A Systematic Review of PCSK9 Inhibitors Alirocumab and Evolocumab

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ABSTRACT

BACKGROUND: The proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors are a new class of cholesterol-lowering medications that provide significant reductions in lipids but at a large cost relative to statins. With 2 such drugs now on the market, alirocumab and evolocumab, comparing the evidence base for these drugs is necessary for informed decision making.

OBJECTIVE: To compare the benefits and harms of the PCSK9 inhibitors alirocumab and evolocumab.

METHODS: The databases Ovid MEDLINE, Cochrane Library, SCOPUS, and ClinicalTrials.gov were used to search for randomized controlled trials of alirocumab or evolocumab with any relevant comparator reporting health outcomes, lipid outcomes, or harms through September 2015, and information was requested from manufacturers. Results were reviewed according to standard review methods.

RESULTS: The database searches revealed 17 fair- and good-quality trials; however, none had primary health outcomes or directly compared PCSK9 inhibitors. Alirocumab (75 mg to 150 mg subcutaneously every 2 weeks) resulted in significantly greater reductions in low-density lipoprotein cholesterol (LDL-C; -8% to -67%) at 12-24 weeks in patients with (a) heterozygous familial hypercholesterolemia and (b) patients at high or varied cardiovascular (CV) risk who were not at LDL-C goals with statin therapy. The highest strength evidence was for patients with high CV risk not at LDL-C goals. Alirocumab also resulted in high-density lipoprotein cholesterol (HDL-C) increases of 6%-12%. Low- and moderate-strength evidence for adjudicated CV events at 52-78 weeks for a priori analyses indicated no benefit. Low- and moderate-strength evidence also found no differences in harms except possibly slightly more injection-site reactions. Evolocumab (120 mg subcutaneously every 2 weeks to 420 mg every 4 weeks) resulted in significantly greater reductions in LDL-C (-32% to -71%) at 12-52 weeks in patients with heterozygous or homozygous familial hypercholesterolemia, patients intolerant of statins, and patients with varied CV risk not at LDL-C goal with statin therapy. The highest strength evidence was for heterozygous familial hypercholesterolemia and patients not at LDL-C goals. Moderate-strength evidence showed HDL-C increases in the range of 4.5%-6.8%. Harms were not different between groups, except possibly slightly greater overall adverse event reporting. Evidence on adjudicated CV outcomes was insufficient to draw conclusions because of sparseness of events, study limitations, and inability to assess consistency of findings.

CONCLUSIONS: Alirocumab and evolocumab have evidence of large improvements in lipid levels. The strength of the evidence is greater for alirocumab than evolocumab in patients with high CV risk who were not at LDL-C target goals, while evidence for evolocumab is stronger in patients with heterogeneous familial hypercholesterolemia and patients with varied CV risk who were not at LDL-C target goals. Evidence on adjudicated CV outcomes for a priori analyses is unable to show benefit for alirocumab and is insufficient to draw conclusions for evolocumab. Important questions remain about the comparative effects on long-term health outcomes.

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What is already known about this subject

- The proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors alirocumab and evolocumab produce large reductions in low-density lipoprotein cholesterol (LDL-C) when given in addition to statins in a variety of populations with hypercholesterolemia or alone or in combination with ezetimibe in patients intolerant to statins.
- Cardiovascular benefits are as yet not clearly established, with some analyses of incidentally reported or secondary outcomes indicating benefit.
- Concerns raised about the evidence include the methodology behind cardiovascular endpoint analyses, long-term effects of large reductions in lipids, whether comparison groups were optimal, and cost of the drugs in light of these concerns.

What this study adds

- This study compared the strength of the evidence base for each of the PCSK9 inhibitors alirocumab and evolocumab.
- The evidence base for alirocumab is stronger than evolocumab for patients at high cardiovascular risk who have not reached LDL-C targets with statin therapy. Although there is strong evidence that alirocumab lowers lipids significantly, there is currently no evidence of a benefit in cardiovascular outcomes when limiting to adjudicated cardiovascular events and a priori analyses.
- Evidence for evolocumab is stronger than alirocumab for patients with heterogeneous familial hypercholesterolemia and patients with varied cardiovascular risk not at LDL-C target, but evidence on cardiovascular events is insufficient or absent. Evolocumab also has evidence in these other populations: homozygous familial hypercholesterolemia, populations of patients with varied cardiovascular risk, and follow-up studies of varied populations.

HMG-CoA reductase inhibitors, or statins, have been the primary therapeutic intervention for hypercholesterolemia for decades. They have been successful in reducing the risk of major cardiovascular events and mortality in a wide range of at-risk individuals.^{1,2} However, there are patients for whom statins alone or in combination with other lipid-lowering therapies are not always adequate to reduce cardiovascular risk, even at maximally tolerated doses. There are also patients who are intolerant of statin therapy, in whom treatment with

drugs such as ezetimibe alone are also inadequate. Monoclonal antibodies that inhibit proprotein convertase subtilisin/kexin type 9 (PCSK9) have been under development as novel therapies, potentially filling these gaps in current standard therapies for hypercholesterolemia. The first 2 drugs in this new class of antihyperlipidemic treatments received U.S. Food and Drug Administration (FDA) approval in mid-2015. In combination with other treatments—typically maximally tolerated statins—alirocumab was approved for use in heterozygous familial hypercholesterolemia or clinical atherosclerotic cardiovascular disease who required additional low-density lipoprotein cholesterol (LDL-C) lowering, and evolocumab was approved for patients with clinical atherosclerotic cardiovascular disease or heterozygous and homozygous familial hypercholesterolemia who required additional LDL-C lowering.

Alirocumab (Praluent) and evolocumab (Repatha) have shown striking LDL-C reductions over 10 to 78 weeks (26%-67%). But, as with many novel specialty drugs, the promise of better results with PCSK9 inhibitors comes with a high price tag—in this case, the cost is estimated at more than \$14,000 per patient per year.³⁻⁵ In this cost-conscious era of health care, clinicians, payers, and the public are already questioning how to best manage this costly new drug class.⁶ While there have been reviews of the evidence published,^{7,8} there has been concerning criticism of the analysis of the evidence, as well as the evidence itself. These concerns center around long-term health outcomes (including handling of data in meta-analyses)^{9,10} and comparison groups in trials (e.g., high-intensity statins).¹¹⁻¹⁴

To date, no clinical trial of a PCSK9 inhibitor designed a priori, with adequate size and duration, to assess cardiovascular outcomes as the primary outcomes has yet been completed. However, 4 such trials are underway and are expected to be completed in 2018.¹⁵⁻¹⁸ In the meantime, Navarese et al. (2015) pooled data from the 24 available smaller studies with follow-up ranging from 2 months to 2 years and reported that PCSK9 inhibitors as a group reduce all-cause mortality (odds ratio [OR]=0.45; 95% confidence interval [CI]=0.23-0.86) and rates of myocardial infarction (OR=0.49; 95% CI=0.26-0.93).⁷ However, these findings have been questioned based on concerns that the statistical approach used by Navarese et al. is biased in how study arms with zero events were handled.^{9,10} Critics demonstrated that use of a few different less-biased conventional methods produced results of consistently smaller magnitude and in 1 case lost statistical significance. Because of the instability and imprecision of these findings, critics urge us to wait for the results of the adequately designed cardiovascular endpoint trials now underway before promoting use of these drugs. Given the increased demand by payers such as Medicare for definitive evidence that interventions improve health outcomes, and not merely intermediate endpoints,¹⁹ this debate has important implications for coverage policy determinations as well.

Additionally, there has been criticism that even the LDL-C benefits of PCSK9 inhibitors may have been overestimated because of underutilization of high-intensity statin therapy.^{11,12} In the largest PCSK9 inhibitor trial to date, the ODYSSEY LONG-TERM trial of alirocumab,²⁰ which alone accounts for 45% of mortality events in the Navarese 2015 meta-analysis,⁷ only 47% of patients were receiving high-dose statins, despite the trial's focus on high-risk patients. In their published response to this criticism, the ODYSSEY LONG-TERM authors agreed with this limitation and promised that the ongoing ODYSSEY Outcomes study (NCT01663402) will address this uncertainty.²¹

To support the work of the participating organizations of the Drug Effectiveness Review Project, the Pacific Northwest Evidence-based Practice Center conducted a systematic review of the comparative effectiveness of alirocumab and evolocumab versus each another, other lipid-lowering regimens, or placebo.²² The purpose of this review was to evaluate the body of evidence for each drug based on the population and comparators studied to better stratify the evidence for decision making with regard for their place in therapy and for selecting a specific PCSK9 inhibitor.

Methods

For this systematic review, randomized controlled trials (RCTs) of alirocumab or evolocumab were included that reported 1 or more health outcomes (e.g., cardiovascular events), lipid outcomes (e.g., LDL-C), or harms (e.g., withdrawal from study because of adverse events). For cardiovascular events, only those that were adjudicated through a formal process were included; those events that were reported as incidental findings were excluded.

To identify relevant studies, Ovid MEDLINE (through week 2, September 2015), the Cochrane Library databases (2009 through 2015), and Scopus (2010 through 2015) were searched, using drug names as search terms. Additional studies were located by hand searching reference lists of included studies, ClinicalTrials.gov, and requested information from drug manufacturers. Two reviewers, using consensus to resolve disagreements, assessed studies for eligibility. Study characteristics, including baseline patient characteristics, and study results were abstracted by 1 reviewer and checked by a second reviewer for accuracy.

The internal validity (quality) of individual studies were assessed based on predefined criteria developed for the Drug Effectiveness Review Project (see Appendix A for individual study ratings, available in online article).²³ Individual studies were assigned ratings of good, fair, or poor. Studies with major flaws were rated as poor; those with essentially no flaws were rated as good; and the remainder were rated as fair. Data in studies that were clinically and methodologically similar were pooled using random effects models, and statistical heterogeneity was explored using the I-squared statistic.²⁴

FIGURE 1 Results of Literature Search^a

^aThe Drug Effectiveness Review Project uses a modified PRISMA flow diagram.⁴⁶

For studies with multiple arms of differing doses, the doses within the FDA-approved dosing range were analyzed. Body of evidence strength was graded for a given key outcome based on the guidance established for the Evidence-based Practice Center Program of the Agency for Healthcare Research and Quality.²⁵ This grading assessed the limitations, directness, consistency, and precision of the body of evidence for each outcome and resulted in evidence rating of high strength (★★★★), moderate strength (★★★), low strength (★★), or insufficient (★) to draw conclusions. In the tables presented in this review, these ratings are shown as stars. Individual study quality and the strength of evidence ratings were dually reviewed with disagreements resolved using consensus.

Results

For this review, 17 trials were included in 19 publications (Figure 1).^{20,26-43} There are no completed or ongoing studies that directly compared different PCSK9 inhibitors. Study details are summarized in Table 1, and results are shown in Tables 2-4. Study quality assessments and strength of evidence by outcome are presented in Appendices A and B (available in online article). No studies were found to be of poor quality.

Heterozygous and Homozygous Familial Hypercholesterolemia

Compared with placebo, there was low-strength evidence that alirocumab achieved a higher LDL-C reduction in patients with heterozygous familial hypercholesterolemia who took a maximum statin dose plus ezetimibe, based on 1 fair-quality trial (N=77). Similar effects were shown for high-density lipoprotein cholesterol (HDL-C), but there was insufficient evidence

to draw conclusions about harms.³⁸ Evidence for alirocumab compared with placebo in patients with heterozygous familial hypercholesterolemia who took a low- to moderate-intensity statin was insufficient (1 fair-quality RCT, N=22).³⁹ There were no studies of alirocumab in patients with homozygous familial hypercholesterolemia.

