dose plus 70 days (3 RCTs)[12-14]	Moderate	Similar incidence	Downgraded for imprecision
Alirocumab vs. Standard of Care			
LDL-C decrease at 24 weeks (1 RCT)[15]	Moderate	Statistically significant greater reduction of LDL-C with alirocumab compared to SOC	Downgraded for imprecision
Overall adverse events at 24 weeks (1 RCT)[15]	Moderate	Similar incidence	Downgraded for imprecision
Discontinuation because of adverse events at 24 weeks (1 RCT)[15]	Low	Similar incidence	Downgraded for very serious imprecision

Outcome	Quality of the Evidence	Relationship	Rationale
Serious adverse events at 24 weeks (1 RCT)[15]	Low	Similar incidence	Downgraded for very serious imprecision
Alirocumab vs. Placebo (With Statin Background Therapy)			
Cardiovascular events (composite outcome) at 34 months (1 RCT)[24]	High	Statistically significant reduction in cardiovascular risk with alirocumab compared to placebo	Not downgraded for any domain
Death from cardiovascular causes at 34 months (1 RCT) [24]	Moderate	Similar incidence	Downgraded for imprecision
Evolocumab vs. Ezetimibe (With Statin Background Therapy)			
Cardiovascular events at the mean of weeks 10 and 12 (1 RCT)[16]	Very low	No relationship can be determined	Downgraded for indirectness and very serious imprecision
LDL-C decrease at the mean of weeks 10 and 12 (1 RCT)[16]	Moderate	Statistically significant greater reduction of LDL-C with evolocumab compared to ezetimibe	Downgraded for risk of bias
Overall adverse events at the mean of weeks 10 and 12 (1 RCT)[16]	High	Similar incidence	Not downgraded for any domain
Discontinuation because of adverse events at the mean of weeks 10 and 12 (1 RCT)[16]	Low	Similar incidence	Downgraded for very serious imprecision
Serious adverse events at the mean of weeks 10 and 12 (1 RCT)[16]	Low	Similar incidence	Downgraded for very serious imprecision
Evolocumab vs. Placebo (With Statin Background Therapy)			
Cardiovascular events (composite outcome) at 26 months (1 RCT)[21-23]	High	Statistically significant reduction in cardiovascular risk with evolocumab compared to placebo	Not downgraded for any domain

Note. Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach used. Abbreviations. LDL-C: low-density lipoprotein-cholesterol; SOC: standard of care.

Table 7 summarizes the study characteristics, primary study endpoint findings, serious adverse events, and discontinuations because of adverse events for included comparisons in this population. We assessed 2 studies as good methodological quality for efficacy and adverse events outcomes and 5 studies as fair methodological quality for efficacy and adverse events outcomes because of imprecision and risk of bias including potential funding bias. Detailed evidence tables are in Appendix Tables B1 (study characteristics), B2 (efficacy outcomes), and B3 (adverse event outcomes).

Table 7. Summary of Evidence—RCTs of PCSK9 Inhibitors for Nonfamilial Hypercholesterolemia Not Achieving Target Levels

Study; Registration Number; Trial Name	Dose, Frequency, and N Randomized	Primary Study Endpoint; Difference From Comparator (95% CI, or SE and P Value)	N (%) With at Least 1 Serious Adverse Event	N (%) With Adverse Event Leading to Discontinuation
Alirocumab vs. Other Lipid-Lowering Regimens				
Cannon et al., 2015[12] NCT 01644188 ODYSSEY COMBO II	75 mg SC Q2W = 479 Increased to 150 mg SC Q2W if goal not met at 12 weeks (18% required this increase) 10 mg ezetimibe oral QD= 241 Total N = 720	Difference in mean percentage change from baseline in LDL-C reduction at 24 weeks vs. ezetimibe: 75–150 mg Q2W vs. 10 mg ezetimibe: -29.8% (-34.4% to -25.3%); *P* < .0001	75–150 mg Q2W: 90 (18.8) 10 mg ezetimibe oral QD: 43 (17.8)	75–150 mg Q2W: 36 (7.5) 10 mg ezetimibe oral QD: 13 (5.4)
Bays et al., 2015[13] NCT01730040 ODYSSEY OPTIONS I	75–150 mg SC Q2W + 20 mg atorvastatin QD = 57 75–150 mg SC Q2W + 40 mg atorvastatin QD = 47 10 mg ezetimibe oral QD + 20 mg atorvastatin QD = 55 10 mg ezetimibe oral QD + 40 mg atorvastatin QD = 47 40 mg atorvastatin QD = 57 80 mg atorvastatin QD = 47 40 mg rosuvastatin QD = 45 Total N = 355	Difference in mean percentage change from baseline in LDL-C at 24 weeks vs. each comparator: 75–150 mg + 20 mg atorvastatin vs. 10 mg ezetimibe oral + 20 mg atorvastatin: -23.6% (6.6%); *P* < .0004 75–150 mg SC Q2W + 20 mg atorvastatin vs. 40 mg atorvastatin: -39.1% (6.4%); *P* < .0001 75–150 mg + 40 mg atorvastatin vs. 10 mg ezetimibe + 40 mg atorvastatin: -31.4% (6.1%); *P* < .0001 75–150 mg + 40 mg atorvastatin vs. 80 mg atorvastatin: -49.2% (6.1%); *P* < .0001 75–150 mg SC + 40 mg atorvastatin vs. 40 mg rosuvastatin: -32.6% (6.0%); *P* < .0001	Pooled alirocumab: 4 (3.8) Pooled ezetimibe: 7 (6.9) Pooled atorvastatin or switch to rosuvastatin: 8 (5.4)	Pooled alirocumab: 7 (6.7) Pooled ezetimibe: 4 (4.0) Pooled double atorvastatin or switch to rosuvastatin: 8 (5.4)
Farnier, 2016[14,34] NCT01730053 ODYSSEY OPTIONS II	75–150 mg SC Q2W + 10 mg rosuvastatin QD = 49 75–150 mg SC Q2W + 20 mg rosuvastatin QD = 54 10 mg ezetimibe oral QD + 10 mg rosuvastatin QD = 48	Difference in mean percentage change from baseline in LDL-C at 24 weeks vs. each comparator: 75–150 mg + 10 mg rosuvastatin vs. 10 mg ezetimibe + 10 mg rosuvastatin: -36.1% (6.1%); *P* < .0001	Pooled alirocumab: 6 (5.8) Pooled ezetimibe: 8 (7.9)	Pooled alirocumab: 5 (4.9) Pooled ezetimibe: 8 (7.9) Pooled double rosuvastatin: 5 (5.0)

Study; Registration Number; Trial Name	Dose, Frequency, and N Randomized	Primary Study Endpoint; Difference From Comparator (95% CI, or SE and P Value)	N (%) With at Least 1 Serious Adverse Event	N (%) With Adverse Event Leading to Discontinuation
	10 mg ezetimibe oral QD + 20 mg rosuvastatin QD = 53 20 mg rosuvastatin QD = 48 40 mg rosuvastatin QD = 53 Total N = 305	75–150 mg + 10 mg rosuvastatin vs. 20 mg rosuvastatin: -34.2% (5.9%); *P* < .0001 75–150 mg + 20 mg rosuvastatin vs. 10 mg ezetimibe + 20 mg rosuvastatin: -25.3% (10.1%); *P* < .0136 75–150 mg + 20 mg rosuvastatin vs. 40 mg rosuvastatin: -20.3% (10.1%); *P* < .0453	Pooled double rosuvastatin: 8 (7.9)	
Alirocumab vs. Standard of Care				
Ray et al., 2017[15] NCT02642159 ODYSSEY DM-DYSLIPIDEMIA	75 mg SC Q2W = 276 Increased to 150 mg SC Q2W if goal not met at 12 weeks SOC= 137 ezetimibe = 53 fenofibrate = 25 omega-3 fatty acid = 21 nicotinic acid = 1 no lipid-lowering therapy = 37 Total N = 413	Difference in mean percentage change from baseline in non-HDL-C reduction at 24 weeks vs. SOC: 75 -150 mg vs. SOC: -32.5% (-38.1% to -27.0%); *P* < .0001 Difference in mean percentage change from baseline in LDL-C at 24 weeks vs. SOC: 75–150 mg vs. SOC: -43.0% (NR); *P* < .0001	75–150 mg: 26 (9.5) SOC: 12 (8.8)	75–150 mg: 10 (3.6) SOC: 4/100[c] (4)
Alirocumab vs. Placebo (With Statin Background Therapy)				
Schwartz et al., 2018[24] NCT: NCT01663402 ODYSSEY OUTCOMES	75 to 150 mg SC Q2W = 9,462 Placebo SC Q2W = 9,462 Total N = 18,924	Composite of death from coronary heart disease, nonfatal myocardial infarction, fatal or nonfatal ischemic stroke, or unstable angina requiring hospitalization at a median of 34 months vs. placebo: HR 0.85 (0.78 to 0.93; *P* < .001)	75 to 150 mg: 7,165 (75.8) Placebo: 7,282 (77.1)	75 to 150 mg: 343 (3.6) Placebo: 324 (3.4)
Evolocumab vs. Ezetimibe (With High- or Moderate-Intensity Background Statin Therapy)				
Robinson et al., 2014[16] NCT01763866 LAPLACE-2	140 mg SC Q2W or 420 mg SC QM = 1,117 Ezetimibe 10 mg QD = 221	Difference in mean percentage change from baseline in LDL-C at the mean of weeks 10 and 12 vs. ezetimibe High-Intensity Statin Subgroup (atorvastatin 80 mg):	140 mg or 420 mg: 23 (2.1) Ezetimibe: 2 (0.9) Placebo: 13 (2.3)	140 mg or 420 mg: 21 (1.9) Ezetimibe: 4 (1.8) Placebo: 12 (2.2)

Study; Registration Number; Trial Name	Dose, Frequency, and N Randomized	Primary Study Endpoint; Difference From Comparator (95% CI, or SE and P Value)	N (%) With at Least 1 Serious Adverse Event	N (%) With Adverse Event Leading to Discontinuation
	Placebo = 558 Total N = 1,899[b]	Every 2 weeks: -44.9% (-454.3% to -35.6%) Monthly: -43.8% (-52.1% to -35.6%) Moderate-Intensity Statin Subgroup (atorvastatin 10 mg): Every 2 weeks: -37.5% (-43.0% to -32.0%) Monthly: -43.5% (-49.7% to -37.3%)		
Evolocumab vs. Placebo (With Statin Background Therapy)				
Sabatine et al., 2017a[21]; Sabatine et al., 2017b[22]; Giugliano et al., 2017[23] NCT01764633 FOURIER	420 mg SC QM or 140 mg SC Q2W = 13,784 Placebo SC =13,780 Total N = 27,564	Composite of cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, or coronary revascularization at a median of 26 months vs. placebo: HR, 0.85 (0.79 to 0.92; *P* < .001)	420 mg or 140 mg: 3,410 (24.8) Placebo: 3,404 (24.7)	420 mg or 140 mg: 628 (4.6) Placebo: 581 (4.2)

Note. [a] Only individuals with additional lipid-lowering therapies; [b] Three did not receive study drug. Abbreviations. FOURIER, Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk; HDL-L: high-density lipoprotein-cholesterol; LAPLACE-2: LDL-C Assessment With PCSK9 Monoclonal Antibody Inhibition Combined With Statin Therapy-2;, LDL-C Assessment With PCSK9 Monoclonal Antibody Inhibition Combined With Statin Therapy-2; LDL-C: low-density lipoprotein-cholesterol; NR: not reported; ODYSSEY COMBO, Efficacy and Safety of Alirocumab (SAR236553/REGN727) Versus Placebo on Top of Lipid-Modifying Therapy in Patients With High Cardiovascular Risk and Hypercholesterolemia; ODYSSEY DM-DYSLIPIDEMIA: Alirocumab vs usual lipid-lowering care as add-on to statin therapy in individuals with type 2 diabetes and mixed dyslipidemia: the ODYSSEY DM-DYSLIPIDEMIA randomized trial; ODYSSEY OPTIONS I, Study of the Efficacy and Safety of Alirocumab (REGN727/SAR236553) in Combination With Other Lipid-modifying Treatment; ODYSSEY OPTIONS II, Study of Alirocumab (REGN727/SAR236553) added-on to Rosuvastatin Versus Other Lipid Modifying Treatments Q2W: dose delivered every 2 weeks; QD; dose delivered daily; QM: dose delivered monthly; SC: subcutaneous; SOC: standard of care.

Alirocumab

Study Characteristics

Four phase 3 RCTs[12-14,24] and 1 phase 3b/4 RCT,[15] of good[24] and fair[12-15] methodological quality, assessed the efficacy of alirocumab (75 mg every 2 weeks increasing to 150 mg at week 12 if target lipid levels were not met) as an add-on to statin therapy for participants with nonfamilial hypercholesterolemia not achieving target lipid levels (typically defined as LDL-C ≥ 100 mg/dl, or high cardiovascular-risk and LDL-C or non-HDL-C ≥ 70 mg/dl).

Two trials (ODYSSEY OPTIONS I[13] [N = 355] and II[14] [N = 305]) randomized high cardiovascular-risk participants according to baseline statin therapy (20 to 40 mg/day atorvastatin or 10 to 20 mg/day of rosuvastatin, respectively) and compared alirocumab to other lipid-lowering regimens. ODYSSEY OPTIONS I compared alirocumab to ezetimibe (10 mg/day) plus the baseline dose of atorvastatin, and to 1 of 3 statin regimens (a doubling of the baseline atorvastatin dose [either 40 mg/day or 80 mg/day], or switching from atorvastatin to rosuvastatin).[13,14] ODYSSEY OPTIONS II compared alirocumab to ezetimibe (10 mg/day) plus baseline rosuvastatin, and to a doubling of the baseline rosuvastatin dose (either 20 mg/day or 40 mg/day).[14] The ODYSSEY COMBO II (N = 750) trial compared alirocumab to ezetimibe (10 mg/day) in participants with high cardiovascular risk and a background of maximally tolerated doses of statins (rosuvastatin 20/40 mg/day, atorvastatin 40 to 80 mg/day, or simvastatin 80 mg/day) or on a lower dose, if the reason for doing so was documented.[12] The ODYSSEY DM-DYSLIPIDEMIA trial (N = 413) compared alirocumab to usual lipid-lowering care (i.e., standard of care) consisting of maximally tolerated statin therapy and add-on fenofibrate, omega-3 fatty acids, ezetimibe (10 mg/day), nicotinic acid, or no additional lipid-lowering therapy in high-cardiovascular-risk participants with type 2 diabetes and mixed dyslipidemia.[15]

The ODYSSEY OUTCOMES study was a multicenter trial (N = 18,924) that randomized participants to alirocumab 75 mg or a placebo every 2 weeks.[24] Eligible participants, aged 40 years or older, had had an acute coronary syndrome 1 to 12 months earlier and did not achieve target LDL-C levels (LDL-C > 70mg/dl) despite receiving statin therapy at a high-intensity dose or at the maximum tolerated dose.[24] Only 3% of the trial population, however, received additional ezetimibe treatment.[24] During the study, the dose of alirocumab was adjusted under blinded conditions to target an LDL cholesterol level of 25 to 50 mg/dl.[24] The trial was conducted at 1,315 sites in 57 countries. The median follow-up time was 34 months.[24]

The average age across studies ranged from 58 to 63 years; trial participants predominantly identified as white (79% to 90% across studies) and male (51% to 75%) The manufacturer of alirocumab funded all 5 studies.

The primary endpoint in 3 trials was the difference in mean percentage change in LDL-C levels from 12 to 24 weeks.[12-14] The primary endpoint in the ODYSSEY DM-DYSLIPIDEMIA trial was the difference in mean percentage change in non-HDL-C at 24 weeks.[15] In the ODYSSEY OUTCOMES trial, the primary endpoint was a composite of death from coronary heart disease, nonfatal

myocardial infarction, fatal or nonfatal ischemic stroke, or unstable angina requiring hospitalization.

Findings

Alirocumab vs. Other Lipid-Lowering Regimens

The ODYSSEY OPTIONS I and II trials found that alirocumab compared to ezetimibe plus the original baseline dose of statin, a doubling of the original statin dose, or switching statins resulted in a statistically significant greater reduction in LDL-C levels from baseline.[13,14] Compared to ezetimibe with the original statin (20 mg/day of atorvastatin or 10 mg/day of rosuvastatin), the difference in mean percentage change from baseline among participants receiving alirocumab ranged from -36.1% (95% CI, -42.2% to -30.0%; *P* < .0001; equivalent to a decrease of *39.6 mg/dl*) to -23.6% (95% CI, -30.2% to -17.0%; *P* = .0004); equivalent to a decrease of *30.2 mg/dl*] across studies (see Table 7).[13,14] Compared to doubling of the statin dose, the difference in mean percentage change from baseline among participants receiving alirocumab ranged from -49.2% (95% CI, -55.3% to -43.1%; *P* < .0001; equivalent to a decrease of *61.4 mg/dl*) to -20.3% 095% CI, -30.4% to -10.2%; *P* = .045, equivalent to a decrease of *25.0 mg/dl*) across studies (see Table 7).[13,14] Compared to switching from atorvastatin to rosuvastatin, the difference in mean percentage change from baseline was -32.6% (95% CI, -38.6% to -26.6%; *P* < .0001, equivalent to a decrease of *37.2 mg/dl;* see Table 7).[13,14]

The ODYSSEY COMBO II trial found that at 24 weeks in participants with high cardiovascular risk and a background of maximally tolerated doses of statins, alirocumab as an add-on to statin therapy resulted in a statistically significant greater reduction in LDL-C levels (from baseline) compared to add-on ezetimibe (difference in mean percentage change from baseline -29.8% [95% CI, -34.4% to -25.3%; *P* < .0001]; see Table 7).[12]

The ODYSSEY COMBO II trial found the incidence of cardiovascular events was similar among participants receiving alirocumab and those receiving ezetimibe (*RR, 1.29; 95% CI, 0.60 to 2.74*).[12] The incidence of cardiovascular-related deaths was reported (2 in each arm), but was too low to draw meaningful conclusions.[12] The ODYSSEY OPTIONS I trial reported the number of treatment-related deaths and cardiovascular events, but the event rates were too low to draw meaningful conclusions (2 treatment-related deaths and 2 cardiovascular events across arms).[13] The ODYSSEY OPTIONS II trial did not report either treatment-related deaths or cardiovascular-related events.[14]

The ODYSSEY OPTIONS I and II trials pooled the numbers of adverse events across statin regimens, and the authors found that the incidence of overall adverse events, serious adverse events, and adverse events leading to treatment discontinuation were similar in participants receiving alirocumab compared to participants receiving ezetimibe with the original statin therapy (*RR, 1.02 [95% CI, 0.83 to 1.24] to 1.05 [95% CI, 0.82 to 1.35]* for any adverse event); (*RR, 0.55 [95% CI, 0.17 to 1.84] to 0.74 [95% CI, 0.27 to 2.04*] for serious adverse events); and (*RR, 1.70 [95% CI, 0.51 to 5.63] to 0.61 [95% CI, 0.21 to 1.81*] for adverse events leading to discontinuation;

see Table 7).[13,14] The results were similar when comparing participants receiving alirocumab to participants receiving a statin dose increase or statin switch for any adverse event (*RR, 1.03 [95% CI, 0.85 to 1.23] to 0.84 [95% CI, 0.67 to 1.04*]); for serious adverse events (*RR, 0.72 [95% CI, 0.22 to 2.32] to 0.74 [95% CI, 0.27 to 2.04*]); and for adverse events leading to discontinuation *(RR, 1.25 [95% CI, 0.47 to 3.35] to 0.98 [95% CI, 0.29 to 3.29*]; see Table 7).[13,14]

In the ODYSSEY COMBO II trial, the incidences of any adverse events and serious adverse events over a mean of 58 weeks were similar among participants receiving alirocumab and those receiving ezetimibe (71.2% vs. 67.2% and 18.8% vs. 17.8%, respectively; see Table 7).[12] The risk ratio for any adverse event among participants receiving alirocumab compared to those receiving ezetimibe was *1.06 (95% CI, 0.95 to 1.18)*.[12] The percentage of participants who experienced an adverse event leading to discontinuation was greater in the alirocumab group (7.5%) compared to the ezetimibe group (5.4%), but with no statistically significant difference and no apparent pattern in the type of adverse event (see Table 7).[12]