Compared with placebo, there is high-strength evidence from two 12-week RCTs (fair- and good-quality, N=499) that evolocumab (140 mg every 2 weeks to 420 mg every 4 weeks) achieved a greater LDL-C reduction in patients with heterozygous familial hypercholesterolemia who were largely taking a high-intensity statin plus ezetimibe, with a greater improvement in HDL-C and no differences in harms (moderate-strength evidence).^{32,34} In patients with homozygous familial hypercholesterolemia who took a maximum statin dose and ezetimibe (Table 3), low-strength evidence based on 1 small, good-quality trial (N=50) suggested that evolocumab (420 mg every 4 weeks) reduced LDL-C significantly more than placebo at 12 weeks.³³ There was no difference in HDL-C change, and there was no difference in the percentage of patients with serious adverse events, neurocognitive events, or those withdrawn because of treatment-emergent adverse events.

Statin-Intolerant Patients

There was no evidence for alirocumab in patients who were intolerant to statins. In statin-intolerant patients, there was low-strength evidence based on 2 fair-quality, 12-week RCTs (GAUSS and GAUSS-2; N=434) that evolocumab (280 mg every 4 weeks or 140 mg every 2 weeks) led to a greater reduction in LDL-C than placebo, with similar effects in HDL-C and harms.^{40,41} There is also low-strength evidence from the

TABLE 1 Characteristics of Included Studies of Alirocumab and Evolocumab

Study Sample Size Study Quality Rating ^a	Population Eligible for Study	Study Interventions Study Duration	Age Gender (n) Ethnicity (n)	Other Population Characteristics (n)
Blom, 2014 ²⁶ DESCARTES N=901 Good	Hyperlipidemia and LDL-C $\geq$ 75 mg/dL.	Subcutaneous evolocumab 420 mg or placebo every 4 weeks. 48 weeks	Age: 56 y Female: 52.3% (471) White: 80.4% (724) Asian: 6.3% (57) Black: 8.4% (76) Other: 4.9% (44)	CAD: 15.1% (136) LDL-C: NR HDL-C: NR
Cannon, 2015 ²⁷ ODYSSEY COMBO II N=720 Good	Hypercholesterolemia. CVD and LDL-C $\geq$ 70 mg/dL or no history of CVD but at high cardiovascular risk and LDL-C $\geq$ 100 mg/dL.	Subcutaneous alirocumab 75 mg every 2 weeks or ezetimibe 10 mg daily (both with statins). 104 weeks	Age: 61.5 y Female: 26.4% (190) White: 84.7% (610) Black: 3.9% (28) Other: 11.4% (82)	CHD: 90.1% (649) LDL-C: 106 mg/dL HDL-C: 46 mg/dL High-intensity statin: 66.7% (480)
Giugliano, 2012 ²⁸ Desai, 2014 ⁴³ LAPLACE-TIMI 57 N=631 Good	Hypercholesterolemia while on statin with LDL-C $>$ 85 mg/dL.	Subcutaneous evolocumab 70 mg, 105 mg, 140 mg, or placebo every 2 weeks or 280 mg, 350 mg, 420 mg, or placebo every 4 weeks. 12 weeks	Age: 62 y Female: 51.0% (320) White: 89.0% (560)	CAD: 30.0% (187) LDL-C: 123 mg/dL HDL-C: 54 mg/dL
Hirayama, 2014 ²⁹ YUKAWA N=310 Fair	Hypercholesterolemia (high risk for cardiovascular events).	Subcutaneous evolocumab 70 mg, 140 mg every 2 weeks, 280 mg, 420 mg every 4 weeks, or placebo. 12 weeks	Age: 61.5 y Female: 37.1% (114) Ethnicity: NR	CAD: 25.1% (77) LDL-C: 139 mg/dL HDL-C: 54 mg/dL Intensive statin: 6.2% (19)
Kereiakes, 2015 ³⁰ ODYSSEY COMBO I N=316 Fair	Hypercholesterolemia. LDL-C $\geq$ 70 mg/dL and established CVD or LDL-C $\geq$ 100 mg/dL with CHD risk equivalents.	Subcutaneous alirocumab 75 mg every 2 weeks or placebo. 52 weeks	Age: 63 y Female: 34.2% (108) White: 81.6% (258) Black: 16.1% (51)	CHD: 78.2% (247) LDL-C: 98 mg/dL HDL-C: 49 mg/dL High-intensity statin: 62.7% (198) Ezetimibe: 8.2% (26)
McKenney, 2012 ³¹ N=183 Fair	Patients with LDL-C $\geq$ 100 mg/ dL on stable dose atorvastatin 10 mg, 20 mg, or 40 mg for $\geq$ 6 weeks.	Subcutaneous alirocumab 50 mg, 100 mg, 150 mg every 2 weeks; 200 mg, 300 mg every 4 weeks or placebo. 12 weeks	Age: 57 y Female: 52.5% (96) White: 86.3% (158) Black: 12.6% (23) Other: 1.0% (2) Hispanic or Latino ethnicity: 21.9% (40)	CAD: 5.5% (10)
Raal, 2012 ³² RUTHERFORD N=167 Fair	Heterozygous familial hyper- cholesterolemia with LDL-C $\geq$ 100 mg/dL despite statin therapy with or without ezetimibe.	Subcutaneous evolocumab 350 mg, 420 mg, or placebo every 4 weeks. 12 weeks	Age: 49.6 y Female: 46.7% (78) White: 88.6% (148) Asian: 4.2% (7) Black: 2.4% (4) Other: 4.8% (8)	CAD: 21.0% (35) LDL-C: 158 mg/dL HDL-C: 46 mg/dL Intensive statin: 89.8% (150) Ezetimibe use: 64.7% (108)
Raal, 2015 ³⁴ RUTHERFORD-2 N=331 Good	Heterozygous familial hypercholesterolemia with LDL-C $\geq$ 100 mg/dL despite statin therapy with or without ezetimibe.	Subcutaneous evolocumab 140 mg every 2 weeks, 420 mg or placebo every 4 weeks. 12 weeks	Age: 50.6 y Female: 42.0% (139) Ethnicity: NR	CAD: 31.1% (103) LDL-C: 154 mg/dL HDL-C: 50 mg/dL Intensive statin: 87.3% (298) Ezetimibe plus statin: 61.6% (204)
Raal, 2015 ³³ TESLA Part B N=49 Good	Homozygous familial hypercholesterolemia with LDL $\geq$ 131 mg/dL.	Subcutaneous evolocumab 420 mg or placebo every 4 weeks. 12 weeks	Age: 31 y Female: 49.0% (24) White: 90.0% (44) Asian: 4.0% (2)	CAD: 43.0% (21) LDL-C: 348 mg/dL HDL-C: 38 mg/dL Atorvastatin $\geq$ 40 mg: 63.0% (31) Rosuvastatin $\geq$ 20 mg: 31.0% (15) Ezetimibe: 92.0% (45)
Robinson, 2014 ³⁵ LAPLACE-2 N=1,899 Fair	Hypercholesterolemia with LDL $\geq$ 150 mg/dL (no statin at screening), $\geq$ 100 mg/dL (nonintensive statin at screening), or $\geq$ 80 mg/dL (intensive statin at screening).	Subcutaneous evolocumab 140 mg every 2 weeks (or 420 mg monthly), ezetimibe 10 mg daily, or placebo. 12 weeks	Age: 60.1 y Female: 45.7% (868) White: 94.0% (1,782) Black: 4.0% (75) Other: 2.0% (39)	CAD: 22.5% (427) LDL-C: 108.9 mg/dL HDL-C: 53.2 mg/dL

TABLE 1 Characteristics of Included Studies of Alirocumab and Evolocumab (continued)

Study Sample Size Study Quality Rating ^a	Population Eligible for Study	Study Interventions Study Duration	Age Gender (n) Ethnicity (n)	Other Population Characteristics (n)
Robinson, 2015 ²⁰ ODYSSEY LONG TERM N = 2,341 Good	Heterozygous familial hypercholesterolemia or with established CHD or a CHD risk equivalent and LDL-C ≥ 70 mg/dL.	Subcutaneous alirocumab 150 mg or placebo every 2 weeks. 78 weeks	Age: 60.5 y Female: 37.8% (884) White: 92.7% (2,171)	HeFH: 17.7% (415) CHD: 68.6% (1,607) CHD risk equivalent: 41.1% (962) LDL-C: 122 mg/dL HDL-C: 50 mg/dL Intensive statin: 46.8% (1,095) Ezetimibe: 14.3% (334)
Roth, 2012 ³⁶ N = 92 Fair	Primary hypercholesterolemia. LDL-C ≥ 100 mg/dL despite atorvastatin.	Subcutaneous alirocumab 150 mg every 2 weeks + 80 mg atorvastatin; + 10 mg atorvastatin; or placebo + 80 mg atorvastatin. 8 weeks	Age: 56.9 y Female: 60.0% (55) White: 87.0% (80) Black: 13.0% (12)	CAD: 3.0% (3) LDL-C: 123 mg/dL HDL-C: 55 mg/dL
Sabatine, 2015 ³⁷ OSLER-1 OSLER-2 N = 4,465 Fair	Heterozygous familial hypercholesterolemia and statin intolerant. Completed 1 of 12 phase 2 or 3 studies of evolocumab. LDL ≥ 100/150 mg/dL without statin/background anti-lipid therapy/statin-intolerant. LDL ≥ 75/80/85/100/116 mg/dL with statin/background anti-lipid therapy.	OSLER-1: Subcutaneous evolocumab 420 mg once per month + standard therapy vs. standard therapy alone. 56 weeks OSLER-2: Subcutaneous evolocumab 420 mg once per month or 140 mg every 2 weeks + standard therapy vs. standard therapy alone. 48 weeks	Age: 58 y Female: 49.5% (2,210) White: 85.7% (3,826)	Known familial hypercholesterolemia: 9.9% (440) Any CAD: 20.1% (896) Family history of premature: CAD: 24.3% (1,086) Median LDL-C: 120 mg/dL Median HDL-C: 51 mg/dL
Stein, 2012 ³⁸ N = 77 Fair	Heterozygous familial hypercholesterolemia. LDL-C ≥ 100 mg/dL.	Subcutaneous alirocumab 150 mg, 200 mg, or 300 mg every 4 weeks or 150 mg every 2 weeks or placebo. 12 weeks	Age: 53.4 y Female: 39.0% (30) White: 95.0% (73)	CAD: 42.0% (32) LDL-C 155 mg/dL Maximum statin dose: 77.0% (59) Ezetimibe use: 71.0% (55)
Stein, 2012 ³⁹ N = 61 Fair	Heterozygous and nonheterozygous familial hypercholesterolemia. Atorvastatin with LDL-C ≥ 100 mg/dL or modified diet with LDL-C = 130 mg/dL.	Subcutaneous alirocumab 50 mg, 100 mg, or 150 mg vs. placebo with and without atorvastatin. 106 days	Age: 47 y Female: 30.0% (18) White: 95.0% (58) Black: 5.0% (3)	LDL-C: 138 mg/dL HDL-C: 48 mg/dL Atorvastatin 10 mg: 26.0% (15) Atorvastatin 20 mg: 23.0% (14) Atorvastatin 40 mg: 18.0% (11)
Stroes, 2014 ⁴⁰ GAUSS-2 N = 307 Fair	Statin intolerant to ≥ 2 statins. LDL-C > NCEP ATP III goal.	Ezetimibe daily + placebo every 2 weeks, evolocumab 140 mg every 2 weeks + placebo daily, ezetimibe daily + placebo monthly, evolocumab 420 mg monthly + placebo daily. 12 weeks	Age: 61.5 y Female: 45.9% (141) White: 93.5% (287) Black: 2.3% (7)	≥ 2 cardiovascular risk factors ^b : 47.9% (147)
Sullivan, 2012 ⁴¹ GAUSS N = 160 Fair	Statin intolerant to at least 1 statin.	Evolocumab 280 mg, 350 mg, and 420 mg; evolocumab 420 mg with ezetimibe 10 mg; ezetimibe 10 mg + placebo (all administered subcutaneously every 4 weeks). 12 weeks	Age: 61.8 y Female: 63.7% (100) White: 88.5% (139) Black: 5.1% (8)	NCEP CHD risk category: High: 39.5% (62) Moderately high: 10.2% (16) Moderate: 28.0% (44) Lower: 22.3% (35)

^aStudy quality ratings = assessments of individual study internal validity.

^bCardiovascular risk factors: current cigarette use, type 2 diabetes, hypertension, family history of premature CHD, and low HDL-C.

ATP III = Adult Treatment Panel III; CAD = coronary artery disease; CHD = coronary heart disease; CVD = cardiovascular disease; HDL-C = high-density lipoprotein cholesterol; HeFH = heterozygous familial hypercholesterolemia; LDL-C = low-density lipoprotein cholesterol; NCEP = National Cholesterol Education Program; NR = not reported; y = years.

GAUSS study (N=62) that the combination of evolocumab (420 mg every 4 weeks) plus ezetimibe (10 mg) led to a greater percentage of LDL-C reduction than ezetimibe (10 mg) alone, but there was insufficient evidence to draw conclusions on other outcomes.⁴¹

Secondary Treatment in Patients at High Cardiovascular Risk (Not Achieving Study Targets with First-Line Therapies)

Several studies evaluated a PCSK9 inhibitor in patients with varying levels of cardiovascular risk, who had not achieved an LDL-C of ≤ 100 mg/dL or ≤ 70 or 75 mg/dL using mainly statin-based therapy before randomization. Very few patients had familial forms of hypercholesterolemia in these studies. In high-risk patients, moderate-strength evidence based on a good-quality trial (ODYSSEY COMBO II, N=720) demonstrated that alirocumab (75 mg to 150 mg given every 2 weeks) resulted in a higher proportion of patients with high cardiovascular risk reaching the study goal of LDL-C < 70 mg/dL at 24 weeks (relative risk [RR] = 1.70, 95% CI = 1.46-1.95) than ezetimibe (10 mg).²⁷ Similarly, the difference in the percentage of change in LDL-C and HDL-C at 24 weeks was greater with alirocumab (-29.8% and 8.1%, $P < 0.001$). Moderate-strength evidence found that there was no difference in overall adverse event reporting between alirocumab and ezetimibe and that the rate for reporting any adverse event was high (69%). Low-strength evidence found that withdrawal because of adverse events and serious adverse events were not different between the groups. Low-strength evidence suggested a higher rate of injection-site reactions with alirocumab than with placebo injection plus ezetimibe, but this estimate was imprecise (wide confidence interval, inadequate sample size to evaluate this outcome). Neurocognitive events were rare.

Based on 2 trials (ODYSSEY COMBO I and ODYSSEY Long-Term; N=2,656), there was high-strength evidence that alirocumab (75 mg to 150 mg given every 2 weeks) resulted in a higher proportion of patients with high cardiovascular risk reaching the study goal of LDL-C < 70 mg/dL at 24 weeks than placebo (pooled RR=9.65, 95% CI=7.7-12.0).^{20,30} The difference in the percentage of reduction in LDL-C and HDL-C was also greater. High-strength evidence found no statistical difference in overall adverse event reporting and that the rate for reporting any adverse event was high (75%). Moderate-strength evidence found that withdrawal because of adverse events and serious adverse events were also not different between groups. Low-strength evidence suggested that the risk of injection-site reactions (pooled RR=1.4, 95% CI=0.98-2.1) or neurocognitive events were not increased, although the estimates were imprecise because of few events.

In a comparison of evolocumab and ezetimibe (both with statin therapy) in patients with high cardiovascular risk, the LAPLACE-2 study (N=329 for this comparison) provided low-strength evidence that when added to either atorvastatin

(10 mg or 80 mg), compared with ezetimibe (10 mg), evolocumab (420 mg monthly) resulted in higher rates of meeting an LDL-C target of < 70 mg/dL at 12 weeks, with similar rates of patients with overall adverse events.³⁵ This study provided insufficient evidence to draw conclusions about HDL-C, serious adverse events, or withdrawal because of adverse events because of the small magnitude of change or event rates. In patients with high cardiovascular risk, a small 12-week (N=104 for placebo comparison) study provided low-strength evidence that evolocumab (420 mg monthly) resulted in higher rates of meeting LDL-C targets of < 100 mg/dL and < 70 mg/dL when added to statins in Japanese patients, compared with placebo.²⁹ There was greater mean change in LDL-C but insufficient evidence to draw conclusions about other outcomes.

There was moderate- and low-strength evidence of no difference in adjudicated cardiovascular events between alirocumab and ezetimibe at 52 weeks or between alirocumab and placebo at 52-78 weeks (Table 4).^{20,27,30} For evolocumab, adjudicated cardiovascular events were reported as secondary or post hoc outcomes, but evidence was insufficient to draw conclusions because of too few events (imprecise estimates), study limitations, and lack of ability to verify findings across multiple studies (Table 4).^{29,37}

Secondary Treatment in Patients at Varied Cardiovascular Risk (Not Achieving Study Targets with First-Line Therapies)

Low-strength evidence from 2 small (N=154 total) fair-quality RCTs indicated that in patients stabilized on statins who have not achieved an LDL-C of < 100 mg/dL, alirocumab (150 mg subcutaneously every 2 weeks for 8-10 weeks) resulted in significantly more patients achieving study goal (LDL-C < 100 mg/dL) and a greater percentage of reductions (49%-67% more) than statins alone.^{31,36} Evidence for adverse events and in subgroups, compared with statins alone, was insufficient because of small sample sizes.

In short-term comparisons of evolocumab and placebo, LAPLACE-TIMI 57 and LAPLACE-2 (N=996 for placebo comparison) provided high-strength evidence that, at 12 weeks in patients with varying risk levels and not meeting LDL targets, significantly more patients taking evolocumab (420 mg monthly) than taking placebo (both with statin therapy) achieved an LDL-C of < 70 mg/dL and had a greater percentage of reduction in LDL-C.^{28,35} There is also moderate-strength evidence of modest HDL-C increases with evolocumab (420 mg monthly) and moderate- to high-strength evidence of no differences in adverse events. Based on 1 good-quality longer-term trial (N=901; 52 weeks), there is moderate-strength evidence that evolocumab (420 mg given every 4 weeks) also results in significantly more patients achieving a goal of LDL-C < 70 mg/dL, compared with placebo; low-strength evidence of a modest increase in HDL-C; and evidence of no difference in harms (low- and moderate-strength evidence depending on outcome).

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TABLE 2 Lipid and Adverse Event Outcomes for Alirocumab and Evolocumab

Intervention	Study, n Sample Size Endpoint	Concomitant Lipid Therapy (% High-Dose) Baseline LDL-C	PCSK9 Inhibitor Dose	Difference in LDL-C Change	Difference in % Meeting LDL-C Goal	Difference in HDL-C Change	Harms
Heterozygous familial hypercholesterolemia versus placebo							
Alirocumab	2 RCTs ^{38,39} N=99 12 weeks	High-dose statin (51.0%-77.0%)+ ezetimibe. 151-170 mg/dL	150 mg, 200 mg, or 300 mg every 4 weeks or 150 mg every 2 weeks	-8.0% to -57.4% ★★	NR	150 mg every 2 weeks: 12.3% (P=0.050) Other doses NSD ★★	★
Evolocumab	2 RCTs ^{32,34} N=499 12 weeks	High-intensity statin (89.7%)+ ezetimibe. 150-155 mg/dL	140 mg every 2 weeks to 420 mg every 4 weeks	-44.1% to -61.3% ★★★★	NR	6.8% (P<0.010) to 9.2% (95% CI=4.7%-13.7%) ★★★	No differences for overall AEs (55.0%-66.1% vs. 43.0%-58.9%; pooled RR=1.12; 95% CI=0.94- 1.33), SAEs (3.0%-4.0% vs. 4.0%-5.0%; pooled RR=0.81; 95% CI=0.28-2.33), and injection-site reactions (6.3% vs. 3.6%; pooled RR=0.76; 95% CI=0.76-5.21).★
High cardiovascular risk (not achieved LDL-C targets <100 mg/dL or <70 mg/dL)							
Versus ezetimibe 10 mg							
Alirocumab	1 RCT ²⁷ N=720 24 weeks	Statin, range of doses (66.6%). 106 mg/dL	75 to 150 mg every 2 weeks	-29.8% (P<0.001) ★★★	LDL goal <70 mg/dL: RR=1.70 (95% CI=1.46-1.95) ★★★	8.1% (P<0.001) ★★★	No differences for overall AEs, WAEs, or SAEs. ★★★ More injection site reactions with alirocumab (2.5% vs. 0.8%).★★
Evolocumab	1 RCT ³⁵ N=329 for 420 mg dose or ezetimibe 12 weeks	Statin, range of doses (37.5%). 126-129 mg/dL or 92-94 mg/dL	420 mg every 4 weeks	NR	LDL goal <70 mg/dL with atorvastatin 10 mg: 85.8% vs. 5.6%; unadjusted RR= 5.22 (95% CI=3.00-9.69) LDL goal <70 mg/dL with atorvastatin 80 mg: 92.5% vs. 62.3%; unadjusted RR=1.47 (95% CI=1.23-1.88) ★★	★	Similar rates of overall AEs ★★ but ★ on other harms outcomes.
Versus placebo							
Alirocumab	2 RCTs ^{20,30} N=2,656 24 weeks	High-dose statin (46.8%-63.1%). 100-123 mg/dL	75 to 150 mg every 2 weeks	-45.9% to -61.9% (P<0.001) LDL goal <70 mg/dL: RR=9.65 (95% CI=7.7-12.0) ★★★★	LDL goal <70 mg/dL: RR=9.65 (95% CI=7.7- 12.0) ★★★★★	7.3% to 7.6% (P<0.001) ★★★★	No difference in overall AEs, WAEs, SAEs. ★★★★ to ★★ No difference in injection-site reactions (pooled RR=1.4; 95% CI=0.98-2.1) or neurocognitive events (pooled RR=1.8; 95% CI=0.37-8.5).★★

TABLE 2 Lipid and Adverse Event Outcomes for Alirocumab and Evolocumab (continued)

Intervention	Study, n Sample Size Endpoint	Concomitant Lipid Therapy (% High-Dose) Baseline LDL-C	PCSK9 Inhibitor Dose	Difference in LDL-C Change	Difference in % Meeting LDL-C Goal	Difference in HDL-C Change	Harms
Evolocumab	1 RCT ²⁹ N=310 12 weeks	High-dose statin (5.9%; 24.8% per Japanese standard). 139 mg/dL	420 mg every 4 weeks	-63.9% ($P<0.001$) ★★	LDL goal <100 mg/dL: 96.0% vs. 1.0% ($P<0.001$) LDL goal <70 mg/dL: 82.0% vs. 0.0% ($P<0.001$) ★★	★	★
Varied cardiovascular risk (not achieved LDL-C targets <100 mg/dL or <70 mg/dL) versus placebo							
Alirocumab	2 RCTs ^{31,36} N=124 at 150 mg dose 10 weeks	Statin, range of doses (0.0%- 66.3%). 123-124 mg/dL	150 mg every 2 weeks	-49.0% to -67.0% ★★	LDL <100 mg/dL: 100.0% vs. 16.1% to 52.0% (150 mg every 2 weeks) ★★	6.3% to 8.5% ★★	★
Evolocumab	2 RCTs ^{28,35} N=1,375 12 and 52 weeks	Statin, range of doses accord- ing to risk level (29.0%-37.5%). 104 mg/dL	420 mg every 4 weeks	52 weeks: -57.0% (± 2.1 SD) ★★★ 12 weeks: -53.0% (95% CI=56.0- 44.6) to -70.5% (95% CI=-79.8 to -61.2)	52 weeks: LDL goal <70 mg/dL: 82.3% vs. 6.4% ($P<0.001$) ★★★ 12 weeks: LDL goal <70 mg/dL: 71.8%-94.5% vs. 0%-9.3% ($P<0.001$) ★★★★	52 weeks: 5.4% ($P<0.001$) 12 weeks: 4.5% (95% CI=0.4-8.7) to 9.1% (95% CI=4.4-13.7) ★★ to ★★★	52 weeks: no differences ★★ to ★★★ 12 weeks: more overall AEs (60.0% vs. 42.0%), no difference in WAEs, SAEs, or injection site reactions ★★ to ★★★★

Note: Strength of evidence: ★★★★★=High; ★★★=Moderate; ★★=Low; ★=Insufficient.