Alirocumab vs. Standard of Care

The ODYSSEY DM-DYSLIPIDEMIA trial found that at week 24 in participants with type 2 diabetes mellitus and mixed dyslipidemia at high cardiovascular risk and a background of maximally tolerated doses of statins, alirocumab as an add-on to statin therapy resulted in a statistically significant greater reduction in non-HDL-C levels (difference in mean percentage change from baseline -32.5% [95% CI, -38.1% to -27.0%; *P* < .0001, equivalent to a decrease of *50.3 mg/dl*]) compared to standard of care (defined as maximally tolerated statin therapy and add-on fenofibrate, omega-3 fatty acids, ezetimibe [10 mg/day], nicotinic acid, or no additional lipid-lowering therapy; see Table 7).[15] The difference in mean percentage change from baseline in LDL-C levels at 24 weeks was a secondary endpoint of the trial; alirocumab as an add-on to maximally tolerated statin therapy resulted in a statistically significant greater reduction in LDL-C levels compared to standard of care (difference in mean percentage change from baseline -43.0% [95% CI, NR; *P* < .0001, equivalent to a decrease of *33.2 mg/dl*]).[15]

The ODYSSEY DM - DYSLIPIDEMIA trial authors[15] did not report CVD outcomes. The percentages of participants with any adverse events, serious adverse events, and adverse events leading to discontinuation were similar among participants receiving alirocumab and those receiving standard of care (68.4% vs. 66.4%, 9.5% vs. 8.8%, and 3.6% vs. 4.0%, respectively; see Table 7).[15] The risk ratio for any adverse event among participants receiving alirocumab compared to those receiving standard of care was *1.03 (95% CI, 0.89 to 1.19)*.[15]

Alirocumab vs. Placebo

In the ODYSSEY OUTCOMES trial, alirocumab led to a statistically significant reduction (9.5% vs. 11.1%; HR, 0.85 [95% CI, 0.78 to 0.93]) in the incidence of a composite cardiovascular event outcome (death from coronary heart disease, nonfatal myocardial infarction, fatal or nonfatal ischemic stroke, or unstable angina requiring hospitalization) compared to a placebo after 34 months of follow-up.[24] The absolute risk reduction of 1.6 percentage points is equivalent to a

number needed to treat of 63; meaning that 63 patients would need to be treated with alirocumab for 34 months to prevent 1 cardiovascular event.[24]

Overall mortality, a secondary outcome, was statistically significantly lower in the alirocumab group than the placebo group (3.5% vs. 4.1%; HR, 0.85 [95% CI, 0.73 to 0.99]). Death from cardiovascular causes, however, was not significantly different between treatment groups (2.5% vs. 2.9%; HR 0.88 [95% CI, 0.74 to 1.05]).[24] The measures of association for overall mortality and cardiovascular-related deaths were similar (HR, 0.85 vs. HR, 0.88); the likely reason that one outcome was significantly different and the other was not might be that the lower number of cardiovascular-related deaths reduced the precision of the estimate.

Prespecified subgroup analyses did not render any statistically significant differences for the primary composite outcome between participants who were younger than 65 years and those 65 years or older (P = .19), men and women (P = .35), and different ethnicities (P = .09).[24]

Evolocumab

Study Characteristics

Two phase 3 trials (1 of good methodological quality and 1 of fair methodological quality) described in 4 publications[16,21-23] assessed the efficacy of evolocumab (420 mg monthly or 140 mg every 2 weeks) as an add-on to statin therapy in participants with nonfamilial hypercholesterolemia not otherwise achieving target lipid levels.

The LDL-C Assessment With PCSK9 Monoclonal Antibody Inhibition Combined With Statin Therapy-2 (LAPLACE-2) trial (N = 1,899) compared evolocumab to 10 mg/day of ezetimibe or a placebo in participants on background therapy of a moderate- or high-intensity statin with a screening LDL-C level of at least 150 mg/dl when not taking a statin, 100 mg/dl with a non-intensive statin, or 80 mg/dl with an intensive statin therapy.[16] The trial included 198 sites from 18 countries and randomized participants to 24 treatment groups in 2 steps.[16] The first step involved randomization to 1 of either 3 moderate-intensity statins or 2 high-intensity statins.[16] The second step involved randomization to evolocumab, ezetimibe, or a placebo.[16] The primary endpoint was reduction in LDL-C from baseline at the mean of weeks 10 and 12 and at 12 weeks.[16] For the purpose of this report, we focus on the difference in mean percentage change in LDL-C at the mean of weeks 10 and 12 for the comparison of evolocumab and ezetimibe only.

The Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk (FOURIER) trial (N = 27,564) compared evolocumab (either 140 mg every 2 weeks or 420 mg once per month, per patient preference) to a placebo in a population of participants with baseline LDL-C ≥ 70 mg/dl or non-HDL-C ≥ 100 mg/dl and on ≥ 20 mg/day of atorvastatin or its equivalent, with or without ezetimibe.[21-23] The trial included 1,242 sites across 49 countries and participants were followed for a median of 26 months.[21-23] With cardiovascular outcomes as the primary endpoint, the placebo-controlled FOURIER trial met criteria for inclusion in this update.[21-23] Specifically, the primary endpoint of the trial was the composite of cardiovascular

death, myocardial infarction, stroke, hospitalization for unstable angina, or coronary revascularization.[21-23] A key secondary endpoint was the composite of cardiovascular death, myocardial infarction, or stroke.[21-23]

Both trials enrolled patients of similar ages (mean age of 63 and 60 years in FOURIER[21-23] and LAPLACE-2,[16] respectively) but the 2 trials differed in some other key participant characteristics. FOURIER enrolled 72% men compared to 54% men in LAPLACE-2.[16,21-23] All participants in the FOURIER trial had atherosclerotic CVD compared to 33% in the LAPLACE-2 trial.[16,21-23] In the FOURIER trial, 37% of participants had diabetes compared to 16% in the LAPLACE-2 trial.[16,21-23]

Findings

Evolocumab vs. Ezetimibe (With Background Statin Therapy)

The LAPLACE-2 trial found that at the mean of weeks 10 and 12 in participants on background therapy of a high-intensity statin (80 mg/day of atorvastatin), evolocumab (420 mg monthly) as an add-on to statin therapy resulted in a statistically significant greater reduction in LDL-C levels compared to 10 mg/day of ezetimibe (difference in mean percentage change from baseline -43.8% [95% CI, -52.1% to -35.6%]; equivalent to a decrease of 38.8 mg/dl; see Table 7).[16] Similarly, for participants on background therapy of a moderate-intensity statin (10 mg/day of atorvastatin), evolocumab (420 mg monthly) resulted in a statistically significant greater reduction in LDL-C levels compared to 10 mg/day of ezetimibe (difference in mean percentage change from baseline -43.5% [95% CI, -49.7% to -37.3%; equivalent to a decrease of -55.0 mg/dl]; see Table 7).[16]

The incidences of cardiovascular events and cardiovascular-related deaths were reported, but the number of events was too low to draw meaningful conclusions.[16] The incidences of any adverse events, serious adverse events, and adverse events leading to discontinuation were similar among participants receiving evolocumab and those receiving ezetimibe (36.3% vs. 40.3%, 2.1% vs. 0.9%, and 1.9% vs. 1.8%, respectively) (see Table 7).[16] The risk ratio for any adverse event among participants receiving evolocumab compared to those receiving ezetimibe was *0.9 (95% CI, 0.76 to 1.08)*.[16]

Evolocumab vs. Placebo (With Statin and Ezetimibe Background Therapy)

The FOURIER trial found that at a median of 26 months in participants with atherosclerotic CVD, evolocumab as an add-on to statin therapy (with or without ezetimibe) resulted in a statistically significant greater reduction in the primary composite outcome of cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, or coronary revascularization compared to a placebo (HR, 0.85 [95% CI, 0.79 to 0.92]; see Table 7).[21] The absolute risk reduction of this composite outcome was 1.5 percentage points (9.8% vs. 11.3%), which is equivalent to a number needed to treat of 67; meaning that 67 patients would have to be treated with evolocumab for 26 months to prevent 1 cardiovascular event. Similar results were observed for the secondary composite outcome of cardiovascular death, myocardial infarction, or stroke (HR, 0.80 [95% CI, 0.73 to 0.88]).[21] The absolute risk reduction was also 1.5 percentage

points (5.9% vs. 7.4%). The incidence of death from any cause was similar between treatment groups after 26 months (HR, 1.04 [95% CI, 0.91 to 1.19]; 3.2% vs. 3.1%).

In a prespecified subgroup analysis, participants with diabetes (N = 11,031) experienced a statistically significant greater reduction in the primary composite outcome of cardiovascular events compared to a placebo (HR, 0.83 [95% CI, 0.75 to 0.93; *P* = .0008]).[22] A similar reduction was observed in the subgroup of participants without diabetes (N = 16,533) (HR, 0.87 [95% CI, 0.79 to 0.96; *P* = .005]).[22]

Patients Who Received PCSK9 Inhibitors as Adjunct Therapy (Key Question 4)

For this key question, we summarize evidence on mixed populations of patients with familial or nonfamilial hypercholesterolemia who received a PCSK9 inhibitor as an adjunct treatment to standard of care or as a first-line treatment. If adjunct PCSK9 therapy was assessed in a narrow population that met any of the other key questions (e.g., patients with statin intolerance), we have reported those findings in the previous sections. Table 8 summarizes the findings (GRADE) for the primary research evidence for patients who received PCSK9 inhibitors as an adjunct therapy to standard of care. The evidence was limited to 2 RCTs of evolocumab.

Table 8. Summary of Findings (GRADE) for Mixed Populations with Hypercholesterolemia

Outcome	Quality of the Evidence	Relationship	Rationale
Alirocumab			
No eligible evidence			
Evolocumab Plus Standard of Care vs. Standard of Care			
Death from cardiovascular events at 48 weeks (pooled analysis of 2 RCTs)[8]	Very low	No relationship can be determined	Downgraded for risk of bias and very serious imprecision
Cardiovascular events at 48 weeks (pooled analysis of 2 RCTs)[8]	Low	Significantly lower incidence for evolocumab + SOC than SOC	Downgraded for risk of bias and imprecision
LDL-C decrease at 48 weeks (pooled analysis of 2 RCTs)[8]	Low	Significantly greater reduction for evolocumab + SOC than SOC	Downgraded for serious risk of bias
Overall risk of adverse events at 48 weeks (pooled analysis of 2 RCTs)[8]	Moderate	Significantly higher incidence for evolocumab + SOC than SOC	Downgraded for risk of bias
Serious adverse events at 48 weeks (pooled analysis of 2 RCTs)[8]	Low	Similar incidence between treatment groups	Downgraded for risk of bias and imprecision

Note. Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach used. Abbreviations. LDL-C: low-density lipoprotein-cholesterol; SOC: standard of care; RCT: randomized controlled trial.

Because of methodological limitations such as lack of blinding and the authors' use of baseline values of the original phase 2 or phase 3 trials for statistical analyses instead of baseline lipid values at randomization of the OSLER studies, we rated the quality of the evidence as low for LDL-C decrease and risk of adverse events. Because of risk of bias and imprecision, we rated the quality of evidence as low for cardiovascular events and serious adverse events, and as very low for death from cardiovascular events.

Table 9 summarizes the study characteristics, primary study endpoint findings, serious adverse events, and discontinuations because of adverse events for the included studies on PCSK9 inhibitors as adjunct therapy in mixed populations. We assessed both studies as poor methodological quality for efficacy outcomes because the statistical analysis compared follow-up data with baseline data that were not collected at randomization, and because of potential funding bias. For adverse events outcomes, we rated the study as poor methodological quality because of lack of blinding and potential funding bias. Detailed evidence tables are in Appendix Tables B1 (study characteristics), B2 (efficacy outcomes), and B3 (adverse event outcomes). We did not find any eligible evidence involving other cardiovascular risk reduction methods.

Table 9. Summary of Evidence Table—RCTs of PCSK9 Inhibitors for Mixed Populations with Hypercholesterolemia

Study; Registration Number; Trial Name	Dose, Frequency, and N Randomized	Primary Study Endpoint; N (%)	N (%) With at Least 1 Serious Adverse Event	N (%) With Adverse Event Leading to Discontinuation
Alirocumab				
No evidence				
Evolocumab Plus Standard of Care vs. Standard of Care				
Sabatine et al. 2015[8] NCT01439880 NCT01854918 OSLER-1, OSLER-2	140 mg SC Q2W or 420 mg SC + SOC = 2,976 SOC = 1,489 Total N = 4,465	Incidence of adverse events: 140 mg or 420 mg + SOC: 2,060 (69.2) SOC: 965 (64.8)	140 mg or 420 mg + SOC: 222 (7.5) SOC: 111 (7.5)	140 mg or 420 mg + SOC: 71 (2.4) SOC: NR
Koren et al., 2014[20] NCT01439880 OSLER-1	420 mg SC + SOC = 736 SOC = 368 Total N = 1,104	Incidence of adverse events: 420 mg + SOC: 599 (81.4) SOC: 269 (73.1)	420 mg + SOC: 52 (7.1) SOC: 23 (6.3)	420 mg + SOC: 27 (3.7) SOC: NR

Abbreviations. LDL-C: low-density lipoprotein-cholesterol; NR: not reported; OSLER: Open-label Study of Long-term Evaluation against LDL-C; Q2W: quality delivered every 2 weeks; SC: subcutaneous; SOC: standard of care.

Alirocumab

We did not find any eligible studies evaluating alirocumab in mixed populations with hypercholesterolemia.

Evolocumab Plus Standard of Care vs. Standard of Care

Two analyses of the Open Label Study of Long Term Evaluation Against LDL-C Trial (OSLER) assessed the efficacy and risk of adverse events of evolocumab plus standard of care versus standard of care alone.[8,20]

Study Characteristics

The OSLER studies included the following populations: 4,465 participants with heterozygous familial hypercholesterolemia, participants with statin intolerance, and participants who did not reach LDL-C target levels despite lipid-lowering therapy with and without ezetimibe.[8,20] Participants had completed 1 of 12 phase 2 or phase 3 double-blind, short-term trials.[8] Regardless of treatment assignment in the short-term trials, OSLER-1 randomized participants who had completed phase 2 trials to 420 mg evolocumab every 4 weeks plus standard of care, or standard of care alone.[8,20] OSLER 2 randomized participants who had completed phase 3 trials to 140 mg evolocumab every 2 weeks or 420 mg every 4 weeks (based on patient choice) plus standard of care, or standard of care alone. Both OSLER trials were open-label.[8,20]

Sabatine et al. pooled 48-week data of both OSLER trials.[8] The second publication (Koren et al.) reported results of OSLER-1 at 52 weeks.[20] Data from OSLER-2 were not reported separately. The primary endpoint for both OSLER trials was the incidence of adverse events.[8,20] The study also assessed adjudicated cardiovascular outcomes as an exploratory analysis, employing a blinded clinical events committee.[8,20] We rated the methodological quality of OSLER-1 and the pooled analysis as poor. The reasons for the rating of poor were lack of intention-to-treat analysis; lack of blinding; and the authors' use of baseline values of the original phase 2 or phase 3 trials for statistical analyses instead of baseline lipid values at randomization of the OSLER studies. The OSLER program was funded by the manufacturer of evolocumab.

Findings

Based on the pooled analysis of OSLER-1 and OSLER-2, participants treated with evolocumab plus standard of care had a statistically significant greater reduction in LDL-C levels than participants receiving standard of care alone at 48 weeks (difference in mean percentage change from baseline -58.4% [95% CI, NR; $P < .001$; equivalent to a decrease of 70.5 mg/dl]; see Table 9).[8] The authors reported results on other lipid parameters at 12 weeks only. Participants on evolocumab plus standard of care had larger increases in HDL-C levels at 12 weeks (difference in mean percentage change from baseline 7% [95% CI, NR; $P < .001$]) compared to standard of care alone.[8] Participants in the evolocumab plus standard of care group had a significantly lower incidence of a composite outcome of cardiovascular events (myocardial infarction, death, unstable angina requiring hospitalization, stroke, transient ischemic attack, and heart failure requiring hospitalization) compared to standard of care alone (HR, 0.47 [95% CI, 0.28 to 0.78]; $P = .003$).[8] The risk of adverse events was significantly higher in the evolocumab plus standard of care group (69.2% vs. 64.8%, *RR, 1.07* [*95% CI, 1.02 to 1.12*]).[8] The incidence of serious adverse

events was similar between the 2 groups (7.5% vs. 7.5%; Table 9).[8] The incidence of individual adverse events was also similar between treatment groups.[8]

Stratified results of OSLER-1 showed that the LDL-C levels of participants treated with evolocumab in the original phase 2-trials who were randomized to standard of care returned to near-baseline LDL-C levels after 12 weeks.[20]

Patients Who Received PCSK9 Inhibitors as First-Line Therapy (Key Question 4)

Table 10 summarizes the findings (GRADE) for the primary research evidence for the comparative effectiveness of PCSK9 inhibitors as first-line therapy in patients with hypercholesterolemia. We rated the quality of evidence for the efficacy outcome as low because of very serious imprecision. We rated the quality of evidence for safety outcomes as low or very low because of risk of bias and imprecision. Table 11 summarizes the study characteristics, primary study endpoint findings, serious adverse events, and discontinuations because of adverse events for the single RCT that reported on the use of alirocumab.[9,10] We considered this study to have fair methodological quality because of unclear concealment of intervention allocation, use of surrogate outcomes only, and potential funding bias. Detailed evidence tables are in Appendix Tables B1 (study characteristics), B2 (efficacy outcomes), and B3 (adverse event outcomes).

Table 10. Summary of Findings (GRADE) for PCSK9 Inhibitors as First-Line Therapy

Outcome	Quality of the Evidence	Relationship	Rationale
Alirocumab vs. Ezetimibe			
LDL-C decrease at 24 weeks (1 study)[9,10]	Low	Statistically significant greater reduction of LDL-C with alirocumab compared to ezetimibe	Downgraded for very serious imprecision
Overall adverse events at 24 weeks (1 RCT)[9,10]	Low	Lower risk, but not statistically significantly different, for adverse events with alirocumab compared to ezetimibe	Downgraded for very serious imprecision
Discontinuation due to adverse events at 24 weeks (1 RCT)[9,10]	Very low	No relationship can be determined	Downgraded for risk of bias and very serious imprecision
Serious adverse events at 34 weeks (1 RCT)[9,10]	Very low	No relationship can be determined	Downgraded for risk of bias and very serious imprecision

Note. Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach used.
Abbreviation. LDL-C: low-density lipoprotein-cholesterol.

Table 11. Summary of Evidence—RCTs for PCSK9 Inhibitors as First-Line Therapy

Study; Registration Number; Trial Name	Dose, Frequency, and N Randomized	Primary Study Endpoint; Difference From Comparator (95% CI; P Value)	N (%) with at Least 1 Serious Adverse Event[a]	N (%) with Adverse Event Leading to Discontinuation[a]
Alirocumab vs. Ezetimibe				
Roth et al., 2014[9] Roth & McKenney, 2015[10] NCT01644474 ODYSSEY MONO	Alirocumab 75–150 mg SC Q2W with daily oral placebo = 52 Ezetimibe 10 mg oral daily with Q2W SC placebo = 51 Total N = 103	Difference in mean percentage change in LDL-C from baseline to 24 weeks: -31.6% (-40.2% to -23.0%; *P* < .0001)	Alirocumab: 1 (1.9) Ezetimibe: 1 (2.0)	Alirocumab: 5 (9.6) Ezetimibe: 4 (7.8)

Note. [a]Defined as a treatment-emergent adverse event that resulted in death, was life-threatening, required hospitalization, resulted in persistent or clinically significant disability or incapacity, or was otherwise considered to be a medically important event. Abbreviations. LDL-C: low-density lipoprotein-cholesterol; SC: subcutaneous; Q2W: dose every 2 weeks.

Alirocumab vs. Ezetimibe

Study Characteristics

A single phase 3 RCT of fair methodological quality assessed the efficacy of 75 to 150 mg alirocumab every 2 weeks compared to 10 mg ezetimibe daily in lowering LDL-C levels among 103 participants with hypercholesterolemia who had moderate cardiovascular risk and were not receiving a statin or other lipid-lowering therapy.[9,10] Baseline LDL-C levels ranged from 73 to 207 mg/dl (mean 141.1 in the alirocumab group and mean 138.3 in the ezetimibe group).[9,10] The change in LDL-C from baseline was evaluated at 24 weeks, and safety was further monitored through week 34.[9,10] Cardiovascular events or other health outcomes were not assessed.[9,10] This study, which was funded by the manufacturer of alirocumab, was conducted at 8 sites in Belgium, Finland, the Netherlands, and the U.S.[9,10]

Findings

At 24 weeks, participants treated with 75 to 150 mg of alirocumab every 2 weeks had statistically significant greater reductions in LDL-C levels than participants receiving 10 mg of ezetimibe daily (difference in mean percentage change from baseline -31.6% [95% CI, -40.2% to -23.0%; *P* < .0001]; see Table 11).[9,10] Greater increases in HDL-C levels for participants receiving alirocumab than those receiving ezetimibe were not statistically significant (difference in mean percentage change from baseline to 24 weeks 4.4% [95% CI, -1.0% to 9.8%; *P* = .11]). [9,10] The risk of experiencing an adverse event was 12% lower in the alirocumab group compared to the ezetimibe group; however, the difference was not statistically significant (69.2% vs. 78.4%; RR,

0.88 [95% CI, 0.70 to 1.11]).[9,10] No meaningful conclusions can be made regarding the differences in the incidence of discontinuations due to adverse events or serious adverse events (see Table 11).

Evolocumab

We did not find any eligible studies that used evolocumab as a first-line therapy.

Findings From Systematic Reviews

We identified 1 Cochrane systematic review of good methodological quality for inclusion in this review.[6]

Study Characteristics

The Cochrane review authors searched various sources through May 2016, and included 20 trials with data on more than 67,000 participants treated with alirocumab, bococizumab, evolocumab, and RG7652.[6] Pfizer discontinued the development of bococizumab in November 2016[31]; RG7652 is still under development. The Cochrane review included 16 trials on alirocumab and evolocumab relevant to our review and did not differentiate between types of PCSK9 inhibitors.[6] All analyses investigated a class effect of PCSK9 inhibitors.[6] The Cochrane review authors combined different populations (heterozygous and homozygous familial hypercholesterolemia and patients with nonfamilial hypercholesterolemia) in their analyses.[6]

Efficacy Findings

The eligibility criteria and the analysis strategy of the Cochrane review did not exactly match this review. Schmidt et al.[6] analyzed PCSK9 inhibitors as a class including 2 agents that are not relevant for this review (bococizumab and RG7652, 4 trials). In addition, investigators combined various populations of familial and nonfamilial hypercholesterolemia.[6] Therefore, the results are of limited applicability for this review but, in general, show the same direction and magnitude of effects as the findings in this review. Table 12 presents results comparing treatment effects of PCSK9 inhibitors compared to a placebo, ezetimibe, and ezetimibe plus statins at 6 months.

Table 12. Results of Cochrane Review[6] Assessing Treatment Effects of PCSK9 Inhibitors as a Class at 6 Months

Intervention Groups	LDL-C Mean % Change (95% CI)	HDL-C Mean % Change (95% CI)	Mortality OR (95% CI)	Cardiovascular Events, Odds Ratio (95% CI)	Risk of Adverse Events, Odds Ratio (95% CI)
PCSK9 Inhibitors vs. Ezetimibe	-30.20 (34.18 to -26.23)	+ 7.01 (3.70 to 10.32)	NR	NR	NR
PCSK9 Inhibitors vs. Ezetimibe + Statins	-39.20 (-56.15 to -22.26)	+ 6.42 (1.31 to 11.52)	NR	0.45 (0.27 to 0.75	1.18 (1.05 to 1.34)

Abbreviations. HDL: high-density lipoprotein; LDL-C: low-density lipoprotein-cholesterol; NR: not reported.

Ongoing Studies

We identified 9 recently completed or ongoing phase 2, 3, or 4 studies of adults receiving PCSK9 inhibitors (Table 13); many of which do not provide a head-to-head comparison or are open label. Two studies are of alirocumab and 7 studies are of evolocumab. The primary endpoints of these studies are generally either an intermediate outcome such as change in LDL-C levels (N = 4) or adverse events (N = 5). Studies of intermediate outcomes have a planned follow-up duration of between 12 and 36 weeks; studies on safety have planned follow-up periods of 1.5 to 5 years.

Table 13. Ongoing Studies of PCSK9 Inhibitors

Registry Number, Phase Trial Name	Treatment Groups; Blinded vs. Open Label	N Enrollment	Study Completion Date[a]	Primary Outcome(s)
Alirocumab				
NCT02984982, phase 4 Evaluation of Coronary Artery Plaque Volume Progression/Regression and Safety of Alirocumab in Japanese Patients Hospitalized for Acute Coronary Syndrome with Hypercholesterolemia (ODYSSEY J-IVUS)	Alirocumab Dose NR Standard care; Open label	N = 205	July 2018 (Results not published)	Change in normalized total atheroma volume at 36 weeks
NCT02715726, phase 3 Evaluation of Alirocumab Versus Ezetimibe on Top of Statin in Asia in High Cardiovascular Risk Patients with Hypercholesterolemia (ODYSSEY EAST)	Alirocumab Dose NR, Placebo; Blinded	N = 615	August 2018 (Results not published)	Change in LDL-C levels at 24 weeks
Evolocumab				
NCT01854918, phase 3 Open Label Study of Long Term Evaluation Against LDL-C Trial-2 (OSLER-2)	Evolocumab Dose NR, Standard care; Open label	N = 3,681	May 2018 (Results not published)	Adverse events at 3 years
NCT02634580, phase 3 Goal Achievement After Utilizing an Anti-PCSK9 Antibody in Statin Intolerant Subjects -4 (GAUSS-4)	Evolocumab Dose NR, Placebo; Blinded	N = 61	May 2018 (Results posted on clinical trials.gov)[33]	Change in LDL-C levels at mean of 10 and 12 weeks and at 12 weeks
NCT01439880, phase 2 Open Label Study of Long Term Evaluation Against LDL-C Trial (OSLER)	Evolocumab Dose NR, Standard care; Open label	N = 1,324	June 2018 (Results not published)	Treatment-emergent adverse events at 5 years
NCT02624869, phase 3 Open Label Study to Evaluate Safety, Tolerability and Efficacy of Evolocumab in Pediatric Subjects with Heterozygous or	Evolocumab dose NR; Single group Open label	N = 115 (Estimated)	June 2021 (Estimated)	Treatment-related adverse events at 80 weeks

Registry Number, Phase Trial Name	Treatment Groups; Blinded vs. Open Label	N Enrollment	Study Completion Date[a]	Primary Outcome(s)
Homozygous Familial Hypercholesterolemia (HAUSER-OLE)				
NCT02867813, phase 3 Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk Open-label Extension	Evolocumab 140 mg biweekly or 420 mg monthly; Single group Open label	N = 5,037 (Estimated)	September 2021 (Estimated)	Adverse events at 5 years
NCT03060577, phase 2 An Extension Trial of Inclisiran Compared to Evolocumab in Participants with Cardiovascular Disease and High Cholesterol (ORION-3)	Evolocumab 140 mg biweekly for 1 year followed by 300 mg inclisiran every 26 weeks, 300 mg inclisiran every 26 weeks; Open label	N = 490 (Estimated)	January 2022 (Estimated)	Change in LDL-C levels at 30 weeks
NCT03080935, phase 3 FOURIER Open-label Extension Study in Subjects with Clinically Evident Cardiovascular Disease in Selected European Countries (FOURIER OLE)	Evolocumab 140 mg biweekly or 420 mg monthly; Single group Open label	N = 1,600 (Actual)	November 2022 (Estimated)	Adverse events at 5 years

Notes. [a] Actual or estimated study completion date as indicated on clinicaltrials.gov. Abbreviations. CHD: coronary heart disease; CV: cardiovascular events; LDL-C: low-density lipoprotein cholesterol; MI: myocardial infarction; NR: not reported; TIA: transient ischemic attack.

Discussion

The results of this systematic review show that PCSK9 inhibitors are more effective than other lipid-lowering therapies at reducing LDL-C serum levels in various populations with familial or nonfamilial hypercholesterolemia over treatment periods of up to 12 months. PCSK9 inhibitors lower LDL-C levels from baseline by 20.3% to 56.0% more than other lipid-lowering therapies, which is equivalent to reductions in LDL-C from 25.0 mg/dl to 95.6 mg/dl. Particularly, participants who were intolerant to statins experienced substantial reductions of LDL-C levels. The risks for adverse events, discontinuation due to adverse events, or serious adverse events were, in general, similar between participants who received PCSK9 inhibitors compared to other lipid-lowering treatments. We rated the quality of evidence for the LDL-C decrease of PCSK9

inhibitors as high or moderate for most populations of interest, indicating that future studies will probably have little impact on effect estimates.

These findings confirm the results of the original systematic review. This update, however, provides additional evidence for populations with nonfamilial hypercholesterolemia, for example, treatment with alirocumab for statin-intolerant patients. In addition, this update presents findings of the only trial (FOURIER) that had a sufficiently large sample size to have adequate power to determine the influence of a PCSK9 inhibitor on cardiovascular risks (composite of cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, or coronary revascularization).

In the FOURIER trial, a placebo-controlled RCT, participants treated with evolocumab experienced statistically significant reductions in cardiovascular risks (composite of cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, or coronary revascularization) compared to participants allocated to a statin with or without ezetimibe treatment over 26 months of follow-up.[21-23] Evolocumab reduced the incidence of cardiovascular events by 1.5% (9.8% vs. 11.3%). The incidence of all-cause mortality, however, was similar between treatment groups after 26 months (3.1% vs. 3.2%).

A similar long-term trial on alirocumab (ODYSSEY OUTCOMES, NCT 01663402) enrolled more than 18,900 participants with acute coronary syndrome 1 to 12 months earlier and randomized them to alirocumab 75 mg to 150mg or a placebo every 2 weeks.[24] The median follow-up time was 34 months. The results showed a statistically significant reduction of cardiovascular events (composite outcome of death from coronary heart disease, nonfatal myocardial infarction, fatal or nonfatal ischemic stroke, or unstable angina requiring hospitalization) in participants treated with alirocumab compared to patients who received a placebo (9.5% vs. 11.1%; HR, 0.85 [95% CI, 0.78 to 0.93]).[24] Fewer participants treated with alirocumab than a placebo died during the study (3.5% vs. 4.1%; HR 0.85 [95% CI, 0.73 to 0.98). The incidence of adverse events was similar between the alirocumab and placebo groups (3.8% vs. 2.1%).

Although the body of evidence precludes meaningful conclusions about the influence of PCSK9 inhibitors on mortality compared to other lipid-lowering regimens, the available evidence indicates that PCSK9 inhibitors are an effective treatment option to lower LDL-C for patients with familial or nonfamilial hypercholesterolemia who do not achieve target LDL-C levels with lipid-lowering treatments such as statins or ezetimibe. The long-term efficacy, particularly regarding patient-relevant health outcomes, is unclear. In the ODYSSEY OUTCOMES and FOURIER trials, the large reductions of LDL-C levels with alirocumab or evolocumab resulted in absolute risk reductions of cardiovascular events of only 1.6 and 1.5 percentage points after 34 and 26 months, respectively. The small absolute risk reductions could be the consequence of the relatively short follow-up times for a long-term treatment. A limitation of the FOURIER and the ODYSSEY OUTCOMES trials was the infrequent use of ezetimibe as an additional treatment when participants did not reach target levels with statins.

It is also still unclear at what level of cardiovascular risk (e.g., based on the Atherosclerotic Cardiovascular Disease Risk Algorithm of the American College of Cardiology/American Heart Association) PCSK9 inhibitors should be initiated. The majority of study participants had moderate to high risk for cardiovascular events based on different cardiovascular risk assessment tools. Large proportions of participants in the included studies had already experienced at least 1 cardiovascular event.

Limitations of the Evidence

The available evidence base has 4 primary limitations. First, most studies were short-term (up to 24 weeks) or medium-term (up to 1 year); only 3 studies followed participants for more than 1 year. Long-term studies, in general, maintained the LDL-C lowering effects of PCSK9 inhibitors, but we cannot draw conclusions with strong certainty about beneficial or harmful long-term effects. Second, evidence on differences in the efficacy and risk of adverse events in subgroups was limited. Based on a single study, the beneficial treatment effects of PCSK9 inhibitors appear to be similar between men and women and between participants with and without type 2 diabetes mellitus. Nevertheless, we identified no evidence on effects of PCSK9 inhibitors in participants at different ages or with common comorbidities other than type 2 diabetes mellitus. Third, the manufacturers of PCSK9 inhibitors funded all eligible studies. Consequently, funding bias is a concern,[35] but it seems unlikely that the treatment effects of PCSK9 inhibitors can be attributed exclusively to funding bias. Fourth, we did not find any studies directly comparing alirocumab to evolocumab or assessing the efficacy of PCSK9 inhibitors as adjunct therapies to cardiovascular risk reduction methods (e.g., smoking cessation, diet). Our searches in trial registries identified 10 recently completed or ongoing phase 2, 3, or 4 studies of adults receiving PCSK9 inhibitors; many of which do not provide a head-to-head comparison or are open label.

Limitations of This Review

We included only studies published in English. We did not include data presented in press releases or conference abstracts; thus, this report might not reflect all known data on the efficacy or safety of PCSK9 inhibitors.

Another consideration is that the American Heart Association and the American College of Cardiology taskforce published an updated clinical practice guideline on the management of blood cholesterol on November 10, 2018.[36] For the first time, the guideline incorporated a value statement into the decision-making process between the health care provider and patient.[36] Overall, the guideline rated PCSK9 inhibitors as having *low* cost value for individuals with very high-risk atherosclerotic CVD because of uncertainty about long-term safety and low cost-effectiveness.[36] This new guideline exemplifies the complicated nature of making coverage decisions related to PCSK9 inhibitors because despite their effectiveness at reducing LDL-C levels, they are much more costly than other therapeutic options. State Medicaid administrators will have to consider the findings of this DERP report and recent clinical practice guidelines when reviewing their coverage criteria for PCSK9 inhibitors.

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Appendix A. Clinical Evidence Methods

Search Strategy

We searched Drug Effectiveness Review Project (DERP) clinical evidence sources to identify systematic reviews (with and without meta-analyses), technology assessments, and randomized controlled trials (RCTs) using the terms *alirocumab, evolocumab, praluent, repatha*, and *pcsk9 inhibitor*. We did not limit searches of evidence sources by any dates.

The following DERP evidence sources were searched:

- Agency for Healthcare Research and Quality (AHRQ)
- Evidence-based Practice Centers (EPC) Reports
- Effective Health Care (EHC) Program
- Canadian Agency for Drugs and Technologies in Health (CADTH)
- Cochrane Library (Wiley Interscience)
- National Institute for Health and Care Excellence (NICE), Evidence
- Ovid MEDLINE
- Veterans Administration Evidence-based Synthesis Program (ESP)

We conducted gray literature searches of Google and Google Scholar using the following search terms *PCSK9 inhibitor, alirocumab, praluent, evolocumab, repatha*.

Ovid MEDLINE Search Strategy

Database: Ovid MEDLINE(R) < 1946 to July Week 4 2018 >

Search Strategy:

1. alirocumab.mp.
2. evolocumab.mp.
3. praluent.mp.
4. repatha.mp.
5. pcsk9 inhibit*.mp.
6. 1 or 2 or 3 or 4 or 5
7. limit 6 to english language
8. limit 7 to animals
9. 7 not 8
10. limit 9 to (clinical trial, all or controlled clinical trial or meta-analysis or RCT or systematic reviews)

Cochrane Library Search Strategy

Database: EBM Reviews - Cochrane Central Register of Controlled Trials < August 2018 >

Search Strategy:

1. alirocumab.mp.
2. evolocumab.mp.

3. praluent.mp.
4. repatha.mp.
5. pcsk9 inhibit*.mp.
6. 1 or 2 or 3 or 4 or 5
7. limit 6 to english language
8. limit 7 to (clinical trial or controlled clinical trial or RCT)

Database: EBM Reviews - Cochrane Database of Systematic Reviews < 2005 to August 6, 2018 >

Search Strategy:
1. alirocumab.mp.
2. evolocumab.mp.
3. praluent.mp.
4. repatha.mp.
5. pcsk9 inhibit*.mp.
6. 1 or 2 or 3 or 4 or 5

The following DERP sources for ongoing studies were searched using the search terms *alirocumab, praluent, evolocumab, repatha, praluent*:
- ClinicalTrials.gov
- ISRCTN Registry
- U.S. Food and Drug Administration
- [Manufacturer's website]

On December 14, 2018, before finalizing the report, we searched Ovid MEDLINE and Google Scholar using NCT identifiers from the ongoing studies list (see Table 13) to identify additional publications since the main searches in August 2018.

Inclusion Criteria

Populations
- Patients with heterozygous and homozygous familial hypercholesterolemia
- Patients with hypercholesterolemia who are unable to use statins because of intolerance or for any other reasons
- Patients with nonfamilial hypercholesterolemia who have not achieved LDL-C < 100 mg/dl or < 70 mg/dl

Comparators
- Head-to-head comparisons of included interventions
- Active pharmacological treatments (e.g., statins and ezetimibe), including trials of add-on therapy that provide comparative data on an included drug versus another active treatment
- Placebo (if CVD was the primary outcome)

Outcomes

- Survival and health events: reduction in nonfatal myocardial infarction, coronary heart disease, mortality (coronary heart disease and all-cause), stroke, and need for revascularization (including coronary artery bypass grafting, angioplasty, and coronary stents)
- LDL-C decrease
- HDL-C raising ability
- Overall adverse events
- Withdrawals due to adverse events
- Serious adverse events
- Specific adverse events (including, but not limited to, serious hypocholesterolemia, neurocognitive dysfunction, injection site reactions, nasopharyngitis, gastrointestinal disturbance)
- Defect, other events that do not fit any of the previous categories but that may jeopardize the patient or require medical or surgical intervention and are considered significant by the investigator
- Withdrawals due to adverse events

Setting

- Outpatient/clinic
- Office
- Home

Study Designs

- RCTs
- Systematic reviews (with or without a meta-analysis)

Exclusion Criteria

We excluded studies if they were not published in English.

Screening

Two experienced researchers independently screened all titles and abstracts of identified documents. In cases in which researchers disagreed about eligibility, a third experienced researcher resolved the disagreement. We repeated this method for full-text review of documents that could not be excluded by title and abstract screening.

Data Abstraction

One experienced researcher abstracted and entered data from eligible studies in a standardized way. A second experienced researcher reviewed all the data entered. We attempted to resolve discrepancies through discussion. When discussion did not resolve the issue, a third experienced researcher settled disagreements.

Quality Assessment

Methodological Quality of Included Studies

We assessed the methodological quality of the included RCTs using standard instruments developed and adapted by DERP that are modifications of instruments used by national and international standards for quality.[1,2] Two experienced researchers independently rated all included studies. In cases in which there was disagreement about the methodological quality of a study, a third rater resolved the disagreement.

Systematic Reviews and Randomized Controlled Trials

If a meta-analysis or network meta-analysis was conducted, we considered the methodological quality of the analyses in the overall rating for the systematic review. In brief, Good-quality systematic reviews include a clearly focused question, a literature search sufficiently rigorous to identify all relevant studies, criteria used to assess study quality and select studies for inclusion (e.g., RCTs), and assessments of heterogeneity to determine whether a meta-analysis would be appropriate. Good-quality RCTs include a clear description of the population, setting, intervention, and comparison groups; a random and concealed allocation of patients to study groups; low dropout rates; and intention-to-treat analyses. Good-quality systematic reviews and RCTs also have low potential for bias from conflicts of interest and funding source(s). Fair-quality systematic reviews and RCTs have incomplete information about methods that might mask important limitations. Poor-quality systematic reviews and RCTs have clear flaws that could introduce significant bias.