AEs=adverse events; CI=confidence interval; HDL-C=high-density lipoprotein cholesterol; LDL-C=low-density lipoprotein cholesterol; NR=not reported; NSD=no significant difference; PCSK9=proprotein convertase subtilisin/kexin type 9; RCT=randomized controlled trial; RR=relative risk; SAEs=serious adverse events; SD=standard deviation; WAEs=withdrawal due to adverse events.

Varied Populations: Heterozygous Familial, Statin Intolerant, and Not at Target for Risk Level

There is moderate-strength evidence, based on a pooled analysis of 2 open-label extension studies (OSLER 1 and 2), of patients completing 1 of 12 previous trials (patients not at target, with heterozygous familial hypercholesterolemia, or statin intolerance; N=4,465), that evolocumab (420 mg monthly or 140 mg every 2 weeks plus standard care—primarily statins) reduced LDL-C by 61% more than standard care alone at 12 weeks.³⁷ This reduction was largely sustained at 48 weeks (58.4% more than usual care at week 48). This analysis of the 2 studies also provided low-strength evidence of a greater proportion of patients meeting an LDL-C goal of <100 mg/dL or <70 mg/dL and a greater increase in HDL-C at 12 weeks than with standard therapy alone.

There is low-strength evidence that slightly more patients on evolocumab experienced any adverse event at 12 weeks, compared with statins alone, without differences in serious adverse events but insufficient evidence to draw conclusions about other adverse event outcomes.

Discussion

This systematic review of PCSK9 inhibitor drugs finds low- to high-strength evidence of moderate-to-large magnitude reduction in LDL-C when added to statin therapy in patients with familial forms of hypercholesterolemia and alone or added to ezetimibe in those who are intolerant of statins. Although there are no direct comparison studies, and the lipid outcomes are fairly similar across the trials, the strength of this evidence varies by population and by drug. In patients with heterozygous hypercholesterolemia, the trials of evolocumab were larger (499 vs. 98), and the strength of the evidence was consistently stronger than for alirocumab (moderate to high vs. low or insufficient; Table 2). In contrast, the evidence for patients with high cardiovascular risk is stronger for alirocumab. Studies comparing alirocumab with ezetimibe were somewhat larger (720 vs. 329), twice as long (24 weeks vs. 12 weeks), and the strength of evidence was better (low to moderate vs. low and insufficient) than those of evolocumab. Studies comparing alirocumab with placebo in this population were much larger (2,656 vs. 310), twice as long (24 weeks vs. 12 weeks), and had much better

TABLE 3 Evidence for Evolocumab in Other Populations

Study, n Sample Size Endpoint	Concomitant Lipid Therapy (% High-Dose) Baseline LDL-C	PCSK9 Inhibitor Dose	Difference in LDL-C Change	Difference in % Meeting LDL-C Goal	Difference in HDL-C Change	Harms
Homozygous familial hypercholesterolemia versus placebo						
1 RCT ³³ N=50 12 weeks	High-dose statin (94.0%)+ ezetimibe. 348 mg/dL	420 mg every 4 weeks	-32.1% (95% CI= -45.1 to -19.2) ★★	NR	-0.1% (P=NSD) ★★	No differences in overall AEs ★★ ★ for specific AEs
Unable to use statins (evolocumab alone or combined with ezetimibe 10 mg versus ezetimibe 10 mg alone)						
2 RCTs ^{40,41} N=496 12 weeks	None. 192-195 mg/dL	140 mg every 2 weeks or 280 mg, 350 mg, or 420 mg given every 4 weeks	Versus ezetimibe alone: -26.0% (95% CI= -34.1% to -17.9%) for 280 mg every 4 weeks to -38.1% (95% CI= -43.7 to -32.4) for 140 mg every 2 weeks ★★ Combined vs. ezeti- mibe alone: -47.3% (95% CI= -53.7% to -40.8%) ★★	NR	Versus ezetimibe alone: 3.6%-8.5% ★★ Combined vs. ezetimibe alone: ★	No difference in overall AEs (63.0% vs. 69.0%; pooled RR=0.92; 95% CI=0.80-1.06) and SAEs (3.0% vs. 3.0%; pooled RR=1.04; 95% CI=0.34-3.15). Significantly lower WAEs with evolocumab (3.0% vs. 12.0%; pooled RR=0.29; 95% CI=0.14-0.63). ★★ No neurocognitive events and few injection site reactions.
Varied population versus placebo, with extended follow-up						
2 extensions of RCTs ³⁷ N=4,465 12-48 weeks	Usual care (27.3%). NR	420 mg every 4 weeks	Versus placebo: 12 weeks: -61.0% (95% CI=59.0-63.0, P<0.001) ★★★	12 weeks: LDL goal <100 mg/dL: 90.2% vs. 26.0% ★★★ LDL goal <70 mg/dL: 73.6% vs. 3.8% 48 weeks: 58.4% (P<0.001) ★★	12 weeks: 7.0% (P<0.001) ★★	48 weeks: overall AEs: 69.2% vs. 64.8% (P=0.003). No difference in SAEs. ★★ ★ for other harms

Note: Strength of evidence: ★★★★★=High; ★★★=Moderate; ★★=Low; ★=Insufficient

AEs=adverse events; CI=confidence interval; HDL-C=high-density lipoprotein cholesterol; LDL-C=low-density lipoprotein cholesterol; NR=not reported; NSD=no significant difference; PCSK9=proprotein convertase subtilisin/kexin type 9; RCT=randomized controlled trial; RR=relative risk; SAEs=serious adverse events; WAEs=withdrawal due to adverse events.

strength of evidence (high for lipid outcomes, low to moderate for harms vs. low and insufficient). Additionally, evidence for adjudicated cardiovascular outcomes is low to moderate for alirocumab, showing no differences compared with ezetimibe or placebo, while evidence for evolocumab is insufficient (Table 4). The final population in which both drugs were being studied was a varied cardiovascular risk group that had not met study-defined LDL-C targets while taking risk-appropriate treatment. Here, evolocumab had a much larger study group (1,375 vs. 124), longer trials (52 weeks vs. 10 weeks), and much better strength of evidence (low to high vs. low and insufficient). Of the populations studied with both drugs, this is the one that is least clear on how it fits into step therapy with numerous other antihyperlipidemic drugs available. Evolocumab also has

low-strength evidence in patients with homozygous familial hypercholesterolemia and patients deemed intolerant to statin therapy and low- to moderate-strength evidence in broadly varied populations of all of the studied populations but with longer follow-up (Table 4). Homozygous familial hypercholesterolemia is a difficult to treat form of familial hypercholesterolemia, but with evolocumab, patients achieved reductions of 32% from a mean baseline LDL-C of 348 mg/dL; however, this finding is based on only 50 patients.

Unfortunately, the evidence for the long-term health benefits and harms of the PCSK9 inhibitors alirocumab and evolocumab is insufficient to draw conclusions at this time, mainly because of limited or no information on the long-term impact of the large reductions in LDL-C. The current evidence

TABLE 4 Cardiovascular Event Outcomes for Alirocumab and Evolocumab

Study, n Sample Size Endpoint for CV Events	Treatments	Strength of Evidence	Adjudicated CV Events
High cardiovascular risk (not achieved LDL-C targets <100 mg/dL or <70 mg/dL)			
1 RCT ²⁷ ODYSSEY COMBO II N=720 52 weeks	Alirocumab 75 to 150 mg every 2 weeks + maximal dose statin vs. ezetimibe 10 mg	Low. Downgraded for study limitations, lack of confirmatory evidence, and low precision of estimates.	No difference between alirocumab and ezetimibe (4.8% vs. 3.7%; RR=1.29; 95% CI=0.30-2.74).
2 RCTs ^{20,30} ODYSSEY COMBO I N=2,656 78 weeks	Alirocumab 75 to 150 mg every 2 weeks + statin, range of doses vs. placebo	Moderate. Downgraded for study limitations and low precision of estimates.	No difference between alirocumab and placebo (2.4% vs. 3.2%; pooled RR=0.91; 95% CI=0.63-1.31).
1 RCT ²⁹ YUKAWA N=310	Evolocumab 70 or 140 mg every 2 weeks or 280 mg or 420 mg every month + moderate-intensity statins vs. placebo.	Insufficient to draw conclusions. Downgraded for study limitations, lack of ability to assess consistency, and very low precision of estimate.	No difference between evolocumab and placebo (0/53 with 420 mg evolocumab monthly vs. 1/50 with placebo).
Varied population with extended follow-up versus placebo			
Pooled analysis of 2 extension studies ³⁷ N=4,465 48 weeks	Evolocumab 420 mg every 4 weeks + usual care vs. usual care (primarily statins)	Insufficient to draw conclusions. Downgraded for study limitations, lack of ability to assess consistency, and low precision of estimate.	Lower risk with evolocumab vs. standard care (0.95% vs. 2.18%; HR=0.47; 95% CI=0.28-0.78). Post hoc analysis limited to MACE: 0.95% vs. 2.11% (HR=0.47; 95% CI=0.28-0.78).

CI=confidence interval; CV=cardiovascular; HR=hazard ratio; MACE=composite of death, major coronary events, and major cerebrovascular events; RCT=randomized controlled trial; RR=relative risk.

on health outcomes such as cardiovascular events is limited because these studies reported them as secondary outcomes and were not designed to assess cardiovascular events. This review differs from others because it was limited to the assessment of cardiovascular outcomes that were adjudicated, rather than including cases reported incidentally (Table 4). For evolocumab, the evidence available was insufficient to make any conclusions. For alirocumab, the findings, although of low and moderate strength, did not identify statistically significant differences in high-risk patients compared with placebo or ezetimibe with 52-78 weeks of follow-up. Although these findings are not causal, as hypothesis-generating outcomes, they raise important questions about the long-term benefits of these drugs. As previously noted, we must await the outcome of ongoing trials with predefined cardiovascular endpoints as primary outcomes.

In addition to the uncertainty around long-term outcomes, and with an estimated price of almost \$14,000 per year,³ determining the place these drugs have in the therapy for hypercholesterolemia is critical. Economic modeling may be helpful, but it is limited without evidence of the health outcomes of these drug treatments. A recent economic model, using assumed cardiovascular benefits, found that the cost-effectiveness ratio (cost per quality adjusted life-year [QALY]) was \$681,000 for those with familial hypercholesterolemia (either type) and \$557,000 for patients with established cardiovascular disease and LDL-C>70 mg/dL.⁴⁴ Although these are estimates for

comparison with continuing statins alone, they clearly exceed the typical threshold for cost-effectiveness of \$50,000 to \$100,000 per QALY.⁴⁴ The analyses using this model suggest that in order for the drugs to be cost-effective, the price range should be closer to \$3,600 per year than the current price range of approximately \$14,000 per year.

Another important issue raised about this evidence is the comparison groups, including the concomitant antihyperlipidemic therapy given. Clearly, in a step-therapy approach, the choices in the face of inadequate treatment include continuing to maximize the current therapy, add a second treatment, or even switch treatments. Pharmacologically, the PCSK9 inhibitors are likely to work better when used alongside a statin, and most of the studies continue statin therapy in PCSK9 inhibitor-treated patients. A fair comparison, then, would be maximization of the statin therapy (i.e., using high-intensity statins and/or maximally tolerated doses) in the control group in particular. Most of these studies do not adhere to this standard (Tables 2 and 3); consequently, future studies are required to determine the true incremental benefits of PCSK9 inhibitors.

The bulk of the evidence, then, is from patients currently receiving varying doses of statins who have not achieved study-specified target LDL-C levels. While this less than optimal use of statins is not an ideal comparator as an alternative strategy to PCSK9 inhibitors, it may reflect real-world statin use. When limited to populations of patients who are at high cardiovascular risk and whose baseline LDL-C on statin therapy are

above targets of 70 mg/dL to 75 mg/dL or <100 mg/dL, we find large absolute reductions in LDL-C and higher proportions of patients achieving these study goals. However, with recent guidelines suggesting that therapy be directed by risk level and not specific LDL-C targets,⁴⁵ and without good-quality evidence on cardiovascular outcomes for the PCSK9 inhibitors, it is less clear how to interpret and apply the findings of these studies. Using the percentage of reduction in LDL-C from baseline is not a better marker, since we do not yet understand the implications of 30%-60% above and beyond any initial reductions with a statin. Adding to this lack of clarity, are the several studies in varied- or average-risk populations. In a recent editorial, Shrank et al. (2015) discussed the challenges and implications of determining the best use of PCSK9 inhibitors in light of the recent changes in recommendations for treating hyperlipidemia but recommends a step-approach that promotes maximizing the use of low-cost statin medications rather than PCSK9 inhibitors.¹⁴

With 2 PCSK9 inhibitors approved and others in the pipeline, there will not only be questions about the role of this new class of drugs in the treatment of hypercholesterolemia, but also comparative questions about whether there are important differences among the drugs. Because these drugs will be taken for many years and are expensive, and because there are still questions regarding long-term benefit and harm, studies in the highest risk populations that are designed to assess cardiovascular and potential harm outcomes with appropriate comparison groups (guideline-recommended statin-intensity level or maximally tolerated high-intensity statins) are needed in order to shed light on these important questions.

Limitations

The main limitations of this review are those related to the evidence itself, as previously described (e.g., lack of true optimization of statin therapy in control groups). Additional potential limitations of this review include the search strategy and the exclusion of studies published in languages other than English. It was attempted to locate all studies relevant to the scope of this review, but it is possible that evidence was missed. There was limited ability to assess potential publication and reporting bias because of the few opportunities to pool studies and the lack of availability of study protocols. Finally, the scope of this review limited the inclusion of some studies included in other reviews (i.e., comparisons to no treatment) and within those incidentally reported cardiovascular outcomes.

Conclusions

Alirocumab and evolocumab have evidence of large improvements in lipids and limited evidence on cardiovascular outcomes, but the strength of evidence differs between the drugs. The strength of evidence is greater for alirocumab than

evolocumab in patients with high cardiovascular risk not at LDL-C target, while evidence for evolocumab is stronger in patients with heterogeneous familial hypercholesterolemia and patients with varied cardiovascular risk not at LDL-C target. Important questions remain about the comparative effects of either drug on long-term health outcomes.

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REFERENCES

- Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive summary of the third report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA*. 2001;285(19):2486-97.
- Cholesterol Treatment Trialists' (CTT) Collaborators, Mihaylova B, Emberson J, et al. The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised trials. *Lancet*. 2012;380(9841):581-90.

3. Evolocumab (Repatha)—a second PCSK9 inhibitor to lower LDL-cholesterol. *JAMA*. 2015;314(21):2298-99.
4. Carroll J. UPDATED: Amgen gets a big win with FDA OK for PCSK9 cholesterol drug Repatha. *FierceBiotech*. August 27, 2015. Available at: <http://www.fiercebiotech.com/story/amgen-gets-big-win-fda-ok-pcsk9-drug-repatha/2015-08-27>. Accessed April 12, 2016.
5. Pollack A. New drug sharply lowers cholesterol, but it's costly. *The New York Times*. July 24, 2015. Available at: <http://www.nytimes.com/2015/07/25/business/us-approves-drug-that-can-sharply-lower-cholesterol-levels.html?ref=health>. Accessed April 12, 2016.
6. Staton T. Payers fret about the next drug doomsday: pricey PCSK9 cholesterol meds. *FiercePharmaMarketing*. May 7, 2014. Available at: <http://www.fiercepharmamarketing.com/story/payers-already-fretting-about-next-pharm-apocalypse-pricey-pcsk9-cholesterol/2014-05-07>. Accessed April 12, 2016.
7. Navarese EP, Kolodziejczak M, Schulze V, et al. Effects of proprotein convertase subtilisin/kexin type 9 antibodies in adults with hypercholesterolemia: a systematic review and meta-analysis. *Ann Intern Med*. 2015;163(1):40-51.
8. Zhang XL, Zhu QQ, Zhu L, et al. Safety and efficacy of anti-PCSK9 antibodies: a meta-analysis of 25 randomized, controlled trials. *BMC Med*. 2015;13:123.
9. Liakos A, Athanasiadou E, Mainou M, et al. Effects of proprotein convertase subtilisin/kexin type 9 antibodies in adults with hypercholesterolemia [editorial]. *Ann Intern Med*. 2015;163(3):241.
10. Battaggia A, Donzelli A, Font M. Effects of proprotein convertase subtilisin/kexin type 9 antibodies in adults with hypercholesterolemia [editorial]. *Ann Intern Med*. 2015;163(3):241-42.
11. Auer J, Berent R, Primus C. PCSK9 inhibitors and cardiovascular events [editorial]. *N Engl J Med*. 2015;373(8):773.
12. Goemann IM, Londero TM, Dora JM. PCSK9 inhibitors and cardiovascular events [editorial]. *N Engl J Med*. 2015;373(8):773-74.
13. Giugliano RP, Sabatine MS. Are PCSK9 inhibitors the next breakthrough in the cardiovascular field? *J Am Coll Cardiol*. 2015;65(24):2638-51.
14. Shrank WH, Barlow JF, Brennan TA. New therapies in the treatment of high cholesterol: an argument to return to goal-based lipid guidelines. *JAMA*. 2015;314(14):1443-44.
15. Pfizer. The evaluation of bococizumab (PF-04950615; RN316) in reducing the occurrence of major cardiovascular events in high risk subjects (SPIRE-1). ClinicalTrials.gov Identifier NCT01975376. March 2016. Available at: <https://clinicaltrials.gov/ct2/show/NCT01975376?term=NCT01975376&rank=1>. Accessed April 12, 2016.
16. Pfizer. The evaluation of bococizumab (PF-04950615; RN316) in reducing the occurrence of major cardiovascular events in high risk subjects (SPIRE-2). ClinicalTrials.gov Identifier NCT01975389. March 2016. Available at: <https://clinicaltrials.gov/ct2/show/NCT01975389?term=NCT01975389&rank=1>. Accessed April 12, 2016.
17. Sanofi. ODYSSEY outcomes: evaluation of cardiovascular outcomes after an acute coronary syndrome during treatment with alirocumab SAR236553 (REGN727). ClinicalTrials.gov Identifier NCT01663402. April 2016. Available at: <https://clinicaltrials.gov/ct2/show/NCT01663402?term=NCT01663402&rank=1>. Accessed April 12, 2016.
18. Amgen. Further cardiovascular outcomes research with PCSK9 Inhibition in subjects with elevated risk (FOURIER). ClinicalTrials.gov Identifier NCT01764633. January 2016. Available at: <https://clinicaltrials.gov/ct2/show/NCT01764633?term=NCT01764633&rank=1>. Accessed April 12, 2016.
19. Chambers JD, Chenoweth M, Cangelosi MJ, Pyo J, Cohen JT, Neumann PJ. Medicare is scrutinizing evidence more tightly for national coverage determinations. *Health Aff (Millwood)*. 2015;34(2):253-60.
20. Robinson JG, Farnier M, Krempf M, et al. Efficacy and safety of alirocumab in reducing lipids and cardiovascular events. *N Engl J Med*. 2015;372(16):1489-99.
21. Robinson JG, Kastelein JJ. PCSK9 inhibitors and cardiovascular events [editorial]. *N Engl J Med*. 2015;373(8):774.
22. Center for Evidence-based Policy. Drug Effectiveness Review Project (DERP). Oregon Health & Science University. Available at: <http://www.ohsu.edu/xd/research/centers-institutes/evidence-based-policy-center/evidence/derp/index.cfm>. Accessed April 12, 2016.
23. McDonagh MS, Jonas DE, Gartlehner G, et al. Methods for the Drug Effectiveness Review Project. *BMC Med Res Methodol*. 2012;12:140.
24. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ*. 2003;327(7414):557-60.
25. Berkman N, Lohr K, Ansari M, et al. Grading the strength of a body of evidence when assessing health care interventions for the effective health care program of the Agency for Healthcare Research and Quality: an update. Methods Guide for Comparative Effectiveness Reviews. (Prepared by the RTI-UNC Evidence-based Practice Center under Contract No. 290-2007-10056-I). AHRQ Publication No. 13(14)-EHC130-EF. Rockville, MD: Agency for Healthcare Research and Quality. November 2013. Available at: <https://www.effectivehealthcare.ahrq.gov/ehc/products/457/1752/methods-guidance-grading-evidence-131118.pdf>. Accessed April 12, 2016.
26. 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):1809-19.
27. Cannon CP, Carriou B, Blom D, et al. Efficacy and safety of alirocumab in high cardiovascular risk patients with inadequately controlled hypercholesterolemia on maximally tolerated doses of statins: the ODYSSEY COMBO II randomized controlled trial. *Eur Heart J*. 2015;36(19):1186-94.
28. Giugliano RP, Desai NR, Kohli P, et al. Efficacy, safety, and tolerability of a monoclonal antibody to proprotein convertase subtilisin/kexin type 9 in combination with a statin in patients with hypercholesterolemia (LAPLACE-TIMI 57): a randomised, placebo-controlled, dose-ranging, phase 2 study. *Lancet*. 2012;380(9858):2007-17.
29. Hirayama A, Honarpour N, Yoshida M, et al. Effects of evolocumab (AMG 145), a monoclonal antibody to PCSK9, in hypercholesterolemic, statin-treated Japanese patients at high cardiovascular risk—primary results from the phase 2 YUKAWA study. *Circ J*. 2014;78(5):1073-82.
30. Kereiakes DJ, Robinson JG, Cannon CP, et al. Efficacy and safety of the proprotein convertase subtilisin/kexin type 9 inhibitor alirocumab among high cardiovascular risk patients on maximally tolerated statin therapy: The ODYSSEY COMBO I study. *Am Heart J*. 2015;169(6):906-15.
31. McKenney JM, Koren MJ, Kereiakes DJ, Hanotin C, Ferrand A-C, Stein EA. Safety and efficacy of a monoclonal antibody to proprotein convertase subtilisin/kexin type 9 serine protease, SAR236553/REGN727, in patients with primary hypercholesterolemia receiving ongoing stable atorvastatin therapy. *J Am Coll Cardiol*. 2012;59(25):2344-53.
32. Raal F, Scott R, Somaratne R, et al. Low-density lipoprotein cholesterol-lowering effects of AMG 145, a monoclonal antibody to proprotein convertase subtilisin/kexin type 9 serine protease in patients with heterozygous familial hypercholesterolemia: the Reduction of LDL-C with PCSK9 Inhibition in Heterozygous Familial Hypercholesterolemia Disorder (RUTHERFORD) randomized trial. *Circulation*. 2012;126(20):2408-17.
33. Raal FJ, Honarpour N, Blom DJ, et al. Inhibition of PCSK9 with evolocumab in homozygous familial hypercholesterolemia (TESLA Part B): a randomised, double-blind, placebo-controlled trial. *Lancet*. 2015;385(9965):341-50.
34. Raal FJ, Stein EA, Dufour R, et al. PCSK9 inhibition with evolocumab (AMG 145) in heterozygous familial hypercholesterolemia (RUTHERFORD-2): a randomised, double-blind, placebo-controlled trial. *Lancet*. 2015;385(9965):331-40.