Quality of Evidence Assessment

Overall Quality of Evidence

We assigned each outcome a summary judgment for the overall quality of evidence based on the system developed by the Grading of Recommendations, Assessment, Development, and Evaluation Working Group (GRADE).[4,5] Two independent experienced researchers assigned ratings, with disagreements resolved by a third rater. The GRADE system defines the overall quality of a body of evidence for an outcome in the following manner:

- **High:** Raters are very confident that the estimate of the effect of the intervention on the outcome lies close to the true effect. Typical sets of studies are RCTs with few or no limitations, and the estimate of effect is likely stable.
- **Moderate:** Raters are moderately confident in the estimate of the effect of the intervention on the outcome. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is different. Typical sets of studies are RCTs with some limitations or well-performed nonrandomized studies with additional strengths that guard against potential bias and have large estimates of effects.
- **Low:** Raters have little confidence in the estimate of the effect of the intervention on the outcome. The true effect may be substantially different from the estimate of the effect. Typical sets of studies are RCTs with serious limitations or nonrandomized studies without special strengths.

- **Very low:** Raters have no confidence in the estimate of the effect of the intervention on the outcome. The true effect is likely to be substantially different from the estimate of effect. Typical sets of studies are nonrandomized studies with serious limitations or inconsistent results across studies.
- **Not applicable:** Researchers did not identify any eligible articles.

Appendix B. Full Evidence Tables

Table B1. Characteristics of Studies Evaluating PCSK9 Inhibitors

Author, Year Trial Name Registry Number	Study Design Drug and Comparator (N randomized) Follow-up Duration Background Therapy N (%)	Population of Interest Demographic Characteristics, Mean (SD) or N (%) Key Inclusion and Exclusion Criteria	Sites Sponsor Quality Rating
Bays et al., 2015[13,34] ODYSSEY OPTIONS I NCT01730040	Phase 3, double-blind, parallel group RCT **Alirocumab** 75–150 mg once every 2 weeks SC plus an oral placebo daily plus atorvastatin 20 mg every day = 57 plus atorvastatin 40 mg every day = 47 Ezetimibe: 10 mg every day plus placebo every 2 weeks SC plus atorvastatin 20 mg every day = 55 plus atorvastatin 40 mg every day = 47 Atorvastatin: 40 mg every day plus placebo every 2 weeks SC plus an oral placebo daily = 57 Atorvastatin: 80 mg every day plus placebo every 2 weeks SC plus an oral placebo daily = 47 Rosuvastatin: 40 mg every day plus placebo every 2 weeks SC plus an oral placebo daily = 45 Total N = 355 All participants followed the NCEP III therapeutic lifestyle changes diet and all participants got the placebo alirocumab every 2 weeks SC, and 2 oral blinded	Patients with hypercholesterolemia who have not achieved LDL-C < 100 mg/dl or < 70 mg/dl with their current lipid-lowering regimen Age: 62.9 (10.2) Female: 124 (35%) Race, white: 306 (86%) Baseline cardiovascular disease: 211 (59%) Baseline LDL-C: 105.1 (34.1) Hypertension: 278 (78%) Type II diabetes mellitus: 178 (50%) Current cigarette smoking: 66 (19%) 10-year predicted cardiovascular risk, by group: NR Inclusion: • Age ≤ 18 with hypercholesterolemia • Very high CVD risk and LDL-C of ≥ 70 mg/dl or high risk and LDL-C of ≥ 100 mg/dl • On stable dose of atorvastatin 20 mg or 40 mg with or without other lipid-lowering treatment (not ezetimibe) Exclusion: • Fasting serum, TG > 400 mg/dl during screening period • Uncontrolled endocrine disease known to influence serum lipids	85 sites in Australia, Canada, France, Germany, Italy, Mexico, Spain, the United Kingdom, and the United States Sanofi and Regeneron Pharmaceuticals, Inc. Fair

Author, Year Trial Name Registry Number	Study Design Drug and Comparator (N randomized) Follow-up Duration Background Therapy N (%)	Population of Interest Demographic Characteristics, Mean (SD) or N (%) Key Inclusion and Exclusion Criteria	Sites Sponsor Quality Rating
	placebo medications daily representing the statins or ezetimibe 24 weeks Statin use: 100% Ezetimibe use: 0%	• Currently taking ezetimibe or had received ezetimibe within 4 weeks of screening visit • Currently taking a statin that is not rosuvastatin daily at 10 or 20 mg	
Cannon, 2015[12] NCT01644188 ODYSSEY COMBO II	Phase NR, double-blind, double-dummy, parallel group RCT **Alirocumab** 75 to 150 mg every 2 weeks SC plus oral placebo daily = 479 Ezetimibe 10 mg daily plus SC placebo every 2 weeks = 241 Total N = 720 24 weeks for efficacy and 52 weeks for adverse events Statin use, by group: Atorvastatin or rosuvastatin: 719 (99.9%) Alirocumab: 478 (99.8%) Ezetimibe use: 241 (100%)	Patients with hypercholesterolemia who have not achieved LDL-C < 100 mg/dl or < 70 mg/dl with their current lipid-lowering regimen Age: 61.6 (9.3) Female: 26.4% Race, white, by group: Alirocumab: 404 (84.3) Ezetimibe: 206 (85.5) CHD: 90.1% Baseline LDL-C, mg/dl: *108.5 (34.7)* Baseline HDL-C, mg/dl by group: Alirocumab: 46.3 (11.6) Ezetimibe: 46.3 (15.4) Hypertension: NR Type II diabetes mellitus: 30.7% Current cigarette smoking: NR 10-year predicted cardiovascular risk: NR Inclusion: • Hypercholesterolemia and established CHD or CHD risk equivalents • LDL-C ≥ 70 mg/dl and CVD diagnosis or risk equivalent, LDL-C ≥ 100 mg/dl without CVD diagnosis or risk equivalent and ≥ 2 risk factors, or LDL-C ≥ 160 mg/dl without CHD diagnosis or risk	126 sites in Canada, Denmark, France, Hungary, Israel, Russia, South Africa, South Korea, Ukraine, United States Sanofi and Regeneron Pharmaceuticals, Inc. Fair

Author, Year Trial Name Registry Number	Study Design Drug and Comparator (N randomized) Follow-up Duration Background Therapy N (%)	Population of Interest Demographic Characteristics, Mean (SD) or N (%) Key Inclusion and Exclusion Criteria	Sites Sponsor Quality Rating
		equivalent and with fasting triglyceride values ≤ 400 mg/dl at screening Exclusion: • Age < 18 • Fasting serum triglycerides > 4.5 mmol/L during screening • Currently on a statin other than simvastatin, atorvastatin, or rosuvastatin • Use of concomitant medications: ezetimibe, omega-3 fatty acids, nicotinic acid, bile-acid-binding sequestrant or red yeast rice products in the past 3 weeks prior to screening or use of fibrates in the past 6 weeks prior to screening	
Farnier, 2016[14,34] ODYSSEY OPTIONS II NCT01730053	Phase 3, double-blind, parallel group RCT **Alirocumab** 75 to 150 mg once every 2 weeks SC plus an oral placebo daily plus rosuvastatin 10 mg every day = 49 plus rosuvastatin 20 mg every day =54 Ezetimibe: 10 mg every day plus placebo every 2 weeks SC plus an oral placebo daily plus rosuvastatin 10 mg every day = 48 plus rosuvastatin 20 mg every day = 53	Patients with hypercholesterolemia at very-high or high CVD risk who have not achieved LDL-C < 100 mg/dl or < 70 mg/dl with their current lipid-lowering regimen Age: 60.9 (10.3) Female: 118 (39%) Race, white: 256 (84%) Baseline cardiovascular disease: 177 (58%) Coronary heart disease by group: Alirocumab + rosuvastatin 10 mg: 23 (47%) Ezetimibe + rosuvastatin 10 mg: 29 (60%) Rosuvastatin 20 mg: 25 (52%) Alirocumab + rosuvastatin 20 mg: 32 (59%) Ezetimibe + rosuvastatin 20 mg: 32 (60%) Rosuvastatin 40 mg: 36 (68%) Baseline LDL-C, mg/dl: 111.3 (39.0) Hypertension: 221 (72%)	79 sites in Australia, Canada, Germany, Italy, Mexico, Spain, the United Kingdom, and the United States Sanofi and Regeneron Pharmaceuticals, Inc. Fair

Author, Year Trial Name Registry Number	Study Design Drug and Comparator (N randomized) Follow-up Duration Background Therapy N (%)	Population of Interest Demographic Characteristics, Mean (SD) or N (%) Key Inclusion and Exclusion Criteria	Sites Sponsor Quality Rating
	Rosuvastatin: 20 mg every day plus placebo every 2 weeks SC plus oral placebo daily = 48 Rosuvastatin: 40 mg every day plus placebo every 2 weeks SC plus an oral placebo daily = 53 Total N = 305 All participants followed the NCEP III therapeutic lifestyle changes diet and all participants got the placebo alirocumab every 2 weeks SC, and 2 oral blinded placebo medications daily representing the statins or ezetimibe 24 weeks Statin use: 100% Ezetimibe use: 0%	Type II diabetes mellitus: 126 (41%) Current cigarette smoking: 56 (18%) 10-year predicted cardiovascular risk, by group: NR Inclusion: • Age ≤ 18 with hypercholesterolemia • Very high CVD risk* and LDL-C of ≥ 70 mg/dl or high risk** and LDL-C of ≥ 100 mg/dl • On stable dose of rosuvastatin 10 mg or 20 mg per day with or without other lipid-lowering treatment (not ezetimibe) Exclusion: • Fasting serum, TG > 400 mg/dl during-screening period • Uncontrolled endocrine disease known to influence serum lipids • Currently taking ezetimibe or had received ezetimibe within 4 weeks of screening visit • Currently taking a statin that is not rosuvastatin daily at 10 or 20 mg per day	
Hovingh, 2017[7] OSLER I and II (RUTHERFORD, phase 2 and RUTHERFORD - 2, phase 3) NCT01375751 NCT01763918	Open-Label extension, parallel-assignment RCT **Evolocumab** 420 mg SC monthly or 140 mg SC biweekly plus standard care = 289 Standard care alone = 151 Total N = 440 48 weeks Moderate or high - intensity statin use:	Heterozygous familial hypercholesterolemia • Age: 50.8 (12.4) • Female: 187 (42.5) • Race, white: 397 (90.2) • Cardiovascular disease: 150 (34.1) • Baseline LDL-C, mg/dl: *155 (46.4)* • Hypertension: NR • Type II diabetes mellitus: NR	Rutherford phase 2: 24 sites in North America, Western Europe, Hong Kong, Singapore, and South Africa Rutherford II phase 3: 39 sites in Australia, Asia, Europe, New Zealand, North

Author, Year Trial Name Registry Number	Study Design Drug and Comparator (N randomized) Follow-up Duration Background Therapy N (%)	Population of Interest Demographic Characteristics, Mean (SD) or N (%) Key Inclusion and Exclusion Criteria	Sites Sponsor Quality Rating
	428 (97.3) Ezetimibe use: 283 (64.3)	• Current cigarette smoking: NR • 10-year predicted cardiovascular risk: NR Inclusion: • Participants who completed RUTHERFORD, phase 2 or RUTHERFORD 2, phase 3 • Aged 18 to 75, diagnosed with HeFH • LDL-C of 100 mg/dl at baseline despite statin therapy with or without ezetimibe • Triglycerides (400 mg/dl despite at least 4 weeks of stable statin and other lipid-lowering therapy (ezetimibe, bile-acid sequestering resin, stanols, or regulatory-approved and marketed niacin) before screening • No treatment-related serious adverse event that led to discontinuation of treatment, or required unblinded lipid measurements or adjustment of background lipid-regulating therapy Exclusion: • Diagnosed with homozygous FH • LDL or plasma apheresis within 12 months of randomization • Heart failure or left ventricular ejection fraction < 30% • Any acute or unstable cardiac event with planned intervention within 3 months of randomization • Type 1 diabetes mellitus or newly diagnosed or poorly controlled (hemoglobin A1c > 8.5%) type 2 diabetes mellitus	America, and South Africa Amgen, Inc. Poor

Author, Year Trial Name Registry Number	Study Design Drug and Comparator (N randomized) Follow-up Duration Background Therapy N (%)	Population of Interest Demographic Characteristics, Mean (SD) or N (%) Key Inclusion and Exclusion Criteria	Sites Sponsor Quality Rating
		• Systolic blood pressure > 160 mm Hg or diastolic blood pressure > 100 mm Hg • Persistent aspartate aminotransferase or alanine aminotransferase > 2 x ULN or creatine kinase > x ULN	
Koren, 2014[20] OSLER I NCT01439880	Open-Label extension, parallel-assignment RCT **Evolocumab** 420 mg SC monthly plus standard care = 736 Standard care alone = 368 Total N = 1,104 52 weeks Nonintensive statin use: 396 (35.9) Intensive statin use (including statin plus ezetimibe): 295 (26.7)	Patients with hypercholesterolemia Age: 56 (12) Female: 610 (55.3) Race, white: 972 (88.0) Coronary artery disease: 210 (19.0) Baseline LDL-C, mg/dl, by group: Evolocumab: *139 (38.7)* Standard care: *143 (38.7)* Type II diabetes mellitus: 109 (9.9) Current cigarette smoking: 175 (15.9) 10-year predicted cardiovascular risk: NR Inclusion: • Participants who completed any evolocumab phase 2 parent study (MENDEL, LAPLACE-TIMI 57, GAUSS, RUTHERFORD) • No treatment-related serious adverse event that led to discontinuation of treatment or anticipated to require unblinded lipid measurements or adjustment of background lipid-regulating therapy Exclusion: • Heart failure, history of coronary heart disease or risk equivalent • Uncontrolled cardiac arrhythmia or hypertension	156 sites globally: MENDEL: 52 sites in Europe, United States and Canada LAPLACE-TIMI 57: 78 sites in Canada, Denmark, Hungary, the Czech Republic, United States GAUSS: 33 sites in North America, Australia and Europe RUTHERFORD: 25 sites in North America, Western Europe, Hong Kong, South Africa, Singapore Amgen, Inc. Poor

Author, Year Trial Name Registry Number	Study Design Drug and Comparator (N randomized) Follow-up Duration Background Therapy N (%)	Population of Interest Demographic Characteristics, Mean (SD) or N (%) Key Inclusion and Exclusion Criteria	Sites Sponsor Quality Rating
		• Thyroid disease • Aspartate aminotransferase or alanine amino transferase more than two times the upper limit of normal • Creatine kinase greater than three times ULN • Use of lipid-regulating drugs • Systemic corticosteroids, or ciclosporin within the past 3 months • Use of anticoagulants	
Moriarty, 2015[11,37] ODYSSEY ALTERNATIVE NCT01709513	Phase 3, double-blind, parallel group RCT **Alirocumab** 75 to 150 mg once every 2 weeks SC plus oral placebo = 126 Ezetimibe 10 mg oral plus SC placebo = 125 Total N = 250[a] Participants in both arms followed the NCEP III therapeutic lifestyle changes diet 24 weeks Statin use: NR	Patients with primary hypocholesterolemia and statin intolerance Age, by group: Alirocumab: 64.1 (9) Ezetimibe: 62.8 (10.1) Female, by group: Alirocumab: 56 (44%) Ezetimibe: 58 (46%) Race, white, by group: Alirocumab: 117 (93%) Ezetimibe: 116 (93%) Coronary heart disease, by group: Alirocumab: 64 (51%) Ezetimibe: 54 (43%) Baseline LDL-C, mg/dl by group: Alirocumab: 191.1 (72.7) Ezetimibe: 193.5 (70.9) Hypertension, by group: Alirocumab: 85 (68%) Ezetimibe: 77 (62%)	67 sites in 8 countries, including Austria, Canada, France, Israel, Italy, Norway, the UK and US Sanofi and Regeneron Pharmaceuticals, Inc. Fair

Author, Year Trial Name Registry Number	Study Design Drug and Comparator (N randomized) Follow-up Duration Background Therapy N (%)	Population of Interest Demographic Characteristics, Mean (SD) or N (%) Key Inclusion and Exclusion Criteria	Sites Sponsor Quality Rating
		Type II diabetes mellitus, by group: Alirocumab: 36 (29%) Ezetimibe: 24 (19%) Current cigarette smoking, by group: Alirocumab: 11 (8%) Ezetimibe: 5 (4%) 10-year predicted cardiovascular risk, by group: Moderate Risk[b] Alirocumab: 19 (15.1) Ezetimibe: 14 (11.2) High Risk[c] Alirocumab: 29 (23.0) Ezetimibe: 47 (37.6) Very High Risk[d] Alirocumab: 73 (57.9) Ezetimibe: 62 (49.6) Inclusion: • ≥ 18 years of age with primary hypercholesterolemia • Moderate or high cardiovascular risk and LDL-C ≥ 100 mg/dl at screening, or at high cardiovascular risk with LDL-C ≥ 70 mg/dl • Inability to tolerate 2 or more statins because of unexplained skeletal muscle-related symptoms and 1 of the 2 statins had to have been discontinued while at or below the lowest-approved daily starting dose. • Receiving a stable dose of other lipid-lowering therapy, including ezetimibe, a bile acid sequestrant, nicotinic acid, omega-3 fatty acids (≥ 1,000 mg daily),	

Author, Year Trial Name Registry Number	Study Design Drug and Comparator (N randomized) Follow-up Duration Background Therapy N (%)	Population of Interest Demographic Characteristics, Mean (SD) or N (%) Key Inclusion and Exclusion Criteria	Sites Sponsor Quality Rating
		or fenofibrate, for at least 4 weeks before screening (6 weeks for fenofibrate) Exclusion: • Receiving fibrates other than fenofibrate within 6 weeks of screening • Patients who experienced unexplained skeletal muscle-related AEs during the single-blind placebo run - in or at randomization • Triglycerides > 400 mg/dl (one repeat lab allowed) • eGFR < 30 mL/min/1.73 m^2 • ALT or AST > 3 x ULN • Contraindications to the use of atorvastatin or ezetimibe	
Nissen, 2016[17,38] GAUSS-3 NCT0198442	Phase 3, double-blind, parallel-assignment RCT **Evolocumab** 420 mg SC monthly plus oral placebo daily = 145 Ezetimibe 10 mg oral daily plus placebo SC monthly = 73 Total N = 218 24 weeks Statin use: 0 Ezetimibe use: 0	Patients with hypercholesterolemia who have not achieved LDL-C < 100 mg/dl with their current lipid-lowering regimen Age: 58.8 (10.5) Female: 106 (48.6) Race, white: 207 (95.0) Coronary heart disease: 69 (31.7) Baseline LDL-C, mg/d: 219.9 (72.0) Hypertension: 112 (51.4) Type II diabetes mellitus: 26 (11.9) Current cigarette use: 29 (13.3) 10-year predicted cardiovascular risk: NR Inclusion: • Aged 18 to 80 years with hypercholesterolemia • Classified as statin intolerant with:	~45 sites in Asia, Australia, Europe, and North America, including academic centers, research centers, hospitals Amgen, Inc. Fair

Author, Year Trial Name Registry Number	Study Design Drug and Comparator (N randomized) Follow-up Duration Background Therapy N (%)	Population of Interest Demographic Characteristics, Mean (SD) or N (%) Key Inclusion and Exclusion Criteria	Sites Sponsor Quality Rating
		- LDL-C ≥ 100 mg/dl and CHD diagnosis or risk equivalent - LDL-C ≥ 130 mg/dl without CHD diagnosis or risk equivalent and ≥ 2 risk factors - LDL-C ≥ 160 mg/dl without CHD diagnosis or risk equivalent and ≥ 1 risk factors or - LDL-C ≥ 190 mg/dl without CHD diagnosis or risk equivalent and with fasting triglyceride values ≤ 400 mg/dl at screening • Statin intolerance was defined as inability to tolerate atorvastatin at 10 mg and any other statin at any dose or, alternatively, 3 or more statins, with 1 at the lowest average daily starting dose and 2 other statins at any dose. The lowest average starting dose was defined as 5 mg for rosuvastatin, 10 mg for simvastatin, 40 mg for pravastatin, 20mg for lovastatin, 40mg for fluvastatin, or 2 mg for pitavastatin. Exclusion: • Prior exposure to a PCSK9 inhibitor • History of MI, unstable angina, coronary revascularization, or stroke ≤ 3 months before randomization • Use of systemic corticosteroids or cyclosporine ≤ 3 months before randomization • History or evidence of clinically significant disorder	