35. Robinson JG, Nedergaard BS, Rogers WJ, et al. Effect of evolocumab or ezetimibe added to moderate- or high-intensity statin therapy on LDL-C lowering in patients with hypercholesterolemia: the LAPLACE-2 randomized clinical trial. *JAMA*. 2014;311(18):1870-82.
36. Roth EM, McKenney JM, Hanotin C, Asset G, Stein EA. Atorvastatin with or without an antibody to PCSK9 in primary hypercholesterolemia. *N Engl J Med*. 2012;367(20):1891-900.
37. Sabatine MS, Giugliano RP, Wiviott SD, et al. Efficacy and safety of evolocumab in reducing lipids and cardiovascular events. *N Engl J Med*. 2015;372(16):1500-09.
38. Stein EA, Gipe D, Bergeron J, et al. Effect of a monoclonal antibody to PCSK9, REGN727/SAR236553, to reduce low-density lipoprotein cholesterol in patients with heterozygous familial hypercholesterolaemia on stable statin dose with or without ezetimibe therapy: a phase 2 randomised controlled trial. *Lancet*. 2012;380(9836):29-36.
39. Stein EA, Mellis S, Yancopoulos GD, et al. Effect of a monoclonal antibody to PCSK9 on LDL cholesterol. *N Engl J Med*. 2012;366(12):1108-18.
40. Stroes E, Colquhoun D, Sullivan D, et al. Anti-PCSK9 antibody effectively lowers cholesterol in patients with statin intolerance: the GAUSS-2 randomized, placebo-controlled phase 3 clinical trial of evolocumab. *J Am Coll Cardiol*. 2014;63(23):2541-48.
41. Sullivan D, Olsson AG, Scott R, et al. Effect of a monoclonal antibody to PCSK9 on low-density lipoprotein cholesterol levels in statin-intolerant patients: the GAUSS randomized trial. *JAMA*. 2012;308(23):2497-506.
42. Koren MJ, Blom D, Giugliano RP, et al. Safety and tolerability of very low LDL-C levels in patients treated with 52 weeks of evolocumab (AMG 145). *Circulation*. 2014;130(Suppl 2):A16865. [Abstract 16865]
43. Desai NR, Giugliano RP, Zhou J, et al. AMG 145, a monoclonal antibody against PCSK9, facilitates achievement of national cholesterol education program-adult treatment panel III low-density lipoprotein cholesterol goals among high-risk patients: an analysis from the LAPLACE-TIMI 57 trial (LDL-C assessment with PCSK9 monoclonal antibody inhibition combined with statin therapy-thrombolysis in myocardial infarction 57). *J Am Coll Cardiol*. 2014;63(5):430-33.
44. Tice JA, Ollendorf DA, Cunningham C, et al. PCSK9 inhibitors for treatment of high cholesterol: effectiveness, value, and value-based price benchmarks: draft report. A technology assessment. Institute for Clinical and Economic Review. September 8, 2015. Available at: http://icer-review.org/wp-content/uploads/2015/04/PCSK9_Draft_Report_0908151.pdf. Accessed April 12, 2016.
45. Stone NJ, Robinson JG, Lichtenstein AH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2014;129(25 Suppl 2):S1-45.
46. Liberati A, Altman DG, Tetzlaff J. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *J Clin Epidemiol*. 2009;62(10):e1-34.

APPENDIX A Quality Assessment of Randomized Controlled Trials of Alirocumab and Evolocumab

Author, Year Study Name	Randomization Adequate?	Allocation Concealment Adequate?	Groups Similar at Baseline?	Outcome Assessors Blinded?	Clinician Blinded?
Alirocumab					
Cannon, 2015 ¹	Yes	Yes, IVRS	Yes	Unclear; outcome assessors not explicitly noted	Yes; double-blind, double dummy
Kereiakes, 2015 ²	Unclear	Unclear	Unclear; fewer males (63% vs 72%) and less other lipid-lowering therapy use (38% vs. 49%) in alirocumab group	Unclear	Yes
McKenney, 2012 ³	Unclear	Unclear	Some differences in % white, % with diabetes, hypertension, smokers; lipid values similar at baseline	Unclear	Unclear
Robinson, 2015 ⁴ ODYSSEY	Yes	Yes	Yes	Yes	Yes
Roth, 2012 ⁵	Yes, computer-generated	Yes, IVRS	No; the placebo group had fewer patients > 65 y, fewer white patients, and more with diabetes	Yes	Yes
Stein, 2012 ⁶	Yes, IVRS	Yes, IVRS	Some differences in % male (47% to 81%) and CAD (25% to 53%)	Yes	Yes
Stein, 2012 ⁷	Unclear	Yes, using an electronic data capture tool	Some differences in age, sex, race, baseline statin use, but lipid values similar	Yes	Yes
Evolocumab					
Blom, 2014 ⁸ DESCARTES	Yes, stratified by background therapy	Yes, IVRS	Yes	Yes	Yes
Giugliano, 2012 ⁹ Desai, 2014 ¹⁰ LAPLACE-TIMI 57	Yes, computer-generated	Yes, IVRS	Some differences in % female (range 32% to 54%), % white (range 81% to 92%), % with diabetes (range 11% to 24%), etc. No difference in baseline lipid values, statin use	Yes for lipid outcomes	Yes for lipid outcomes
Hirayama, 2014 ¹¹ YUKAWA	Unclear	Unclear	Unclear; in evolocumab groups, higher % female (32% to 49% vs. 29% to 31%), higher T2DM (34% to 49%), ≥ 2 CV risk factors (48% to 65% vs. 46% to 52%)	Unclear	Yes to dose, but not frequency
Author, Year Study Name	Patient Blinded?	Intention to Treat?	Acceptable Level of Overall Attrition (≤20%)?	Acceptable Level of Differential Attrition (<10%)?	Overall Quality
Alirocumab					
Cannon, 2015 ¹	Yes, double-blind, double dummy	Yes	Yes	Yes	Good
Kereiakes, 2015 ²	Yes	Yes	Yes; 26% for 52 weeks	Yes	Fair
McKenney, 2012 ³	Unclear	Yes	Yes	Yes	Fair
Robinson, 2015 ⁴ ODYSSEY	Yes	No	Yes	Yes	Good
Roth, 2012 ⁵	Yes	Yes	Yes	Yes, except at visit 16 (28% missing from placebo group vs. 17% and 11% in active groups)	Fair
Stein, 2012 ⁶	Yes	Yes	Yes, only 1 patient discontinued	Yes	Fair
Stein, 2012 ⁷	Yes	Yes	Yes	Yes	Fair

APPENDIX A Quality Assessment of Randomized Controlled Trials of Alirocumab and Evolocumab (continued)

Evolocumab

Blom, 2014 ⁸ DESCARTES	Yes	Yes	Yes	Yes	Good
Giugliano, 2012 ⁹ Desai, 2014 ¹⁰ LAPLACE-TIMI 57	Yes	Yes, some with small numbers missing but < 5%	Yes	Yes	Good
Hirayama, 2014 ¹¹ YUKAWA	Yes to dose, but not frequency	Yes	Yes	Yes	Fair
Author, Year Study Name	Randomization Adequate?	Allocation Concealment Adequate?	Groups Similar at Baseline?	Outcome Assessors Blinded?	Clinician Blinded?
Raal, 2012 ¹² RUTHERFORD	Yes, IVRS	Yes, IVRS	Unclear; % male ranged from 42.9% to 62.5%	Unclear; lipid analysis performed by central lab; blinding NR	Unclear; described as double-blind; full study team blinded to lab values; but treatment appearance NR
Raal, 2015 ¹³ RUTHERFORD-2	Yes, computer-generated	Yes, IVRS	Unclear; CAD ranged from 18% to 35%	Yes; patients, study personnel, investigators, and Amgen study staff masked to treatment assignments within dosing groups; masking achieved by identical look of autoinjector pens containing study drug (evolocumab) or placebo	Yes
Raal, 2015 ¹⁴ TESLA Part B	Yes, computer-generated, stratified by LDL-C at screening and implemented by computerized IVRS	Yes; IVRS	Yes; groups differ slightly by ethnicity and clinically evident CAD but are similar for other baseline characteristics	Yes	Yes
Robinson, 2014 ¹⁵	Unclear	Unclear	Some differences in female sex (22% to 59%), CAD (7% to 36%)	Yes	Yes
Sabatine, 2015 ¹⁶ OSLER-1 and OSLER-2	Yes	Yes	Yes	No	No
Stroes, 2014 ¹⁷ GAUSS-2	Unclear	Unclear	Some differences in # of intolerable statins (% patients with 2 = 33% to 49%), diabetes (15% to 31%), hypertension (55% to 75%), but similar LDL and HDL	Yes	Yes
Sullivan, 2012 ¹⁸ GAUSS	Unclear	Yes, IVRS	Some differences in % female (range 56% to 77%), % white (80% to 94%), # of previous statin intolerances, but similar LDL and HDL	No for ezetimibe; unclear for evolocumab	No for ezetimibe; unclear for evolocumab
Author, Year Study Name	Patient Blinded?	Intention to Treat?	Acceptable Level of Overall Attrition (≤ 20%)?	Acceptable Level of Differential Attrition (< 10%)?	Overall Quality
Raal, 2012 ¹² RUTHERFORD	Unclear; described as double-blind; full study team blinded to lab values; but treatment appearance NR	Yes	Yes	Yes	Fair
Raal, 2015 ¹³ RUTHERFORD-2	Yes	Yes	Yes	Yes	Good
Raal, 2015 ¹⁴ TESLA Part B	Yes	Yes	Yes	Yes	Good
Robinson, 2014 ¹⁵	Yes	Yes	Yes	No; range, 2% to 25%	Fair
Sabatine, 2015 ¹⁶ OSLER-1 and OSLER-2	No	Yes	Yes	Yes	Fair

APPENDIX A Quality Assessment of Randomized Controlled Trials of Alirocumab and Evolocumab (continued)

Author, Year Study Name	Patient Blinded?	Intention to Treat?	Acceptable Level of Overall Attrition (≤20%)?	Acceptable Level of Differential Attrition (<10%)?	Overall Quality
Stroes, 2014 ¹⁷ GAUSS-2	Yes	Yes	Yes	Yes	Fair
Sullivan, 2012 ¹⁸ GAUSS	No for ezetimibe; unclear for evolocumab	Yes	Yes	Yes	Fair

Note: Numbered footnotes refer to citations in the References at the end of the appendices.

CAD=coronary artery disease; CV=cardiovascular; HDL=high-density lipoprotein; IVRS=interactive voice response system; LDL-C=low-density lipoprotein cholesterol; NR=not reported; T2DM=type 2 diabetes mellitus.

APPENDIX B Strength of Evidence

Strength of Evidence Grade	Study Design; No. Studies (N)	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Other Issues	Finding
Key Question 1. Heterozygous Familial Hypercholesterolemia								
Alirocumab vs. placebo × 6 weeks in patients taking atorvastatin 10 mg-40 mg⁷								
LDL-C lowering ability								
LDL-C: Insufficient	1 RCT, N = 21	Medium	Direct	Unknown	Imprecise	Undetected	None	No conclusion; range in difference in percent change from baseline vs. placebo (% points): -41.4% to -55.7%
HDL-C raising ability								
HDL-C: Insufficient	1 RCT, N = 21	Medium	Direct	Unknown	Imprecise	Undetected	None	No conclusion; significant difference in % change from baseline for 50 mg or 100 mg dose, but greater increase for 150 mg vs. placebo = 23.0% (P = 0.033)
Overall adverse events								
Overall AE: Insufficient	1 RCT, N = 21	Medium	Direct	Unknown	Imprecise	Undetected	None	Greater only for 150 mg dose: 80% vs. 0%; EPC-calculated P = 0.015
Withdrawals due to adverse events								
AE withdrawal: Insufficient	1 RCT, N = 21	Medium	Direct	Unknown	Imprecise	Undetected	None	No difference; no events
Serious adverse events								
Serious AE: Insufficient	1 RCT, N = 21	Medium	Direct	Unknown	Imprecise	Undetected	None	No difference; no events
Specific adverse events: neurocognitive events								
Neurocognitive dysfunction: Insufficient	1 RCT, N = 21	Medium	Direct	Unknown	Imprecise	Undetected	None	No difference; no events
Specific adverse events: injection site								
Injection site erythema: Insufficient	1 RCT, N = 21	Medium	Direct	Unknown	Imprecise	Undetected	None	No difference; no events
Alirocumab vs. placebo × 12 weeks in patients taking mixed max statin plus ezetimibe⁶								
LDL-C lowering ability								
LDL-C: Low	1 RCT, N = 77	Medium	Direct	Unknown	Imprecise	Undetected	None	Greater reduction; range in absolute difference in percent change from baseline vs. placebo (% points): -18% to -57%
HDL-C raising ability								
HDL-C: Low	1 RCT, N = 77	Medium	Direct	Unknown	Imprecise	Undetected	None	No significant difference in % change from baseline except for 150 mg every 2 weeks: +12.34% vs. +2.20%; P = 0.050
Overall adverse events								
Overall AE: Insufficient	1 RCT, N = 77	Medium	Direct	Unknown	Imprecise	Undetected	None	No difference: 75% to 87% for alirocumab vs. 60% for placebo

APPENDIX B Strength of Evidence *(continued)*

Strength of Evidence Grade	Study Design; No. Studies (N)	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Other Issues	Finding
Withdrawals due to adverse events								
AE withdrawal: Insufficient	1 RCT, N = 77	Medium	Direct	Unknown	Imprecise	Undetected	None	No difference; only 1 patient taking alirocumab 300 mg every 4 weeks
Serious adverse events								
Serious AE: Insufficient	1 RCT, N = 77	Medium	Direct	Unknown	Imprecise	Undetected	None	No difference; only 1 patient in the placebo group with GI disorder
Specific adverse events: neurocognitive events								
Neurocognitive dysfunction: Insufficient	1 RCT, N = 77	Medium	Direct	Unknown	Imprecise	Undetected	None	No difference; no events
Specific adverse events: injection site								
Injection site reactions: Insufficient	1 RCT, N = 77	Medium	Direct	Unknown	Imprecise	Undetected	None	No difference; 27% to 47% vs. 13%
Evolocumab vs. placebo × 12 weeks in patients taking high-intensity statins+ezetimibe (RUTHERFORD 1 and 2)^{12,13}								
LDL-C lowering ability								
LDL-C: High	2 RCTs, N = 499	Low	Direct	Consistent	Precise	Undetected	None	Greater reductions for evolocumab: absolute difference vs. placebo in change from baseline (% points): range, -44% to -61%
HDL-C raising ability								
HDL-C: Moderate	2 RCTs, N = 499	Low	Direct	Consistent	Imprecise	Undetected	None	Greater increase for evolocumab: absolute difference vs. placebo in change from baseline (% points): range, 6.8% to 9.2%
Overall adverse events								
Overall AE: Moderate	2 RCTs, N = 499	Low	Direct	Consistent	Imprecise	Undetected	None	No difference; 58% vs. 52%; EPC-pooled RR 1.12 (95% CI, 0.94 to 1.33)
Withdrawals due to adverse events								
AE withdrawal: Moderate	2 RCTs, N = 499	Low	Direct	Consistent	Imprecise	Undetected	None	No difference; 0.6% vs. 0.6%; pooled RR not possible because of no events in RUTHERFORD-2
Serious adverse events								
Serious AE: Moderate	2 RCTs, N = 499	Low	Direct	Consistent	Imprecise	Undetected	None	No difference; 3% vs. 3%; EPC-pooled RR 0.81 (95% CI, 0.28 to 2.33)
Specific adverse events: neurocognitive events								
Neurocognitive dysfunction: Moderate	2 RCTs, N = 499	Low	Direct	Consistent	Imprecise	Undetected	None	No events
Specific adverse events: injection site								
Injection site: Moderate	2 RCTs, N = 499	Low	Direct	Consistent	Imprecise	Undetected	None	6% vs. 3%; EPC-pooled RR 0.76 (95% CI, 0.76 to 5.21)

APPENDIX B Strength of Evidence *(continued)*

Strength of Evidence Grade	Study Design; No. Studies (N)	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Other Issues	Finding
Key Question 2. Homozygous Familial Hypercholesterolemia								
Evolocumab 420 mg Q4 weeks × 12 weeks in patients taking a statin with or without ezetimibe vs. placebo								
LDL-C lowering ability								
Evolocumab vs. Placebo: Low	RCT 1 (50)	Low	Direct	Unknown	Imprecise	Not detected	None	Evolocumab significantly reduced ultra-centrifugation LDL-C at 12 weeks by 32.1% (95% CI, 45.1 to -19.2) compared to placebo
HDL-C raising ability								
Evolocumab vs. Placebo: Low	RCT 1 (50)	Low	Direct	Unknown	Imprecise	Not detected	None	Evolocumab reduced HDL-C by 0.1% (95% CI, -9.4% to 9.2%) at week 12 compared to placebo (NS)
Overall adverse events								
Evolocumab vs. Placebo: Low	RCT 1 (50)	Low	Direct	Unknown	Imprecise	Not detected	None	Any treatment emergent adverse events: Evolocumab vs. Placebo: 36% (12/33) vs. 63% (10/16)
Withdrawals due to adverse events								
Evolocumab vs. Placebo: Low	RCT 1 (50)	Low	Direct	Unknown	Imprecise	Not detected	None	No difference in treatment emergent adverse events leading to discontinuation of study drug: Evolocumab vs. Placebo: 0% (0/33) vs. 0% (0/16)
Serious adverse events								
Evolocumab vs. Placebo: Low	RCT 1 (50)	Low	Direct	Unknown	Imprecise	Not detected	None	No difference in serious treatment emergent adverse events: Evolocumab vs. Placebo: 0% (0/33) vs. 0% (0/16)
Specific adverse events: neurocognitive events^a								
Evolocumab vs. Placebo: Low	RCT 1 (50)	Low	Direct	Unknown	Imprecise	Not detected	None	No difference between groups in neurocognitive events: Evolocumab vs. Placebo: 0% (0/33) vs. 0% (0/16)
Specific adverse events: potential injection-site reactions^b								
Evolocumab vs. Placebo: Low	RCT 1 (50)	Low	Direct	Unknown	Imprecise	Not detected	None	Potential injection-site reactions: Evolocumab vs. Placebo: 0% (0/33) vs. 6% (1/16)
Specific adverse events: gastroenteritis								
Evolocumab vs. Placebo: Low	RCT 1 (50)	Low	Direct	Unknown	Imprecise	Not detected	None	Gastroenteritis: Evolocumab vs. Placebo: 6% (2/33) vs. 0% (0/16)

APPENDIX B Strength of Evidence *(continued)*

Strength of Evidence Grade	Study Design; No. Studies (N)	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Other Issues	Finding
Key Question 3. Not at Target								
Alirocumab 150 mg Q2 weeks × 8-12 weeks vs. placebo								
LDL-C lowering ability								
% at target (<70 mg/dl)								
Alirocumab + low-dose statin vs. Placebo + high-dose statin Low	RCT 1 (61)	Medium	Direct	Unknown	Imprecise	Not detected	None	100% vs. 52%
Alirocumab vs. Placebo + low-moderate dose statin Low	RCT 1 (31)	Medium	Direct	Unknown	Imprecise	Not detected	None	100% vs. 16.1%
Alirocumab vs. Placebo + high-dose statin Low	RCT 1 (62)	Medium	Direct	Unknown	Imprecise	Not detected	None	100% vs. 52%
% change in LDL								
Alirocumab + low-dose statin vs. Placebo + high-dose statin × 8 wks Low	RCT 1 (61)	Medium	Direct	Unknown	Imprecise	Not detected	None	Difference in LDL-C lowering: 48.9%, P<0.001
Alirocumab vs. Placebo + moderate dose statin × 12 wks Low	RCT 1 (31)	Medium	Direct	Unknown	Imprecise	Not detected	None	Difference in LDL-C lowering: 67.3%, P<0.001
% change in LDL								
Alirocumab vs. Placebo + high-dose statin × 8 wks Low	RCT 1 (62)	Medium	Direct	Unknown	Imprecise	Not detected	None	Difference in LDL-C lowering: 55.9%, P<0.001
% change in HDL								
Alirocumab + low-dose statin vs. Placebo + high-dose statin × 8 wks Low	RCT 1 (61)	Medium	Direct	Unknown	Imprecise	Not detected	None	Difference in HDL-C lowering: 6 mg/dl; P=0.06
Alirocumab vs. Placebo + moderate dose statin × 12 wks Low	RCT 1 (31)	Medium	Direct	Unknown	Imprecise	Not detected	None	Difference in HDL-C lowering: 6.5 mg/dl; P=0.057
Alirocumab vs. Placebo + high-dose statin × 8 wks Low	RCT 1 (62)	Medium	Direct	Unknown	Imprecise	Not detected	None	Difference in HDL-C lowering: 9.4 mg/dL; P=0.05

APPENDIX B Strength of Evidence *(continued)*

Strength of Evidence Grade	Study Design; No. Studies (N)	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Other Issues	Finding
Overall adverse events								
Alirocumab + low-dose statin vs. Placebo + high-dose statin Insufficient	RCT 1 (61)	Medium	Direct	Unknown	Imprecise	Not detected	None	61% vs. 45%
Alirocumab vs. Placebo + low/moderate-dose statin Insufficient	RCT 1 (31)	Medium	Direct	Unknown	Imprecise	Not detected	None	61.3% vs. 45.2%
Alirocumab vs. Placebo + high-dose statin Insufficient	RCT 1 (62)	Medium	Direct	Unknown	Imprecise	Not detected	None	61% vs. 60%
Withdrawals due to adverse events								
Alirocumab + low-dose statin vs. Placebo + high-dose statin Insufficient	RCT 1 (61)	Medium	Direct	Unknown	Imprecise	Not detected	None	0% vs. 13%
Alirocumab vs. Placebo + low/moderate-dose statin Insufficient	RCT 1 (31)	Medium	Direct	Unknown	Imprecise	Not detected	None	3.2% vs. 0%
Alirocumab vs. Placebo + high-dose statin Insufficient	RCT 1 (62)	Medium	Direct	Unknown	Imprecise	Not detected	None	3% vs. 13%
Serious adverse events								
Alirocumab + low-dose statin vs. Placebo + high-dose statin Insufficient	RCT 1 (61)	Medium	Direct	Unknown	Imprecise	Not detected	None	0 vs. 0
Alirocumab vs. Placebo + low/moderate-dose statin Insufficient	RCT 1 (31)	Medium	Direct	Unknown	Imprecise	Not detected	None	0% vs. 3.2%
Alirocumab vs. Placebo + high-dose statin Insufficient	RCT 1 (62)	Medium	Direct	Unknown	Imprecise	Not detected	None	0% vs. 3%
Specific adverse events: potential injection-site reactions^b								
Alirocumab + low-dose statin vs. Placebo + high-dose statin Insufficient	RCT 1 (61)	Medium	Direct	Unknown	Imprecise	Not detected	None	0% vs. 6.5%
Alirocumab vs. Placebo + low/moderate-dose statin Insufficient	RCT 1 (31)	Medium	Direct	Unknown	Imprecise	Not detected	None	3.2 to 32% vs. 0%
Alirocumab vs. Placebo + high-dose statin Insufficient	RCT 1 (62)	Medium	Direct	Unknown	Imprecise	Not detected	None	3.3% vs. 6.5%