Ray, 2017[15,39] ODYSSEY DM - DYSLIPIDEMIA NCT02642159	Phase IIIb/IV, Open-Label, parallel group RCT **Alirocumab** 75 to 150 mg once every 2 weeks SC plus standard care = 276 Standard care only = 137 Ezetimibe (96.2% received 10 mg daily) = 53 Fenofibrate (dose varied from 134 to 325 mg daily) = 25 Omega-3 fatty acid = 21 Nicotinic acid = 1 No lipid-lowering therapy = 37 Total N = 413 24 weeks Statin use, by group: Alirocumab: 231 (84%) Standard care: 105 (77%) Ezetimibe: NR	Patients with hypercholesterolemia and non-HDL-C was not adequately controlled Age, by group: Alirocumab: 63 (9.3) Standard care: 64 (8.8) Female, by group: Alirocumab: 129 (47%) Standard care: 68 (50%) Race, white, by group: Alirocumab: 247 (90%) Standard care: 123 (90%) Cardiovascular disease, by group: Atherosclerotic CVD Alirocumab: 95 (13%) Standard care: 47 (34%) Baseline LDL-C, by group: Alirocumab: 110.4 (40%) Standard care: 117 (44%) Hypertension, by group: Alirocumab: 241 (87%) Standard care: 123 (90%) Type II diabetes mellitus: 413 (100%) Current cigarette smoking, by group: Alirocumab: 38 (14%) Standard care: 23 (17%) 10-year predicted cardiovascular risk: NR Inclusion: • Aged ≥ 18 years) with Type 2 diabetes • Mixed dyslipidemia whose non-HDL cholesterol was not adequately controlled despite stable maximally tolerated statin dose for ≥ 4 weeks prior to screening visit, without other LLTs • Either a documented history of ASCVD or at least 1 additional CV risk factor	110 sites in 15 countries (Australia, Brazil, Finland, Germany, Kuwait, Israel, Italy, Lebanon, Norway, Sweden, Switzerland, Turkey, United Arab Emirates, United Kingdom, United States) Sanofi and Regeneron Pharmaceuticals, Inc. Fair

Author, Year Trial Name Registry Number	Study Design Drug and Comparator (N randomized) Follow-up Duration Background Therapy N (%)	Population of Interest Demographic Characteristics, Mean (SD) or N (%) Key Inclusion and Exclusion Criteria	Sites Sponsor Quality Rating
		• HbA1c of < 9% changes to antihyperglycemic medications were to be limited and made only in circumstances of clinical need for the duration of the study Exclusion: • HbA1c of ≥ 9% • Use of any lipid-lowering therapy (other than statin) or over-the-counter product/nutraceuticals known to impact lipids within 4 weeks prior to screening • BMI > 45 kg/m2 • Alcohol consumption > two standard alcoholic drinks/day	
Robinson et al., 2014[16,40] NCT01763866 LAPLACE-2	Phase 3, double-blind, placebo- and ezetimibe-controlled RCT **Evolocumab** 140 mg every 2 weeks or 420 mg monthly SC plus placebo (SC or oral) plus any statin = 1,117 Ezetimibe: 10 mg every day plus placebo (SC or oral) plus atorvastatin 80 mg = 221 Placebo daily oral or 2 weeks SC plus any statin = 558 Total N = 1,899 (3 did not receive study drug) 12 weeks Statin use: Prior to randomization:	Patients with primary hypercholesterolemia and mixed lipedema who have not achieved LDL-C < 100 mg/dl or < 70 mg/dl with their current lipid-lowering regimen; Patients with hypercholesterolemia on moderate to high intensity statin Age: 59.8 (9.9) Female: 868 (45.8) Race, white: 1782 (94.0) Coronary artery disease: 427 (22.5) Baseline LDL-C, mg/dl: 108.9 Baseline HDL-C, mg/dl: 53.2 Hypertension: 1072 (56.5) Type II diabetes mellitus: 293 (15.5) Current cigarette smoking: 290 (15.3) 10-year predicted cardiovascular risk: NR Inclusion: [key inclusion criteria] • Age 18 to 80 years	198 sites in Australia, Belgium, Canada, Czech Republic, Denmark, France, Germany, Hong Kong, Hungary, Italy, The Netherlands, Russia, Sweden, Switzerland, United Kingdom United States Amgen, Inc. Fair

Author, Year Trial Name Registry Number	Study Design Drug and Comparator (N randomized) Follow-up Duration Background Therapy N (%)	Population of Interest Demographic Characteristics, Mean (SD) or N (%) Key Inclusion and Exclusion Criteria	Sites Sponsor Quality Rating
	High Intensity (includes statin plus ezetimibe): 591 (29%) Nonintensive: 618 (41%) Ezetimibe use: NR, but only in those randomized to atorvastatin arms	• Screening LDL-C of ≥ 150 mg/dl (no statin) or ≥ 100 mg/dl (nonintensive statin) screening), or ≥ 80 mg/dl (intensive statin) • Fasting triglyceride levels of ≤ 400 mg/dl. Exclusion: • Cardiovascular risk factors (e.g., MI, PCI, CABG, stroke ≤ 6 months prior to randomization; planned cardiac surgery or revascularization; LVEF <30%; etc.): History of statin intolerance	
Roth, 2014[9] **Roth, 2015**[10] ODYSSEY MONO NCT01644474	Phase 3, double-blind, parallel-assignment RCT **Alirocumab** 75 to 150 mg once every 2 weeks SC plus oral placebo ezetimibe, N = 52 Ezetimibe: 10 mg every day plus SC placebo alirocumab every 2 weeks, N = 51 Total N = 103 24 weeks of treatment (primary endpoint visit) plus 8 weeks of follow-up Statin use: 0 Ezetimibe use: 0	Patients with hypercholesterolemia Age, by group: Alirocumab: 60.8 (4.6) Ezetimibe: 59.6 (5.3) Female, by group: Alirocumab: 24 (47.2%) Ezetimibe: 24 (47.1%) Race, white, by group: Alirocumab: 46 (88.5%) Ezetimibe: 47 (92.2%) Baseline LDL-C, mg/dl, by group: Alirocumab: 141.1 (27.1) Ezetimibe: 138.3 (24.5) Hypertension: NR Type II diabetes mellitus by group: Alirocumab: 3 (5.8%) Ezetimibe: 1 (2.0%) Current cigarette smoking: NR	8 sites in USA, Belgium, Finland and the Netherlands Sanofi (France) and Regeneron (NY, USA) Fair

Author, Year Trial Name Registry Number	Study Design Drug and Comparator (N randomized) Follow-up Duration Background Therapy N (%)	Population of Interest Demographic Characteristics, Mean (SD) or N (%) Key Inclusion and Exclusion Criteria	Sites Sponsor Quality Rating
		10-year predicted cardiovascular risk, by group (SCORE %): Alirocumab: 2.97 (1.29) Ezetimibe: 2.68 (1.14) Inclusion: • ≥ 18 years of age • 10-year risk of fatal CV events of - ≥ 1% and < 5%, based on the SCORE • LDL-C between 100 mg/dl and 190 mg/dl • Not receiving statin or any other lipid-lowering therapy for at least 4 weeks prior to screening. Exclusion: • Established coronary heart disease or coronary heart disease risk equivalents defined as • Manifestations of noncoronary forms of atherosclerotic disease (peripheral arterial disease, abdominal aortic aneurysm and carotid artery disease) • Use of any LLT within 4 weeks or a fibrate within 6 weeks of the screening visit • Fasting serum triglycerides > 400 mg/dl during the screening period, and systolic blood pressure > 160 mmHg or diastolic blood pressure > 100 mmHg at screening (week -2) or randomization (week 0) visits	

Author, Year Trial Name Registry Number	Study Design Drug and Comparator (N randomized) Follow-up Duration Background Therapy N (%)	Population of Interest Demographic Characteristics, Mean (SD) or N (%) Key Inclusion and Exclusion Criteria	Sites Sponsor Quality Rating
Sabatine et al., 2017a[21]; Sabatine et al., 2017b[22]; Giugliano et al., 2017[23] FOURIER NCT01764633	Phase 3, double-blind, parallel-assignment RCT **Evolocumab** 420 mg SC monthly or 140 mg SC biweekly = 13,784 Placebo SC =13,780 Total N = 27,564 Median 26 months (IQR: 22 to 30) High or moderate - intensity statin use: 27,495 (99.7) Ezetimibe use: 1,440 (5.2) Fenofibrate therapy permitted if stable for ≥ 6 weeks before final screening; other fibrate therapy and derivatives prohibited	Patients with nonfamilial hypercholesterolemia who have not achieved LDL-C < 100 mg/dl or < 70 mg/dl with their current lipid-lowering regimen Age, by group: Evolocumab: 62.5 (9.1) Placebo: 62.5 (8.9) Female: 6,769 (24.6) Race, white: 23,458 (85.1) Previous myocardial infarction: 22,351 (81.1) Previous non-hemorrhagic stroke: 5,337 (19.4) Median (IQR) LDL-C, mg/dl by group: Evolocumab: 92 (80 to 109) Placebo: 92 (80 to 109) Median (IQR) HDL-C, mg/dl by group: Evolocumab: 44 (37 to 53) Placebo: 44 (37 to 53) Hypertension: 22,084 (80.1) Diabetes mellitus: 11,031 (40.0) Current cigarette use: 7,777 (28.2) 10-year predicted cardiovascular risk: NR Inclusion: • Aged 40 to 85 years • Clinically evident atherosclerotic cardiovascular disease • Fasting LDL-C ≥ 70 mg/dl or non-HDL-C ≥ 100 mg/dl while taking lipid-lowering therapy • ≥ 1 major or ≥ 2 minor cardiovascular risk factors Exclusion: • MI or stroke within 4 weeks before randomization	1,242 sites in 49 countries (62.9% participants in Europe, 16.6% in North America, 13.9% in Asia Pacific and South Africa, and 6.6% in Latin America) Amgen, Inc. Good

Author, Year Trial Name Registry Number	Study Design Drug and Comparator (N randomized) Follow-up Duration Background Therapy N (%)	Population of Interest Demographic Characteristics, Mean (SD) or N (%) Key Inclusion and Exclusion Criteria	Sites Sponsor Quality Rating
		• LDL or plasma apheresis within 12 months before randomization • Creatine kinase > 5 times the ULN at final screening • Planned or expected cardiac surgery or revascularization within 3 months after randomization • CETP inhibitor, mipomersen, or lomitapide use within 12 months before randomization • PCSK9 inhibitor use within 12 weeks before final screening • Receiving drugs systematically with known interactions with background statin therapy within 1 month before randomization • Receiving other investigational drug or device within 1 month before randomization • History or evidence of clinically significant disorder	
Sabatine et al. 2015[8] NCT01439880 NCT01854918 OSLER-1, OSLER-2 OSLER Extension Studies	Two open label RCTs of participants who had completed 1 of 12 phase 2 or 3 parent trials **Evolocumab** 140 mg every 2 weeks SC or 420 mg monthly SC plus standard of care = 2,976 Standard of care = 1,489 Total N = 4,465 11.1 months (median) Statin use: 3,128 (70.1) Ezetimibe use: *605 (13.5)*	Mixed population including patients with heterozygous familial hypercholesterolemia, patients with hypercholesterolemia and unable to use statins, patients with nonfamilial hypercholesterolemia who have not achieved adequate LDL-C levels with lipid-lowering regimens, and patients with hypercholesterolemia and no background anti-lipid therapy Age: 58 Female: 2,210 (49.5) Race, white: 3,826 (85.7) Coronary artery disease: *896 (20.1)* Cardiovascular risk factor ≥ 1: *3,590 (80.4)*	OSLER 1: 190 sites OSLER 2: 305 sites across North America, Europe, Asia, Africa and Australia Amgen, Inc. Poor

Author, Year Trial Name Registry Number	Study Design Drug and Comparator (N randomized) Follow-up Duration Background Therapy N (%)	Population of Interest Demographic Characteristics, Mean (SD) or N (%) Key Inclusion and Exclusion Criteria	Sites Sponsor Quality Rating
		Baseline LDL-C, mg/dl, by group: Evolocumab: 120 (97 to 148) Standard of care: 121 (97 to 151) Baseline HDL-C, mg/dl, by group: Evolocumab: 51 (42 to 62) Standard of care: 51 (42 to 62) Hypertension: *2,322 (52.0)* Diabetes mellitus: *599 (13.4)* Current cigarette smoking: *687 (15.4)* 10-year predicted cardiovascular risk: NR Inclusion: • Completed one of 12 parent trials Exclusion: • Adverse event that led to discontinuation of a study drug during parent trial • Unstable medical condition • Expected to need unblinded lipid measurements or adjustment of background lipid-lowering therapy during first 12 weeks of OSLER trials	
Schwartz, 2018[24] ODYSSEY OUTCOMES NCT01663402	Phase 3, double-blind, parallel assignment RCT **Alirocumab** 75 to 150 mg every 2 weeks SC = 9,462 Placebo every 2 weeks SC = 9,462 Total N = 18,924 Median 2.8 years Statin use (atorvastatin [40 to 80 mg once daily] or rosuvastatin [20 to 40 mg once daily]: 16,811 (88.8)	Patients with hypercholesterolemia who have not achieved LDL-C < 100 mg/dL or < 70 mg/dL with their current lipid-lowering regimen Age, by group: Alirocumab: 58.5 (9.3) Placebo: 58.6 (9.4) Female, by group: Alirocumab: 2,390 (25.3) Placebo: 2,372 (25.1) Race, white, by group:	1,315 sites in 57 countries in Africa, Asia, Australia, Europe, North America, and South America Sanofi and Regeneron Pharmaceuticals Good

Author, Year Trial Name Registry Number	Study Design Drug and Comparator (N randomized) Follow-up Duration Background Therapy N (%)	Population of Interest Demographic Characteristics, Mean (SD) or N (%) Key Inclusion and Exclusion Criteria	Sites Sponsor Quality Rating
	Ezetimibe use: 554 (2.9)	Alirocumab: 7,500 (79.3) Placebo: 7,524 (79.5) MI, by group: Alirocumab: 1,790 (18.9) Placebo: 1,843 (19.5) Stroke, by group: Alirocumab: 306 (3.2) Placebo: 305 (3.2) Baseline LDL-C, mg/dL: 92 (31) Baseline HDL-C, mg/dL, by group: Alirocumab: 43 (37-50) Placebo: 42 (36-50) Hypertension, by group: Alirocumab: 6,205 (65.6) Placebo: 6,044 (63.9) Diabetes mellitus, by group: Alirocumab: 2,693 (28.5) Placebo: 2,751 (29.1) Current tobacco smoking, by group: Alirocumab: 2,282 (24.1) Placebo: 2,278 (24.1) 10-year predicted cardiovascular risk: NR Inclusion: • ≥ 40 years of age • Hospitalized with an acute coronary syndrome 1 to 2 months before randomization	

Author, Year Trial Name Registry Number	Study Design Drug and Comparator (N randomized) Follow-up Duration Background Therapy N (%)	Population of Interest Demographic Characteristics, Mean (SD) or N (%) Key Inclusion and Exclusion Criteria	Sites Sponsor Quality Rating
		• Inadequately controlled lipid levels defined as LDL-C ≥ 70 mg/dL, non-HDL ≥ 100 mg/dL, or Apolipoprotein B of ≥ 80 mg Exclusion: • Acute coronary syndrome event < 4 weeks or > 52 weeks before randomization, or recurrent event < 2 weeks of randomization • Not on stable lipid-modifying therapy for ≥ 2 weeks before randomization • Uncontrolled hypertension, Class III or IV CHF, history of hemorrhagic stroke, coronary revascularization procedure < 2 weeks before randomization • Use of fibrates other than fenofibrate or fenofibric acid	
Stroes et al., 2014[18] NCT01763905 GAUSS-2	Phase 3, double-blind, placebo- and ezetimibe-controlled RCT **Evolocumab** 140 mg every 2 weeks SC plus oral placebo daily = 103 420 mg every month SC plus oral placebo daily = 102 Ezetimibe 10 mg daily plus SC placebo every 2 weeks =51 Ezetimibe 10 mg daily plus SC placebo monthly =51 Total N = 307 12 weeks Any statin use, by group: Evolocumab 140 mg: 34 (33)	Patients with hypercholesterolemia with intolerance to previous 2 statins Age: 63 (56 to 68) Female: 141 (46) Race, white: 287 (94) Coronary heart disease, high risk: 56% Baseline LDL-C, mg/dl: 193 (59) Baseline HDL-C, mg/dl, by group: Evolocumab 140 mg: 51 (1.6) Evolocumab 420 mg: 54 (16) Ezetimibe +Q2W placebo: 52 (1.8) Ezetimibe + monthly placebo: 48 (11) Hypertension, by group: Evolocumab 140 mg: 57 (55) Evolocumab 420 mg: 56 (55)	50 sites in North America, Europe, Asia, Africa and Australia Amgen, Inc. Fair

Author, Year Trial Name Registry Number	Study Design Drug and Comparator (N randomized) Follow-up Duration Background Therapy N (%)	Population of Interest Demographic Characteristics, Mean (SD) or N (%) Key Inclusion and Exclusion Criteria	Sites Sponsor Quality Rating
	Evolocumab 420 mg: 37 (36) Ezetimibe use, by group: Ezetimibe +Q2W placebo: 15 (29) Ezetimibe + monthly placebo: 16 (31)	Ezetimibe +Q2W placebo: 30 (59) Ezetimibe + monthly placebo: 38 (75) Type II diabetes mellitus, by group: Evolocumab 140 mg: 20 (19) Evolocumab 420 mg: 15 (15) Ezetimibe +Q2W placebo: 11 (22) Ezetimibe + monthly placebo: 16 (31) Current cigarette smoking, [overall/by group]: Evolocumab 140 mg: 12 (12) Evolocumab 420 mg: 3 (3) Ezetimibe + Q2W placebo: 5 (10) Ezetimibe + monthly placebo: 4 (8) 10-year predicted cardiovascular risk: NR Inclusion: • Age 18 to 80 • Not taking a statin or taking a low-dose statin • LDL-C of ≥ 100 mg/dl with diagnosed CHD or risk equivalent, ≥ 130 mg/dl without CHD or risk equivalent and ≥ 2 risk factors, ≥ 160 mg/dl without CHD or risk equivalent and 1 risk factor, or ≥ 190 mg/dl without CHD or risk equivalent and no risk factors • Triglycerides ≤ 400 mg/dl • Prior intolerance to ≥ 2 statins, defined as inability to tolerate any dose or increase the dose above the smallest tablet strength because of intolerable muscle-related side effects Exclusion:	

Author, Year Trial Name Registry Number	Study Design Drug and Comparator (N randomized) Follow-up Duration Background Therapy N (%)	Population of Interest Demographic Characteristics, Mean (SD) or N (%) Key Inclusion and Exclusion Criteria	Sites Sponsor Quality Rating
		• New York Heart Association class III or IV heart failure or left ventricular injection fraction < 30%, acute coronary syndrome or serious arrhythmia in prior 3 months • Type 1 diabetes mellitus or type 2 that is poorly controlled • Uncontrolled hypertension or thyroid disease • Moderate or severe renal dysfunction, liver enzymes > 2 times the upper limit of normal • Use or prescription lipid-lowering medications other than low-dose statins, ezetimibe or bile-acid sequestrants in the prior 6 weeks (discontinuation of ezetimibe required ≥ 4 weeks before LDL-C screening)	
Sullivan et al., 2012[19] NCT01375764 GAUSS	Phase 2, double-blind, parallel-assignment RCT (ezetimibe use unblinded) **Evolocumab** 280 mg monthly SC = 32 350 mg monthly SC = 32 420 mg monthly SC = 32 420 mg monthly SC plus ezetimibe 10 mg daily= 31 Placebo monthly SC plus ezetimibe 10 mg daily = 33 Total N = 160 12 weeks Statin use: 25 (15.9) Ezetimibe use: 64 (40.0)	Patients with hypercholesterolemia who have statin intolerance Age: 61.8 (8.4) Female: 100 (63.7) Race, white: 139 (88.5) white Coronary artery disease: 27 (17.2) Cerebrovascular or peripheral artery disease: 11 (7.0) Baseline LDL-C, mg/dl: 193.2 (51.0) Baseline HDL-C, mg/dl: 57.8 (19.3) Hypertension: 74 (47.1) Type II diabetes mellitus: 21 (13.4) Current cigarette use: 22 (14.0) 10-year predicted cardiovascular risk: NR Inclusion: • Aged 18 to 75 years with hypercholesterolemia	33 sites in Australia, Belgium, Canada, Denmark, Finland, Spain, Sweden, and United States Amgen, Inc. Fair

Author, Year Trial Name Registry Number	Study Design Drug and Comparator (N randomized) Follow-up Duration Background Therapy N (%)	Population of Interest Demographic Characteristics, Mean (SD) or N (%) Key Inclusion and Exclusion Criteria	Sites Sponsor Quality Rating
		• Classified as statin intolerant with LDL-C ≥ 100 mg/dl and CHD diagnosis or risk equivalent, LDL-C ≥ 130 mg/dl without CHD diagnosis or risk equivalent and ≥ 2 risk factors, or LDL-C ≥ 160 mg/dl without CHD diagnosis or risk equivalent and with fasting triglyceride values ≤ 400 mg/dl at screening • Statin intolerance was defined as the inability to tolerate at least 1 statin at any dose or an increase in dose above weekly maximums of rosuvastatin, 35 mg; atorvastatin, 70 mg; simvastatin, 140 mg; pravastatin, 140 mg; lovastatin, 140 mg; or fluvastatin, 280 mg, because of intolerable myalgia (muscle pain, soreness, weakness, or cramps) or myopathy (myalgia plus elevated creatine kinase [CK]) and having symptom improvement or resolution with statin discontinuation. Exclusion: • Major cardiac, cerebrovascular, pulmonary, or venous event ≤ 3 months before randomization • Use of systemic corticosteroids or cyclosporine ≤ 3 months before randomization • History or evidence of clinically significant disorder	

Notes. Demographic data that are italicized are values we calculated based on data provided in the study report. [a] Total N for trial was 314, but Atorvastatin arm (N = 63) not included here because it is a statin rechallenge arm with no efficacy comparisons made with alirocumab or ezetimibe arms. [b] 10 - y fatal cardiovascular risk Systematic Coronary Risk Evaluation (SCORE) between ≥ 1% and < 5%. [c] 10 - y fatal cardiovascular risk SCORE ≥ 5%; moderate chronic kidney disease; diabetes mellitus without target organ damage; or familial hypercholesterolemia. [d] Documented history of coronary heart disease, ischemic stroke, peripheral artery disease, transient ischemic attack, abdominal aortic aneurysm, or carotid artery occlusion > 50% without symptoms; carotid endarterectomy or carotid artery stent procedure; renal artery stenosis or renal artery stent procedure; or diabetes mellitus with target organ damage. Outcomes that are italicized are values we calculated based on data provided in the study report.

Abbreviations. ALT: alanine aminotransferase; ASCVD: atherosclerotic cardiovascular disease; AST: aspartate aminotransferase; BMI: body mass index; ABG: coronary artery bypass graft; CETP: cholesterylester transfer protein; CHD: coronary heart disease; CVD: cardiovascular disease; eGFR: estimated glomerular filtration rate; GAUSS: Goal Achievement After Utilizing an Anti-PCSK9 Antibody in Statin Intolerant Subjects; HDL-C: high-density lipoprotein cholesterol; HbA1c: hemoglobin A1c, glycated hemoglobin; HeFH: heterozygous familial hypercholesterolemia; IQR: interquartile range; L: liter; LAPLACE-TIMI 57: LDL-C Assessment With PCSK9 Monoclonal Antibody Inhibition Combined With Statin Therapy–Thrombolysis in Myocardial Infarction 57; LDL-C: low-density lipoprotein cholesterol; LLT: lipid-lowering therapy; LVEF: left ventricular ejection fraction; MENDEL: Monoclonal Antibody Against PCSK9 to Reduce Elevated LDL-C in Subjects Currently Not Receiving Drug Therapy for Easing Lipid Levels; MI: myocardial infarction; NCEPIII: National Cholesterol Education Panel III; NCT: clinical trial registry number; non-HDL: non-high density lipoprotein cholesterol; NR: not reported; OSLER: Open-Label Study of Long-term Evaluation Against LDL-C; PCI: percutaneous coronary intervention; PCSK9: proprotein convertase subtilisin/kexin type 9; RCT: randomized controlled trial; RUTHERFORD: Reduction of LDL-C With PCSK9 Inhibition in Heterozygous Familial Hypercholesterolemia Disorder; SC: subcutaneous; SCORE: Systematic Coronary Risk Evaluation; ULN: upper limit of normal; US: unstable angina.

Table B2. Efficacy of PCSK9 Inhibitors in Randomized Trials

Outcome (N Analyzed)	Timing of Follow-up	Active Treatment Groups						
Bays et al., 2015[13,34] ODYSSEY OPTIONS I		Alirocumab 75–150 mg + Atorvastatin 20 mg	Ezetimibe 10 mg + Atorvastatin 20 mg	Atorvastatin 40 mg	Alirocumab 75–150 mg + Atorvastatin 40 mg	Ezetimibe 10 mg + Atorvastatin 40 mg	Atorvastatin 80 mg	Rosuvastatin 40 mg
Mortality outcomes		**N (%)**						
Treatment-related deaths (354)	Time from first dose to last dose plus 70 days	Pooled Alirocumab: 0 (0)	Pooled Ezetimibe: 2 (2.0)	Pooled Atorvastatin 0 (0)	Pooled Alirocumab: 0 (0)	Pooled Ezetimibe: 0 (0)	Pooled double Atorvastatin or Rosuvastatin switch: 0 (0)	Pooled double Atorvastatin or Rosuvastatin switch: 0 (0)
Cardiovascular disease outcomes		**N (%)**						
Treatment-related cardiovascular events (354)	Time from first dose to last dose plus 70 days	Pooled Alirocumab: 1 (1.0)	Pooled Ezetimibe: 1 (1.0)	Pooled Atorvastatin 0 (0)	Pooled Alirocumab: 0 (0)	Pooled Ezetimibe: 0 (0	Pooled double Atorvastatin or Rosuvastatin switch: 0 (0)	Pooled double Atorvastatin or Rosuvastatin switch: 0 (0)
Intermediate outcomes		**Least squares mean % change from baseline (SE)**						
LDL-C decrease* (345)	24 weeks	- 44.1 (4.5)	- 20.5 (4.7)	- 5.0 (4.6)	- 54.0 (4.3)	- 22.6 (4.3)	- 4.8 (4.2)	- 21.4 (4.2)
LDL-C decrease (345)	12 weeks	- 48.4 (3.8)	- 22.6 (3.9)	- 8.5 (3.9)	- 50.5 (3.2)	- 29.7 (3.2)	- 14.5 (3.2)	- 23.3 (3.2)
HDL-C increase (345)	24 weeks	4.8 (2.0)	- 0.1 (2.1)	1.9 (2.0)	7.7 (2.7)	2.0 (2.7)	4.7 (2.7)	5.7 (2.7)
Fasting triglycerides lowering ability (345)	24 weeks	- 12.0 (3.7) %	- 3.3 (4.1)	- 6.7 (3.7)	- 19.1 (4.1)	- 13.9 (4.1)	- 7.3 (4.1)	- 0.5 (4.0)
		Least squares mean mg/dl change from baseline (SE)						
LDL-C change (345)	24 weeks	54.3	81.0	93.9	46.4	85.1	100.0	85.6
LDL-C change (345)	12 weeks	52.8	78.5	89.9	51.8	76.5	90.8	82.4
		Least squares mean % change, difference for alirocumab compared to comparator (SE); P value						
LDL-C decrease (345)	24 weeks	NA	- 23.6 (6.6); *P* = .0004	- 39.1 (6.4); *P* < .0001	NA	- 31.4 (6.1); *P* < .0001	- 49.2 (6.1); *P* < .0001	- 32.6 (6.0); *P* < .0001

Outcome (N Analyzed)	Timing of Follow-up	Active Treatment Groups						
Bays et al., 2015[13,34] ODYSSEY OPTIONS I		Alirocumab 75–150 mg + Atorvastatin 20 mg	Ezetimibe 10 mg + Atorvastatin 20 mg	Atorvastatin 40 mg	Alirocumab 75–150 mg + Atorvastatin 40 mg	Ezetimibe 10 mg + Atorvastatin 40 mg	Atorvastatin 80 mg	Rosuvastatin 40 mg
LDL-C decrease (345)	12 weeks	NA	- 25.8 (5.4); *P* < .0001	- 39.8 (5.4); *P* < .0001	NA	- 20.9 (4.6); *P* < .0001	- 36.0 (4.5); *P* < .0001	- 27.3 (4.6) *P* < .0001
HDL-C increase (345)	24 weeks	NA	4.9 (2.9); *P* =NR	2.9 (2.9); *P* =NR	NA	5.6 (3.8); *P* =NR	2.9 (3.8) *P* =NR	2.0 (3.8); *P* =NR
Fasting triglycerides lowering ability (345)	24 weeks	NA	- 8.6 (5.4); *P* =NR	- 5.3 (5.2); *P* =NR	NA	- 5.2 (5.7); *P* =NR	- 11.8 (5.8); *P* =NR	- 18.7 (5.7); *P* < .01

Outcome (N Analyzed)	Timing of Follow-up	Active Treatment Groups	
Cannon, 2015[12] NCT01644188 ODYSSEY COMBO II		**Alirocumab 75–150 mg**	**Ezetimibe 10 mg**
Mortality outcomes		**N (%)**	
Treatment-emergent adverse event leading to death (720)	52 weeks	2 (0.4)	4 (1.7)
CHD death including undetermined cause (720)	52 weeks	2 (0.4)	2 (0.8)
Cardiovascular disease outcomes		**N (%)**	
Nonfatal myocardial infarction (720)	52 weeks	12 (2.5)	3 (1.2)
Fatal/nonfatal ischemic stroke (including stroke not otherwise specified) (720)	52 weeks	1 (0.2)	1 (0.4)
Unstable angina requiring hospitalization (720)	52 weeks	1 (0.2)	0
Congestive heart failure requiring hospitalization (720)	52 weeks	1 (0.2)	1 (0.4)
Ischemia-driven coronary revascularization procedure (720)	52 weeks	16 (3.3)	4 (1.7)
Intermediate outcomes		**Mean percentage change from baseline**	
LDL-C decrease (707)	24 weeks	-506 (1.4)	-20.7 (1.9)
HDL-C increase (707)	24 weeks	8.6 (0.8)	0.5 (1.1)
		Least squares mean percentage change from baseline (SE) (95% CI; P value)	
LDL-C decrease of alirocumab vs ezetimibe* (707)	24 weeks	-29.8 (2.3) (-34.4 to -25.3; *P* < .0001)	
HDL-C increase of alirocumab vs ezetimibe	24 weeks	8.1 (1.3) (5.4 to 10.7; *P* < .0001)	

Outcome (N Analyzed)	Timing of Follow-up	Active Treatment Groups					
Farnier, 2016[14,34] ODYSSEY OPTIONS II		Alirocumab 75–150 mg + Rosuvastatin 10 mg	Ezetimibe 10 mg + Rosuvastatin 10 mg	Rosuvastatin 20 mg	Alirocumab 75–150 mg + Rosuvastatin 20 mg	Ezetimibe 10 mg + Rosuvastatin 20 mg	Rosuvastatin 40 mg
Mortality outcomes		**N (%)**					
Treatment-related deaths	Time from first to last dose plus 70 days	Pooled Alirocumab: 0 (0)	Pooled Ezetimibe: 1 (1.1)	Pooled Double Rosuvastatin: 0 (0)	Pooled Alirocumab: 0 (0)	Pooled Ezetimibe: 0 (0)	Pooled Double Rosuvastatin: 0 (0)
Cardiovascular disease outcomes		**NR**					
Intermediate outcomes		**Least squares mean % change from baseline (SE)**					
LDL-C decrease* (298)	24 weeks	-50.6 (4.2)	-14.4 (4.4)	-16.3 (4.1)	-36.3 (7.1)	-11.0 (7.2)	-15.9 (7.1)
LDL-C decrease (298)	12 weeks	-49.6 (4.1)	-17.4 (4.2)	-17.1 (4.1)	-32.3 (5.2)	-19.3 (5.4)	-22.1 (5.3)
HDL-C increase (298)	24 weeks	9.1 (2.4)	4.0 (2.5)	1.7 (2.4)	7.2 (2.3)	-1.08 (2.3)	1.5 (2.3)
Fasting triglycerides lowering ability (298)	24 weeks	-11.2 (4.6)	-3.3 (4.1)	-6.7 (3.7)	-19.1 (4.1)	-13.9 (4.1)	- 0.5 (4.0)
		Least squares mean % change from baseline difference of alirocumab versus comparator (SE); P value					
LDL-C decrease (298)	24 weeks	NA	-36.1 (6.1) *P* < .0001	-34.2 (5.9) *P* < .0001	NA	-25.3 (10.1) *P* = .014	-20.3 (10.1) *P* = .045
LDL-C decrease (298)	12 weeks	NA	-32.2% (5.8); *P* < .00001	-32.5% (5.8); *P* < .0001	NA	-12.9% (7.5); *P* = .09	-10.2% (7.4) *P* = .17
HDL-C increase (298)	24 weeks	NA	5.1% (3.5) *P* = .15	7.4% (3.4) P = .03	NA	9.0% (3.3) *P* = .007	5.7% (3.3) *P* = .09
Fasting triglycerides lowering ability (298)	24 weeks	NA	-2.9% (6.6) *P* = NS	-9.3% (6.4) *P* = NS	NA	2.4% (6.2) P = NS	1.2% (6.1) *P* = NS

Outcome (N Analyzed)	Timing of Follow-up	Active Treatment Groups	
Hovingh, 2017[7] **OSLER I and II (RUTHERFORD 1 and 2)**		**Evolocumab 420 mg Monthly or 140 mg Biweekly Plus Standard Care**	**Standard Care**
Mortality outcomes		**NR**	
Cardiovascular disease outcomes		**NR**	
Intermediate outcomes		**Mean % change from baseline of evolocumab compared to standard care (95% CI; P value)**	
Mean percentage change in LDL-C level from parent studies at baseline (418)	48 weeks open label	*-55.7* (NR; NR)	
Mean percentage change in HDL-C level from parent studies baseline (422)	48 weeks open label	*8 (NR; NR)*	

Outcome (N Analyzed)	Timing of Follow-up	Active Treatment Groups	
Koren, 2014[20] OSLER I		**Evolocumab 420 mg Plus Standard Care**	**Standard Care**
Mortality outcomes		**NR**	
Cardiovascular disease outcomes		**NR**	
Intermediate outcomes		**Mean percentage point difference of evolocumab compared to standard care**	
Mean change in LDL-C level from parent studies baseline (1,104)	52 weeks open label	*-49.6*	
Among participants receiving evolocumab in parent studies (288)	52 weeks open label	*-49.3*	
Among participants not receiving evolocumab in parent studies (816)	52 weeks open label	*-50.6*	
		N (%); P value; OR (95% CI)	
Participants achieving LDL-C < 100 mg/dl (935)	52 weeks open label	552 (86.3); *P* < .0001 *20.5 (14.5 to 29.0)*	47 (15.9)
Among participants using statins at baseline, at any follow-up visit (685)	12 to 52 weeks open label	458 (96.2); *P* < .0001 *39.4 (22.8 to 68.1)*	82 (39.2)
Among participants not using statins at baseline, at any follow-up visit (408)	12 to 52 weeks	245 (95.7); *P* < .0001 *74.5 (36.5 to 151.8)*	35 (23.0)
Participants achieving LDL-C < 70 mg/dl (935)	52 weeks open label	400 (62.5); *P* < .0001 *144.8 (46.1 to 455.4)*	3 (1.0)
Among participants using statins at baseline, at any follow-up visit (685)	12 to 52 weeks open label	418 (87.8); *P* < .0001 *243.8 (103.5 to 574.5)*	6 (2.9)
Among participants not using statins at baseline, at any follow-up visit (408)	12 to 52 weeks open label	188 (73.4); *P* < .0001 *57.3 (25.5 to 128.4)*	7 (4.6)
		Mean percentage point difference of evolocumab compared to standard care	
Mean percentage change in HDL-C level from parent studies baseline (1,104)	52 weeks open label	*5.4* (*P* ≤ .0002)	
Among participants receiving evolocumab in parent studies (288)	52 weeks open label	*5.4* (NR)	
Among participants not receiving evolocumab in parent studies (816)	52 weeks open label	*5.0* (NR)	

Outcome (N Analyzed)	Timing of Follow-up	Active Treatment Groups	
Moriarty, 2015[11,37] **ODYSSEY ALTERNATIVE**		**Alirocumab: 75 to 150 mg**	**Ezetimibe 10 mg**
Mortality outcomes		**N (%)**	
Adverse events leading to death (248)		0	0
Cardiovascular disease outcomes		**NR**	
Intermediate outcomes		**Least squares mean % change from baseline (SE)**	
LDL-C decrease* (248)	24 weeks	-45.0 (2.2)	-14.6 (2.2)
LDL-C decrease (248))	12 weeks	-47.0 (1.9)	-15.6 (2.0)
HDL-C increase (248)	24 weeks	7.7 (1.7)	6.8 (1.7)
		Least squares mean % change from baseline difference between alirocumab compared to ezetimibe (SE); (95% CI; P value)	
LDL-C decrease for alirocumab vs ezetimibe* (248)	24 weeks	-30.4 (3.1), (-36.6 to -24.2; *P* < .0001)	
LDL-C decrease for alirocumab vs ezetimibe (248)	12 weeks	-31.5 (2.7) (-36.9 to -26.1; *P* < .0001)	
HDL-C increase for alirocumab vs ezetimibe (248)	24 weeks	0.9 (2.4) (-3.8 to 5.6; *P* = .70)	

Outcome (N Analyzed)	Timing of Follow-up	Active Treatment Groups	
Nissen, 2016[17,38] GAUSS-3		**Evolocumab 420 mg**	**Ezetimibe 10 mg**
Mortality outcomes		**NR**	
Cardiovascular disease outcomes		**N (%); RD (95% CI)**	
Participants with myocardial infarction (218)	24 weeks	1 (0.7) *- 0.68 (-3.7 to 2.3)*	1 (1.4)
Participants with percutaneous coronary intervention (218)	24 weeks	3 (2.1) *- 0.67 (-5.1 to 3.7)*	2 (2.7)
Intermediate outcomes		**Least squares mean percentage change from baseline difference of evolocumab compared to ezetimibe (95% CI, P value)**	
LDL-C decrease* (218)	24 weeks	-36.1 (-41.1 to -31.1; *P* < .001)	
LDL-C decrease* (218)	Mean for week 22 and 24	-37.8 (-42.3 to -33.3; *P* < .001)	
		N (%); RD (95% CI)	
Participants achieving mean LDL-C < 70 mg/dl (218)	24 weeks	32 (27.4) *22.1 (15.3 to 28.8)*	0 (0.0)
Participants achieving mean LDL-C < 70 mg/dl (218)	Mean for week 22 and 24	41 (29.9) *26.9 (19.1 to 34.7)*	1 (1.4)
		Least squares mean percentage change from baseline difference of evolocumab compared to ezetimibe (95% CI, P value)	
HDL-C increase (218)	24 weeks	4.5 (0.0 to 9.0; *P* = .008)	
HDL-C increase (218)	Mean for week 22 and 24	6.2 (2.2 to 10.2; *P* = .008)	
Non-HDL-C increase (218)	24 weeks	-31.1 (-35.4 to -26.8; *P* < .001)	
Non-HDL-C increase (218)	Mean for week 22 and 24	-33.1 (-37.1 to -29.0; *P* < .001)	

Outcome (N Analyzed)	Timing of Follow-up	Active Treatment Groups			
Ray, 2017[15,39] ODYSSEY DM - DYSLIPIDEMIA		Alirocumab: 75 - 150 mg	Ezetimibe: NR	Fenofibrate: NR	Usual Care (Ezetimibe, Fenofibrate, Omega 3 FA, Nicotinic Acid, No LLT): NR
Mortality outcomes		NR			
Cardiovascular disease outcomes		NR			
Intermediate outcomes		Least Squares mean % change from baseline			
Non-HDL change from baseline* (409)	24 weeks	-37.3	-15.7	-8.5	-4.7
		Least squares mean % change from baseline difference for alirocumab compared to comparator (97.5% CI; P value)			
Non-HDL-C increase for alirocumab vs. comparator* (409)	24 weeks		-26.3 (NR; $P < .0001$)	-33.3 (NR; $P < .0001$)	-32.5 (-38.1 to -27.0; $P < .0001$)
LDL-C decrease for alirocumab vs. comparator (409)	24 weeks		-34.2 (NR; $P < .0001$)	-55.7 (NR; $P < .0001$)	-43.0 (NR; $P < .0001$)
HDL-C increase for alirocumab vs. comparator (409)	24 weeks		7.1 (NR; $P = .03$)	1.1 (NR; $P = .82$)	6.2 (NR; $P = .003$)
		Percentage			
Participants achieving non-HDL-C goal ≥ 100 mg/dl (409)	24 weeks	66.9	22.2	10.1	17.7
Participants achieving non-HDL-C goal < 100 mg/dl (409)	12 weeks	59.6	28.8	8.3	18.6
Participants achieving LDL-C goal < 70 mg/dl (409)	24 weeks	70.8	20.8	17.5	16.3
Participants achieving LDL-C goal < 70 mg/dl (409)	12 weeks	66.1	26.9	8.3	18.6

Outcome (N Analyzed)	Timing of Follow-up	Active Treatment Groups			
Robinson et al., 2014[16,40] **NCT01763866** **LAPLACE-2**		**Evolocumab 140 mg**	**Evolocumab 420 mg**	**Ezetimibe 10 mg**	**Placebo**
Mortality outcomes		**N (%)**			
Deaths (1,896)	From first dose to end of study	0 (0)		0 (0)	1 (0.2)
Cardiovascular disease outcomes		**N (%)**			
Positively adjudicated cardiovascular adverse events (1,896)	From first dose to end of study	5 (0.4)		2 (0.9)	8 (1.4)
Intermediate outcomes		**Mean percentage point difference of change from baseline for evolocumab compared to ezetimibe**			
LDL-C decrease* (NR)	Mean of weeks 10 and 12	Atorvastatin 80 mg: -44.9 (-54.3 to -35.6) Atorvastatin 10 mg: -37.5 (-43.0 to -32.0) Atorvastatin 80 mg: -43.8 (-52.1 to -35.6) Atorvastatin 10 mg: -43.5 (-49.7 to -37.3)			NA

Outcome (N Analyzed)	Timing of Follow-up	Active Treatment Groups	
Roth, 2014[9] Roth, 2015[10] ODYSSEY MONO		Alirocumab 75 mg	Ezetimibe 10 mg
Mortality outcomes		NR	
Cardiovascular disease outcomes		NR	
Intermediate outcomes		Least squares mean % change from baseline (SE); (95% CI; P value)	
LDL-C decrease * (103)	24 weeks	-31.6 (4.3); (-40.2 to 23.0; *P* < .0001)	
LDL-C decrease (103)	12 weeks	-28 (4); (NR; *P* < .0001)	
HDL-C increase (103)	24 weeks	4.4 (2.7); (-1.0 to 9.8; *P* = .11)	

Outcome (N Analyzed)	Timing of Follow-up	Active Treatment Groups	
Sabatine, 2017a[21]; Sabatine et al., 2017b[22]; Giugliano et al., 2017[23] FOURIER		Evolocumab 420 mg Monthly or 140 mg Biweekly	Placebo
Mortality outcomes		NR	
Cardiovascular disease outcomes		N (%); Hazard ratio (95% CI; P value)	
Participants with a cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, or coronary revascularization* (27,564)	Median 26 months	1,344 (9.8) 0.85 (0.79 to 0.92; *P* < .001)	1,563 (11.3)
Among participants with diabetes (11,031)	Median 26 months	622 (11.3) 0.83 (0.75 to 0.93; *P* = .0008)	739 (13.4)
Among participants without diabetes (16,533)	Median 26 months	722 (8.7) 0.87 (0.79 to 0.96; *P* = .005)	824 (10.0)
Participants with a cardiovascular death, myocardial infarction, or stroke (27,564)	Median 26 months	816 (5.9) 0.80 (0.73 to 0.88; *P* < .001)	1,013 (7.4)
Among participants with diabetes (11,031)	Median 26 months	417 (7.6) 0.82 (0.72 to 0.93; *P* = .002)	508 (9.2)
Among participants without diabetes (16,533)	Median 26 months	399 (4.8) 0.78 (0.69 to 0.89; *P* = .0002)	505 (6.1)
Participants who died from a cardiovascular event (27,564)	Median 26 months	251 (1.8) 1.05 (0.88 to 1.25; *P* = .62)	240 (1.7)
Among participants with diabetes (11,031)	Median 26 months	137 (2.5) 1.05 (0.83 to 1.34; NR)	131 (2.4)
Among participants without diabetes (16,533)	Median 26 months	114 (1.4) 1.04 (0.80 to 1.35; NR)	109 (1.3)
Participants who died from any cause (27,564)	Median 26 months	444 (3.2) 1.04 (0.91 to 1.19; *P* = .54)	426 (3.1)
Among participants with diabetes (11,031)	Median 26 months	236 (4.3) 1.10 (0.91 to 1.32; NR)	217 (3.9)

Outcome (N Analyzed)	Timing of Follow-up	Active Treatment Groups	
Sabatine, 2017a[21]; Sabatine et al., 2017b[22]; Giugliano et al., 2017[23] FOURIER		**Evolocumab 420 mg Monthly or 140 mg Biweekly**	**Placebo**
Among participants without diabetes (16,533)	Median 26 months	208 (2.5) 0.99 (0.82 to 1.20; NR)	209 (2.5)
Participants with a myocardial infarction (27,564)	Median 26 months	468 (3.4) 0.73 (0.65 to 0.82; *P* < .001)	639 (4.6)
Among participants with diabetes (11,031)	Median 26 months	239 (4.3) 0.77 (0.65 to 0.92; NR)	308 (5.6)
Among participants without diabetes (16,533)	Median 26 months	229 (2.8) 0.69 (0.58 to 0.81; NR)	331 (4.0)
Participants with a stroke (27,564)	Median 26 months	207 (1.5) 0.79 (0.66 to 0.95; *P* = .01)	262 (1.9)
Among participants with diabetes (11,031)	Median 26 months	113 (2.0) 0.79 (0.62 to 1.01; NR)	143 (2.6)
Among participants without diabetes (16,533)	Median 26 months	94 (1.1) 0.79 (0.60 to 1.03; NR)	119 (1.4)
Participants with coronary revascularization (27,564)	Median 26 months	759 (5.5) 0.78 (0.71 to 0.86; *P* < .001)	965 (7.0)
Among participants with diabetes (11,031)	Median 26 months	326 (5.9) 0.77 (0.66 to 0.88; NR)	423 (7.7)
Among participants without diabetes (16,533)	Median 26 months	433 (5.2) 0.79 to (0.70 to 0.90; NR)	542 (6.6)
Intermediate outcomes		**Mean percentage change from baseline, difference in evolocumab compared to placebo (95% CI; P value)**	
LDL-C decrease (NR)	48 weeks	59 (58 to 60; *P* < .001)	
Among participants with diabetes (NR)	48 weeks	57 (56 to 58; *P* < .0001)	
Among participants without diabetes (NR)	48 weeks	60 (60 to 61; *P* < .0001)	

Outcome (N Analyzed)	Timing of Follow-up	Active Treatment Groups	
Sabatine, 2017a[21]; Sabatine et al., 2017b[22]; Giugliano et al., 2017[23] FOURIER		**Evolocumab 420 mg Monthly or 140 mg Biweekly**	**Placebo**
Non-HDL-C increase (NR)	48 weeks	*-51.6* (NR; *P* < .001)	
Among participants with diabetes (NR)	48 weeks	-49.8 (NR; *P* < .0001)	
Among participants without diabetes (NR)	48 weeks	-52.8 (NR; *P* < .0001)	
HDL-C increase (NR)	48 weeks	*8.1* (NR; *P* < .001)	
Among participants with diabetes (NR)	48 weeks	8.4 (NR; *P* < .0001)	
Among participants without diabetes (NR)	48 weeks	7.9 (NR; *P* < .0001)	

Outcome (N Analyzed)	Timing of Follow-up	Active Treatment Groups	
Sabatine et al. 2015[8] **NCT01439880 NCT01854918** **OSLER-1, OSLER-2** **OSLER Extension Studies**		**Evolocumab 140 mg or 420 mg Plus Standard of Care**	**Standard of Care**
Mortality outcomes-		**N (%)**	
Death (4,465)	48 weeks	4 (0.14)	6 (0.41)
Cardiovascular or unknown death (4,465)	48 weeks	4 (0.1)	3 (0.2)
Noncardiovascular death (4,465)	48 weeks	0 (0)	3 (0.2)
Cardiovascular disease outcomes		**N (%); Hazard ratio for evolocumab vs. standard care (95% CI)**	
All cardiovascular events (4,465)	48 weeks	29 (0.95); 0.47 (0.28 to 0.78)	31 (2.18)
Cardiovascular composite of death, major coronary events, and major cerebrovascular events (4,465)		28 (0.95); 0.47 (0.28 to 0.78)	30 (2.11)
		N (%)	
Coronary events (4,465)	48 weeks	22 (0.75)	18 (1.30)
Myocardial infarction (4,465)	48 weeks	9 (0.3)	5 (0.3)
Hospitalization for unstable angina (4,465)	48 weeks	3 (0.1)	3 (0.2)
Coronary revascularization (4,465)	48 weeks	15 (0.5)	17 (1.1)
Cerebrovascular events (4,465)	48 weeks	4 (0.14)	7 (0.47)
Stroke (4,465)	48 weeks	3 (0.1)	2 (0.1)
Transient ischemic attack (4,465)	48 weeks	1 (0.0)	5 (0.3)
Heart failure requiring hospitalization (4,465)	48 weeks	1 (0.3)	1 (0.07)
Intermediate outcomes		**Mean mg/dl absolute reduction of evolocumab compared to standard care**	
LDL-C decrease (4,465)	12 weeks	73.4	

Outcome (N Analyzed)	Timing of Follow-up	Active Treatment Groups	
Sabatine et al. 2015[8] **NCT01439880 NCT01854918** **OSLER-1, OSLER-2** **OSLER Extension Studies**		**Evolocumab 140 mg or 420 mg Plus Standard of Care**	**Standard of Care**
LDL-C decrease (NR)	24 weeks	70.4	
LDL-C decrease (NR)	36 weeks	72.7	
LDL-C decrease (NR)	48 weeks	70.5	
		Mean percentage reduction of evolocumab compared to standard care (P value)	
LDL-C decrease (4,465)	12 weeks	60.9 (*P* < .001)	
LDL-C decrease (NR)	24 weeks	58.8 (*P* < .001)	
LDL-C decrease (NR)	36 weeks	54.0 (*P* < .001)	
LDL-C decrease (NR)	48 weeks	58.4 (*P* < .001)	
		Mean percentage change from baseline (P value for evolocumab plus standard care compared to standard care)	
HDL-C increase (NR)	12 weeks	8.7 (*P* < .001)	1.7

Outcome (N analyzed)	Timing of Follow-up	Active Treatment Groups	
ODYSSEY OUTCOMES Schwartz, 2018[24]		**Alirocumab, 75-150 mg**	**Placebo**
Mortality outcomes		*N (%); Hazard ration (95% CI; P value*	
Death from any cause (18,924)	Median 2.8 years	334 (3.5%) 0.85 (0.73 to 0.98; NR)	392 (4.1%)
Death from coronary heart disease (18,924)	Median 2.8 years	205 (2.2) 0.92 (0.76 to 1.1: *P* = .38)	222 (2.3)
Death from cardiovascular causes (18,924)	Median 2.8 years	240 (2.5) 0.88 (0.74 to 1.05; NR)	271 (2.9)
Adverse event that led to death (18,894)	Median 2.8 years	181 (1.9) NR	222 (2.4)
Cardiovascular disease outcomes		*N (%); Hazard ratio (95% CI; P value); Absolute Risk Reduction % (95% CI; P value)*	
Composite of death from coronary heart disease, nonfatal MI, fatal or nonfatal ischemic stroke, or unstable angina requiring hospitalization* (18,924)	Median 2.8 years	903 (9.5) 0.85 (0.78 to 0.93; *P* < .001) NR	1052 (11.1)
Among those with baseline LDL-C of < 80 mg/dL (7,164)	Median 2.8 years	296 (8.3) 0.86 (0.74 to 1.01; *P* = .09) 1.3 (−0.1 to 2.6; *P* < .001)	341 (9.5)
Among those with baseline LDL-C of 80 to 100 mg/dL (6,128)	Median 2.8 years	283 (9.2) 0.96 (0.82 to 1.14; *P* = .09) 0.3 (−1.2 to 1.8; *P* < .001)	291 (9.5)
Among those with baseline LDL-C of ≥ 100 mg/dL (5,629)	Median 2.8 years	324 (11.5) 0.76 (0.65 to 0.87; *P* = .09) 3.4 (1.6 to 5.2; *P* < .001)	420 (14.9)
		%; Hazard ratio (95% CI)	
Incidence among those < 65 years of age (13840)	Median 2.8 years	8.5 0.89 (0.78 to 0.93)	9.5
Incidence among those ≥ 65 years of age (5084)	Median 2.8 years	12.4 0.79 (0.68 to 0.91	15.5

Incidence among those who are females (4762)	Median 2.8 years	10.7 0.91 (0.77 to 1.08)	11.8
Incidence among those who are males (14162)	Median 2.8 years	9.2 0.83 (0.74 to 0.92)	10.9
Incidence among those who are White (15024)	Median 2.8 years	9.5 0.82 (0.74 to 0.91)	11.4
Incidence among those who are black or African American (473)	Median 2.8 years	14.9 0.64 (0.42 to 0.98)	21.0
Incidence among those who are Asian (2498)	Median 2.8 years	8.4 1.14 (0.86 to 1.51)	(.5
Incidence among those who are of other races (918)	Median 2.8 years	10.4 0.92 (0.62 to 1.36)	11.4
Participants with any coronary heart disease event (18,924)	Median 2.8 years	1,199 (12.7) 0.88 (0.81 to 0.95; *P* = .001)	1,349 (14.3)
Participants with a Major coronary heart disease event (18,924)	Median 2.8 years	793 (8.4) 0.88 (0.80 to 0.96; *P* = .006)	899 (9.5)
Participants with any cardiovascular event (18,924)	Median 2.8 years	1,301 (13.7) 0.87 (0.81 to 0.94; *P* < .001)	1,474 (15.6)
Participants with an adjudicated hemorrhagic stroke (18,894)	Median 2.8 years	9 (<0.1) NR	16 (0.2)
Participants with nonfatal MI	Median 2.8 years	626 (6.6) 0.86 (0.77 to 0.96; NR)	722 (7.6)
Participants with fatal or nonfatal ischemic stroke	Median 2.8 years	111 (1.2) 0.73 (0.57 to 0.93; NR)	152 (1.6)
Participants with unstable angina requiring hospitalization	Median 2.8 years	37 (0.4) 0.61 (0.41 to 0.92; NR)	60 (0.6)
Participants with ischemia-driven coronary revascularization procedure	Median 2.8 years	731 (7.7) 0.88 (0.79 to 0.97)	828 (8.8)
Participants with hospitalization for congestive heart failure	Median 2.8 years	176 (1.9) 0.98 (0.79 to 1.20)	179 (1.9)
Intermediate outcomes: NR			

Outcome (N Analyzed)	Timing of Follow-up	Active Treatment Groups			
Stroes et al., 2014[18] NCT01763905 GAUSS-2		**Evolocumab 140 mg Plus Placebo Every Day**	**Evolocumab 420 mg Plus Placebo Every Day**	**Ezetimibe 10 mg Plus Placebo Every 2 Weeks**	**Ezetimibe 10 mg Plus Placebo Monthly**
Mortality outcomes		**N (%)**			
Deaths (307)		0 (0)	0 (0)	0 (0)	0 (0)
Cardiovascular disease outcomes		**N (%)**			
Cardiovascular disease outcomes		0 (0)	0 (0)	0 (0)	0 (0)
Intermediate outcomes		**Mean percentage change from baseline (95% CI; P value)**			
LDL-C decrease* (307)	10 to 12 weeks	-56.1 (-59.7 to -52.4)	-55.3 (-58.3 to -52.3)	-19.2 (-23.9 to -14.5)	-16.6 (-20.6 to -12.6)
LDL-C decrease for evolocumab compared to ezetimibe (307)	10 to 12 weeks	-36.9 (-42.3 to -31.6; *P*<0.001)	-38.7 (-43.1 to 34.3; *P*<0.001)		
LDL-C decrease* (307)	Week 12	-56.1 (-59.9 to -52.4)	-52.6 (-55.7 to -49.5)	-18.1 (-23.1 to -13.1)	-15.1 (-19.3 to -10.9)
LDL-C decrease for evolocumab compared to ezetimibe (307)	Week 12	-38.1 (-43.7 to -32.4; *P*<0.001)	-37.6 (-4 2.2, -32.9; *P*<0.001)		
		Mean mg/dl change from baseline (95% CI; P value)			
LDL-C decrease (307)	Week 12	-106.0 (-114.0 to -97.9)	-99.0 (-105.9 to -92.1)	-36.2 (-46.9 to -25.5)	-30.2 (-39.5 to -20.9)
LDL-C decrease for evolocumab compared to ezetimibe (307)	Week 12	-69.7 (-82.0 to -57.5)	-68.8 (-79.2 to -58.4		
HDL-C increase evolocumab vs. ezetimibe (307)	Week 12	3.6 (-1.5, 8.6; *P* = NR)	4.8 (- 0.2, 9.8; *P* = NR)		

Outcome (N Analyzed)	Timing of Follow-up	Active Treatment Groups		
Sullivan et al., 2012[19] NCT01375764 GAUSS		**Evolocumab 420 mg**	**Evolocumab 420 mg Plus Ezetimibe 10 mg**	**Placebo Monthly Plus Ezetimibe 10 mg**
Mortality outcomes		**N**		
All-cause deaths (94)	12 weeks	0	0	0
Deaths from cardiovascular event (94)	12 weeks	0	0	0
Cardiovascular disease outcomes		**N**		
Cardiovascular event		1	0	0
Intermediate outcomes		**Least squares mean percentage change from baseline, evolocumab compared to placebo (95% CI; P value)**		
LDL-C decrease* (94)	12 weeks	-35.9 (-44.1 to -27.8; *P* < .001)	-47.3 (-53.7 to -40.8; *P* < .001)	
LDL-C decrease* (94)	12 weeks	-51 (-59 to -43; *P* <.001)	-63 (-71 to -55; *P* <.001)	-15 (-23 to -7.0; *P* <.001)
		Mean mg/dl change from baseline (95% CI; P value)		
LDL-C decrease (94)	12 weeks	-90.8 (-108.5 to -73.0)	-109.8 (-131.9 to -87.7)	-14.2 (-31.7 to 3.3)
		Mean percentage change from baseline, evolocumab compared to placebo plus ezetimibe (95% CI; P value)		
HDL-C increase (94)	12 weeks	*8.5* (NR; *P* = .02)	*13.1* (NR; *P* < .001)	

*Notes. Outcomes that are italicized are values we calculated based on data provided in the study report. *Primary outcome studied. Outcomes that are italicized are values we calculated based on data provided in the study report. * Primary outcome studied. Abbreviations. CI: confidence interval; CTTC: Cholesterol Treatment Trialists Collaboration; GAUSS: Goal Achievement after Utilizing an anti-PCSK9 antibody in Statin Intolerant Subjects; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; mg: milligram; NA: not applicable; NR: not reported; OSLER: Open-Label Study of Long-term Evaluation Against LDL-C; RUTHERFORD: Reduction of LDL-C With PCSK9 Inhibition in Heterozygous Familial Hypercholesterolemia Disorder.*

Table B3. Adverse Events from PCSK9 Inhibitors in Randomized Trials

Outcome	Treatment Groups (N Analyzed)		
Bays et al., 2015[13,34] ODYSSEY OPTIONS I	Pooled Alirocumab (104)	Pooled Ezetimibe (101))	Pooled Double Atorvastatin or Switch to Rosuvastatin (149)
N (%) with ≥ 1 adverse event	68 (65.4)	65 (64.4)	95 (63.8)
N (%) with an adverse event leading to discontinuation	7 (6.7)	4 (4.0)	8 (5.4)
N (%) with ≥ 1 serious adverse event/N events	4 (3.8)/NR	7 (6.9)/NR	8 (5.4)/NR
N (%) with specific adverse events			
Injection site reactions	3 (2.9)	3 (3.0)	3 (2.0)
Potential allergic event	2 (1.9)	5 (5.0)	6 (4.0)
Gastrointestinal disorders	12 (11.5)	16 (15.8)	31 (20.8)
ALT greater than 3 x ULN	0/101 (0)	0 (0) (0/99)	1/147 (0.7)
Neurocognitive dysfunction	0 (0)	0 (0)	0 (0)
Nasopharyngitis	5 (4.8)	3 (3.0)	8 (5.4)

Outcome	Treatment Groups (N Analyzed)	
Cannon, 2015[12] **NCT01644188** **ODYSSEY COMBO II**	**Alirocumab 75 to 150 mg (479)**	**Ezetimibe 10 mg (241)**
N (%) with ≥ 1 adverse event	341 (71.2)	162 (67.2)
N (%) with an adverse event leading to discontinuation	2 (0.4)	4 (1.7)
N (%) with ≥ 1 serious adverse event/N events	90 (18.8)/NR	43 (17.8)/NR
N (%) with specific adverse events		
Injection site reaction	12 (2,5)	2 (0.8)
Alanine aminotransferase > 3 X ULN	8/470 (1.7)	1/240 (0.4)
Myalgia	21 (4.4)	12 (0.5)
Neurocognitive disorder	4 (0.8)	3 (1.2)

Outcome	Treatment Groups (N Analyzed)		
Farnier, 2016[14,34] ODYSSEY OPTIONS II	**Pooled Alirocumab (103)**	**Pooled Ezetimibe (101))**	**Pooled Double Rosuvastatin (101)**
N (%) with ≥ 1 adverse event	58 (56.3)	54 (53.5)	68 (67.3)
N (%) with an adverse event leading to discontinuation	5 (4.9)	8 (7.9)	5 (5.0)
N (%) with ≥ 1 serious adverse event/N events	6 (5.8)/NR	8 (7.9)/NR	8 (7.9) /NR
N (%) with specific adverse events			
Injection site reactions	4 (3.9)	0	2 (2.0)
Potential allergic event	9 (8.7)	2 (2.0)	7 (6.9)
Gastrointestinal disorders	13 (12.6)	9 (8.9)	14 (13.9)
ALT greater than 3 x ULN (n/N)	1/101 (1.0)	0/99 (0)	0/100 (0)
Nasopharyngitis	4 (3.9)	5 (5.0)	7 (6.9)
Neurocognitive disorder	1 (1.0)	1 (1.0)	1 (1.0)
Musculoskeletal and connective tissue disorders	13 (12.6)	19 (18.8)	21 (20.8)

Outcome	Treatment Groups (N Analyzed)	
Hovingh, 2017[7] **OSLER I and II (RUTHERFORD and RUTHERFORD 2)**	**Evolocumab 420 mg Monthly or 140 mg Biweekly Plus Standard Care (289)**	**Standard Care (151)**
N (%) with ≥ 1 adverse event	231 (79.9)	101 (66.9)
N (%) with an adverse event leading to discontinuation	0 (0.0)	NA
N (%) with ≥ 1 serious adverse event/N events	21 (7.3)/NR	13 (8.6)/NR
N (%) with specific adverse events[a]		
Hyperglycemia or onset diabetes mellitus	3 (1.0)	3 (2.0)
Aminotransferase level between 3 and 5x ULN	8 (2.8)	0 (0.0)
Aminotransferase level between > 5x ULN	1 (0.3)	0 (0.0)
Muscle-related event	29 (10.0)	7 (4.6)
Neurocognitive event	1 (0.3)	0 (0.0)
Nasopharyngitis	49 (17.0)	9 (6.0)
Arthralgia	26 (9.0)	6 (4.0)

Outcome	Treatment Groups (N Analyzed)	
Koren, 2014[20] **OSLER I**	**Evolocumab 420 mg Plus Standard Care (736)**	**Standard Care (368)**
N (%) with ≥ 1 adverse event	599 (81.4)	269 (73.1)
N (%) with an adverse event leading to discontinuation of evolocumab	27 (3.7)	NA
N (%) with ≥ 1 serious adverse event/N events	52 (7.1)/NR	23 (6.3)/NR
N (%) with specific adverse events		
Injection site reactions	38 (5.2)	NA
Aminotransferase level > 3 x ULN	13 (1.8)	6 (1.6)
Aminotransferase level > 5 x ULN	4 (0.5)	1 (0.3)
Muscle-related event	68 (9.2)	36 (9.8)
Nasopharyngitis	90 (12.2)	36 (9.8)

Outcome	Treatment Groups (N Analyzed)	
Moriarty, 2015[11,37] **ODYSSEY ALTERNATIVE**	**Alirocumab: 75 to 150 mg (126)**	**Ezetimibe 10 mg (124)**
N (%) with ≥ 1 adverse event	104 (83)	100 (81)
N (%) with an adverse event leading to discontinuation	23 (18)	31 (25
N (%) with ≥ 1 serious adverse event/N events	12 (10)/ NR	10 (8)/ NR
N (%) with specific adverse events		
Injection-site reaction	6 (5)	6 (5)
Diarrhea	6 (5)	6 (5)
Vomiting	3 (2)	1 (1)
Constipation	3 (2)	5 (4)
Nausea	1 (1)	1 (1)
Adjudicated cardiovascular events	4 (3)	1 (1)
Nonfatal myocardial infarction	1 (1)	0
Ischemia-driven coronary revascularization procedure	3 (2)	1 (1)
ALT > 3 X ULN	0	0
Nasopharyngitis	8 (6)	10 (8)
Skeletal muscle–related adverse event	41 (33)	51 (41)

Outcome	Treatment Groups (N Analyzed)	
Nissen, 2016[17,38] **GAUSS-3**	**Evolocumab 420 mg (145)**	**Ezetimibe (73)**
N (%) with ≥ 1 adverse event	80 (55.2)	40 (54.8)
N (%) with ≥ 1 serious adverse event/N events	9 (6.2)/NR	10 (13.7)/NR
N (%) discontinuing oral treatment for any reason	23 (15.9)	14 (19.2)
N (%) discontinuing SC treatment for any reason	7 (4.8)	4 (5.5)
N (%) discontinuing oral treatment for muscle symptoms	11 (7.6)	5 (6.8)
N (%) discontinuing SC treatment for muscle symptoms	1 (0.7)	0 (0.0)
N (%) with specific adverse events		
Injection site reaction	7 (4.8)	2 (2.7)
Diarrhea	6 (4.1)	4 (5.5)
With nausea	5 (3.4)	3 (4.1)
Any muscle-related adverse event	30 (20.7)	21 (28.8)
Myalgia	20 (13.8)	16 (21.9)
Musculoskeletal pain	5 (3.4)	1 (1.4)
Muscle weakness	3 (2.1)	0 (0.0)
Muscle spasms	13 (9.0)	5 (6.8)
Nasopharyngitis	14 (9.7)	2 (2.7)

Outcome	Treatment Groups (N Analyzed)	
Ray, 2017[15,39] **ODYSSEY DM - DYSLIPIDEMIA**	**Alirocumab: 75 to 150 mg (275)**	**Usual Care (137)**
N (%) with ≥ 1 adverse event	188 (68.4)	91 (66.4)
N (%) with an adverse event leading to discontinuation	10 (3.6%	4/100 (4.0)[a]
N (%) with ≥ 1 serious adverse event/N events	26 (9.5)/NR	12(8.8)/NR
N (%) with specific adverse events		
Injection site reactions	0	0
Allergic events	1 (0.4)	2 (1.5)
Diarrhea	14 (5.1)	9 (6.6)
Nausea	11 (4.0)	5 (3.6)
Gastroenteritis	3 (1.1)	3 (2.2)
Constipation	2 (0.7)	3 (2.2)
Gastritis	0	3 (2.2)
Type 2 diabetes mellitus	2 (0.7)	3 (2.2)
Increase in ALT	2 (0.7)	0
Muscle-related event (muscle spasms)	6 (2.2)	2 (1.5)
Neurocognitive dysfunction (events)	2 (0.7)	0

Outcome	Treatment Groups (N Analyzed)		
Robinson et al., 2014[16,40] NCT01763866 LAPLACE-2	**Evolocumab 140 mg or 420 mg Plus Any Statin (1117)**	**Ezetimibe 10 mg Plus Atorvastatin (221)**	**Any Statin Plus Placebo (558)**
N (%) with ≥ 1 adverse event	406 (36.3)	89 (40.3)	219 (39.2)
N (%) with an adverse event leading to discontinuation	21 (1.9)	4 (1.8)	12 (2.2)
N (%) with ≥ 1 serious adverse event/N events	23 (2.1)	2 (0.9)	13 (2.3)
N (%) with specific adverse events			
Potential injection site reaction	15 (1.3)	2 (0.9)	13 (2.3)
ALT/AST > 3 x ULN	4 (0.4)	3 (1.4)	6 (1.1)
Neurocognitive adverse events	1 (0.1)	3 (1.4)	0 (0)

Outcome	Treatment Groups (N Analyzed)	
Roth, 2014,[9] Roth, 2015[10] ODYSSEY MONO	**Alirocumab 75 mg (52)**	**Ezetimibe 10 mg (51)**
N (%) with ≥ 1 adverse event	36 (69.2)	40 (78.4)
N (%) with a treatment - related adverse event leading to discontinuation	5 (9.6)	4 (7.8)
N (%) with ≥ 1 serious adverse event/N events	1 (1.9)/NR	1 (2.0)/NR
N (%) with an adverse event leading to death	0 (0)	0 (0)
N (%) with specific adverse events		
Injection site reaction	1 (1.9)	2 (3.9)
Allergic reaction	6 (11.5)	5 (9.8)
Diarrhea	6 (11.5)	2 (3.9)
Nausea	3 (5.8)	3 (5.9)
Glucose > 126 mg/dl	6/51 (11.8)	1/50 (2.0)
Nasopharyngitis	12 (23.1)	8 (15.7)
Musculoskeletal and connective tissue disorders	8 (15.4)	11 (21.6)

Outcome	Treatment Groups (N Analyzed)	
Sabatine., 2017a[21]; Sabatine et al., 2017b[22]; Giugliano et al., 2017[23] **FOURIER**	**Evolocumab 420 mg Monthly or 140 mg Biweekly (13,769)**	**Placebo (13,756)**
N (%) with ≥ 1 adverse event	10,664 (77.4)	10,644 (77.4)
N (%) with a non - fatal adverse event leading to discontinuation	628 (4.6)	581 (4.2)
N (%) with a treatment-related adverse event leading to discontinuation	226 (1.6)	201 (1.5)
N (%) with ≥ 1 serious adverse event/N events	3,410 (24.8)/NR	3,404 (24.7)/NR
N (%) with specific adverse events		
Neurocognitive event	217 (1.6)	202 (1.5)
Injection site reaction	296 (2.1)	219 (1.6)
Allergic reaction	420 (3.1)	393 (2.9)
Muscle-related event	682 (5.0)	656 (4.8)
Aminotransferase level > 3 ULN	240 (1.8 of 13,543)	242 (1.8 of 13,523)
Onset diabetes mellitus	663 (8.0 of 8,256)	631 (7.6 of 8,254)

Outcome	Treatment Groups (N Analyzed)	
Sabatine et al. 2015[8] **NCT01439880 NCT01854918** **OSLER-1, OSLER-2** **OSLER Extension Studies**	**Evolocumab 140 mg or 420 mg Plus Standard of Care (2,976)**	**Standard of Care (1,489)**
N (%) with ≥ 1 adverse event	2,060 (69.2)	965 (64.8)
N (%) with an adverse event leading to discontinuation of evolocumab	71 (2.4)	NA
N (%) with ≥ 1 serious adverse event/N events	222 (7.5)/NR	111 (7.5)/NR
N (%) with specific adverse events		
Injection site reaction	129 (4.3)	NA
Gastroenteritis	44 (1.5)	12 (0.8)
Alanine or aspartate aminotransferase >3 × ULN	31 (1.0)	18 (1.2)
Muscle spasms	73 (2.5)	29 (1.9)
Musculoskeletal pain	62 (2.1)	30 (2.0)
Neurocognitive events	27 (0.9)	4 (0.3)
Nasopharyngitis	280 (9.4)	140 (9.4)

Outcome	Treatment Groups (N analyzed)	
ODYSSEY OUTCOMES Schwartz, 2018[24]	**Alirocumab,75-150 mg (9,451)**	**Placebo (9,443)**
N (%) with ≥ 1 adverse event	7,165 (75.8)	7,282 (77.1)
N (%) with an adverse event leading to discontinuation	343 (3.6)	324 (3.4)
N (%) with ≥ 1 serious adverse event / N events	2,202 (23.3) / NR	2,350 (24.9) / NR
N (%) with specific adverse events		
Injection site reactions	360 (3.8) *(P* < .001)	203 (2.1)
General allergic reaction	748 (7.9)	736 (7.8)
Onset diabetes	648/6,763 (9.6)	676/6,696 (10.1)
Alanine aminotransferase > 3x ULN	212/9,369 (2.3)	228/9,341 (2.4)
Aspartate aminotransferase > 3x ULN	160/9,367 (1.7)	166/9,338 (1.8)
Neurocognitive disorder	143 (1.5)	167 (1.8)

Outcome	Treatment Groups (N Analyzed)			
Stroes et al., 2014[18] NCT01763905 GAUSS-2	**Evolocumab 140 mg (102)**	**Evolocumab 420 mg (103)**	**Ezetimibe 10 mg Plus Placebo Every 2 Weeks (51)**	**Ezetimibe 10 mg Plus Placebo Every Month (51)**
N (%) with ≥ 1 adverse event	63 (61)	72 (71)	35 (69)	39 (77)
N (%) with an adverse event leading to discontinuation	6 (6)	11 (11)	4 (8)	9 (18)
N (%) with ≥ 1 serious adverse event/N events	5 (5)/NR	1 (1)/NR	1 (2)/NR	3 (6)/NR
N (%) with specific adverse events				
Injection site erythema	2 (2)	2 (2)	0	3 (6)
Potential injection site reactions	3 (3)	3 (3)	1 (2)	7 (14)
Diarrhea	3 (3)	2 (2)	3 (6)	4 (8)
Neurocognitive events	0 (0)	0 (0)	0 (0)	0 (0)

Outcome			
Sullivan et al., 2012[19] NCT01375764 GAUSS	**Evolocumab 420 mg (32)**	**Evolocumab 420 mg Plus Ezetimibe 10 mg (30)**	**Placebo Monthly Plus Ezetimibe 10 mg (32)**
N (%) with ≥ 1 treatment-emergent adverse event	18 (56.3)	20 (66.7)	19 (59.4)
N (%) with ≥ 1 treatment-emergent serious adverse event/N events	1 (3.1)/NR	0 (0.0)/0	0 (0.0)/0
N (%) with a treatment-emergent adverse event leading to discontinuation	1 (3.1)	1 (3.3)	2 (6.3)/NR
N (%) with ≥ 1 treatment-related adverse event/N events	6 (18.8)/NR	5 (16.7)/NR	7 (21.9)/NR
N (%) with ≥ 1 treatment-related serious adverse event/N events	0 (0.0)/0	0 (0.0)/0	0 (0.0)/0
N (%) with specific adverse events			
Constipation	1 (3.1)	3 (10.0)	0 (0.0)
Nausea	1 (3.1)	0 (0.0)	1 (3.1)
Aminotransferase level > 3 ULN	0 (0.0)	0 (0.0)	1 (3.1)
Aminotransferase level > 5 ULN	0 (0.0)	0 (0.0)	0 (0.0)
Myalgia	1 (3.1)	6 (20.0)	1 (3.1)
Muscle fatigue	0 (0.0)	0 (0.0)	1 (3.1)
Muscle spasms	0 (0.0)	0 (0.0)	3 (9.4)
Nasopharyngitis	1 (3.1)	3 (10.0)	5 (15.6)

Notes. [a]Adverse events, categorized by system–organ–class that occurred with a 5% absolute frequency in the evolocumab plus SOC arm compared to the SOC alone arm and reported here as the percentage of patients who experienced 1 or more of these events, were infections and infestations (47.8% vs. 37.1%); musculoskeletal and connective tissue disorders (33.2% vs. 21.9%); general disorders and administration site conditions (25.3% vs. 7.3%); gastrointestinal disorders (19.7% vs. 12.6%); and nervous system disorders (14.5% vs. 7.9%). Abbreviations. ALT: alanine aminotransferase; AST: aspartate aminotransferase; GAUSS-3: Goal Achievement after Utilizing an anti-PCSK9 Antibody in Statin-Intolerant Subjects 3; NA: not applicable; NR: not reported; ULN: upper limit of normal; OSLER: Open-Label Study of Long-term Evaluation Against LDL-C.

Appendix C. Bibliography of Excluded Studies

1. Blom DJ, Hala T, Bolognese M, et al. A 52-week placebo-controlled trial of evolocumab in hyperlipidemia. *N Engl J Med*. 2014;370(19):1809-1819. doi: https://dx.doi.org/10.1056/NEJMoa1316222. Exclusion code: E - In Original Report - DESCARTES.

2. Blom DJ, Koren MJ, Roth E, et al. Evaluation of the efficacy, safety and glycaemic effects of evolocumab (AMG 145) in hypercholesterolaemic patients stratified by glycaemic status and metabolic syndrome. *Diabetes Obes Metab*. 2017;19(1):98-107. doi: https://dx.doi.org/10.1111/dom.12788. Exclusion code: E - Wrong Comparison.

3. Cho L, Rocco M, Colquhoun D, et al. Design and rationale of the GAUSS-2 study trial: a double-blind, ezetimibe-controlled phase 3 study of the efficacy and tolerability of evolocumab (AMG 145) in subjects with hypercholesterolemia who are intolerant of statin therapy. *Clin Cardiol*. 2014;37(3):131-139. doi: https://dx.doi.org/10.1002/clc.22248. Exclusion code: E - In Original Report - ODYSSEY COMBO II.

4. Colhoun HM, Robinson JG, Farnier M, et al. Efficacy and safety of alirocumab, a fully human PCSK9 monoclonal antibody, in high cardiovascular risk patients with poorly controlled hypercholesterolemia on maximally tolerated doses of statins: rationale and design of the ODYSSEY COMBO I and II trials. *BMC Cardiovasc Disord*. 2014;14:121. doi: https://dx.doi.org/10.1186/1471-2261-14-121. Exclusion code: E - In Original Report - ODYSSEY COMBO I and II.

5. de Carvalho LSF, Campos AM, Sposito AC. Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors and incident type 2 diabetes: a systematic review and meta-analysis with over 96,000 patient-years. *Diabetes Care*. 2018;41(2):364-367. doi: https://dx.doi.org/10.2337/dc17-1464. Exclusion code: E - Includes older studies (some in Original Report) and PCTs that are no longer includable.

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hypercholesterolemic patients receiving statin therapy: an analysis from the LDL-C assessment with proprotein convertase subtilisin kexin type 9 monoclonal antibody inhibition combined with statin therapy (LAPLACE)-thrombolysis in myocardial infarction (TIMI) 57 trial. *Circulation*. Vol 128. United States2013:962-969. Exclusion code: E - In Original Report.

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Appendix D. Bibliography of Included Studies

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