APPENDIX B Strength of Evidence *(continued)*

Strength of Evidence Grade	Study Design; No. Studies (N)	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Other Issues	Finding
Alirocumab 75 mg to 150 mg Q 2 weeks vs. placebo at 24 weeks in high-risk patients								
LDL-C lowering ability								
% at target (< 70 mg/dl)								
Alirocumab + max-dose statin vs. Placebo + max-dose statin High	RCT 2 (2,656)	Low	Direct	Consistent	Precise	Not detected	None	Pooled RR 9.65 (95% CI, 7.7 to 12.0) (75-79% vs. 8-9%)
Alirocumab + max-dose statin vs. ezetimibe 10 mg + max-dose statin Moderate	RCT 1 (720)	Low	Direct	Unknown	Precise	Not detected	None	77% vs. 45.6% RR 1.70 (95% CI, 1.46 to 1.95)
% change in LDL								
Alirocumab + max-dose statin vs. Placebo + max-dose statin High	RCT 2 (2,656)	Low	Direct	Consistent	Precise	Not detected	None	Differenc = -45.9%, $P < 0.001$ (primarily 75 mg Q2 wks) -61.9%, $P < 0.001$ (150 mg Q2 wks)
Alirocumab + max-dose statin vs. ezetimibe 10 mg + max-dose statin Moderate	RCT 1 (720)	Low	Direct	Unknown	Precise	Not detected	None	Difference = -29.8%, $P < 0.001$
% change in HDL								
Alirocumab + max-dose statin vs. Placebo + max-dose statin Moderate	RCT 2 (2,656)	Low	Direct	Consistent	Imprecise	Not detected	None	7.3, 95% CI, 3.6 to 11.0; $P < 0.001$ (primarily 75 mg Q2 wks) 4.6 (0.7); 3.3 to 5.9, $P < 0.001$ (150 mg Q2 wks)
Alirocumab + max-dose statin vs. ezetimibe 10 mg + max-dose statin Low	RCT 1 (720)	Low	Direct	Unknown	Imprecise	Not detected	None	Difference = 8.1% (1.3), $P < 0.001$
Overall adverse events								
Alirocumab + max-dose statin vs. Placebo + max-dose statin High	RCT 2 (2,656)	Low	Direct	Consistent	Precise	Not detected	None	81.0% vs. 82.5% 75.8% vs. 75.7%
Alirocumab + max-dose statin vs. ezetimibe 10 mg + max-dose statin Moderate	RCT 1 (720)	Low	Direct	Unknown	Precise	Not detected	None	71.2% vs. 67.2%

APPENDIX B Strength of Evidence (continued)

Strength of Evidence Grade	Study Design; No. Studies (N)	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Other Issues	Finding
Withdrawals due to adverse events								
Alirocumab + max-dose statin vs. Placebo + max-dose statin Moderate	RCT 2 (2,656)	Low	Direct	Consistent	Imprecise	Not detected	None	7.2% vs. 5.8% 6.3% vs. 7.5%
Alirocumab + max-dose statin vs. ezetimibe 10 mg + max-dose statin Low	RCT 1 (720)	Low	Direct	Unknown	Imprecise	Not detected	None	7.5% vs. 5.4%
Serious adverse events								
Alirocumab + max-dose statin vs. Placebo + max-dose statin High	RCT 2 (2,656)	Low	Direct	Consistent	Precise	Not detected	None	18.7% vs. 19.5% 12.6% vs. 13.1%
Alirocumab + max-dose statin vs. ezetimibe 10 mg + max-dose statin Low	RCT 1 (720)	Low	Direct	Unknown	Imprecise	Not detected	None	18.8% vs. 17.8%
Specific adverse events: potential injection-site reactions^b								
Alirocumab + max-dose statin vs. Placebo + max-dose statin Low	RCT 2 (2,656)	Low	Direct	Inconsistent	Imprecise	Not detected	None	Pooled RR 1.4 (95% CI, 0.98 to 2.1) Rates 5.9% vs. 4.2% and 5.3% vs. 2.8%
Alirocumab + max-dose statin vs. ezetimibe 10 mg + max-dose statin Low	RCT 1 (720)	Low	Direct	Unknown	Imprecise	Not detected	None	2.5% vs. 0.8%
Specific adverse events								
Neurocognitive events								
Alirocumab + max-dose statin vs. Placebo + max-dose statin Moderate	RCT 2 (2,656)	Low	Direct	Consistent	Imprecise	Not detected	None	1.2% vs. 0.5%; P=0.17; 0 vs. 0.9%
Alirocumab + max-dose statin vs. ezetimibe 10 mg + max-dose statin Low	RCT 1 (720)	Low	Direct	Unknown	Imprecise	Not detected	None	0.8% vs. 1.2%

APPENDIX B Strength of Evidence (continued)

Strength of Evidence Grade	Study Design; No. Studies (N)	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Other Issues	Finding
CV events (adjudicated)								
Alirocumab + max-dose statin vs. Placebo + max-dose statin Moderate	RCT 2 (2,656)	Low	Direct	Consistent	Imprecise	Not detected	None	Pooled RR 0.91 (95% CI, 0.63 to 1.31)
Alirocumab + max-dose statin vs. ezetimibe 10 mg + max-dose statin Low	RCT 1 (720)	Low	Direct	Unknown	Imprecise	Not detected	None	RR 1.29 (95% CI, 0.60 to 2.74)
Evolocumab 420 mg Q4 weeks × 52 weeks vs. placebo								
LDL-C lowering ability								
% at target (<70 mg/dl)								
Evolocumab 420 mg Q 4 weeks × 48 weeks vs. Placebo Moderate	RCT 1 (901)	Low	Direct	Unknown	Precise	Not detected	None	82.3% evolocumab vs. 6.4% placebo; $P < 0.001$
% change in LDL at 52 weeks								
Evolocumab 420 mg Q 4 weeks × 48 weeks vs. Placebo: Moderate	RCT 1 (901)	Low	Direct	Unknown	Precise	Not detected	None	Difference in ultracentrifugation LDL-C at 52 weeks -57% (± 2.1 SD) compared to placebo
% change in HDL at 52 weeks								
Evolocumab 420 mg Q 4 weeks × 48 weeks vs. Placebo: Low	RCT 1 (901)	Low	Direct	Unknown	Imprecise	Not detected	None	Difference vs. placebo in % change from baseline: 5.4%; $P < 0.001$
Overall adverse events								
Evolocumab vs. Placebo: Moderate	RCT 1 (901)	Low	Direct	Unknown	Precise	Not detected	None	Evolocumab vs. Placebo: 75% vs. 74%
Withdrawals due to adverse events								
Evolocumab vs. Placebo: Low	RCT 1 (901)	Low	Direct	Unknown	Imprecise	Not detected	None	Evolocumab vs. Placebo: 2% (13/599) vs. 1% (3/302)
Serious adverse events								
Evolocumab vs. Placebo: Low	RCT 1 (901)	Low	Direct	Unknown	Imprecise	Not detected	None	Evolocumab vs. Placebo: 6% vs. 4%
Specific adverse events: potential injection-site reactions^b								
Evolocumab vs. Placebo: Low	RCT 1 (901)	Low	Direct	Unknown	Imprecise	Not detected	None	Evolocumab vs. Placebo: 5.7% (34/599) vs. 5% (15/302)

APPENDIX B Strength of Evidence *(continued)*

Strength of Evidence Grade	Study Design; No. Studies (N)	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Other Issues	Finding
Evolocumab 420 mg Q4 weeks × 12 weeks vs. placebo								
LDL-C lowering ability								
% at target (<70 mg/dl)								
Evolocumab 420 mg Q4 weeks × 12 weeks vs. Placebo: High	RCT 2 (640 at 420 mg, 356 placebo)	Low	Direct	Consistent	Precise	Not detected	None	72% to 94% for evolocumab vs. 0% to 9% for placebo; $P < 0.001$
% change in LDL at 12 weeks								
Evolocumab 420 mg Q 4 weeks × 12 weeks vs. Placebo: High	RCT 2 (640 at 420 mg, 356 placebo)	Low	Direct	Consistent	Precise	Not detected	None	Difference in ultra-centrifugation LDL-C -53% (95% CI, 56.0 to 44.6) to -70.5% (95% CI, -79.8 to -61.2) compared to placebo.
% change in HDL at 12 weeks								
Evolocumab 420 mg Q4 weeks × 12 weeks vs. Placebo: Moderate	RCT 2 (640 at 420 mg, 356 placebo)	Low	Direct	Consistent	Imprecise	Not detected	None	Difference from placebo in % change from baseline: ranging from 4.5% (95% CI, 0.4 to 8.7) to 9.1% (95% CI, 4.4 to 13.7)
Overall adverse events								
Evolocumab vs. Placebo: High	RCT 2 (640 at 420 mg, 356 placebo)	Low	Direct	Consistent	Precise	Not detected	None	Ranged from 31% to 60% with evolocumab 420 mg every 4 weeks and from 24% to 49% in the placebo group
Withdrawals due to adverse events								
Evolocumab vs. Placebo: Moderate	RCT 2 (640 at 420 mg, 356 placebo)	Low	Direct	Consistent	Imprecise	Not detected	None	Evolocumab vs. Placebo: 1-2% vs. 2-4%
Serious adverse events								
Evolocumab vs. Placebo: Moderate	RCT 2 (640 at 420 mg, 356 placebo)	Low	Direct	Consistent	Imprecise	Not detected	None	No difference, Evolocumab vs. Placebo: 0.9-2.7% vs. 1.8-3.6%
Specific adverse events: potential injection-site reactions^b								
Evolocumab vs. Placebo: Moderate	RCT 2 (640 at 420 mg, 356 placebo)	Low	Direct	Consistent	Imprecise	Not detected	None	No difference, Evolocumab vs. Placebo: 0% vs. 1.3% in LAPLACE-TIMI-57; NR by group in LAPLACE-2
Evolocumab 420 mg Q4 weeks × 12 weeks vs. placebo, both added to primarily moderate-intensity statins in Japanese patients with high cardiovascular risk¹¹								
LDL-C lowering ability								
% at target (<70 mg/dl)								
Evolocumab 420 mg Q4 weeks × 12 weeks vs. placebo: Low	1 RCT; evolocumab 420 mg Q4 weeks N=53, placebo every month N=51	Medium	Direct	Unknown	Imprecise	Not detected	None	Greater for evolocumab: <100: 96% vs. 1%; $P < 0.001$ <70: 82% vs. 0%; $P < 0.001$

APPENDIX B Strength of Evidence (continued)

Strength of Evidence Grade	Study Design; No. Studies (N)	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Other Issues	Finding
% change in LDL at 12 weeks								
Evolocumab 420 mg Q 4 weeks × 12 weeks vs. placebo: Low	1 RCT; evolocumab 420 mg Q4 weeks N=53, placebo every month N=51	Medium	Direct	Unknown	Imprecise	Not detected	None	Greater for evolocumab: Mean % change vs. placebo: -63.9%; <i>P</i> <0.001
% change in HDL at 12 weeks								
Evolocumab 420 mg Q 4 weeks × 12 weeks vs. placebo: Insufficient	1 RCT; evolocumab 420 mg Q4 weeks N=53, placebo every month N=51	Medium	Direct	Unknown	Imprecise	Not detected	None	No conclusion: Mean % change vs. placebo: 13.2%; <i>P</i> <0.001
Overall adverse events								
Evolocumab 420 mg Q4 weeks × 12 weeks vs. placebo: Insufficient	1 RCT; evolocumab 420 mg Q 4 weeks N=53, placebo every month N=51	Medium	Direct	Unknown	Imprecise	Not detected	None	No conclusion; 58.5% vs. 42.0%
Withdrawals due to adverse events								
Evolocumab 420 mg Q4 weeks × 12 weeks vs. placebo: Insufficient	1 RCT; evolocumab 420 mg Q4 weeks N=53, placebo every month N=51	Medium	Direct	Unknown	Imprecise	Not detected	None	No conclusion; 3.8% vs. 0
Serious adverse events								
Evolocumab 420 mg Q4 weeks × 12 weeks vs. placebo: Insufficient	1 RCT; evolocumab 420 mg Q4 weeks N=53, placebo every month N=51	Medium	Direct	Unknown	Imprecise	Not detected	None	No conclusion; 3.8% vs. 0
Specific adverse events: potential injection-site reactions^b								
Evolocumab 420 mg Q 4 weeks × 12 weeks vs. placebo: Insufficient	1 RCT; evolocumab 420 mg Q 4 weeks N=53, placebo every month N=51	Medium	Direct	Unknown	Imprecise	Not detected	None	No conclusion; 1.9% vs. 0
Evolocumab 420 mg Q4 weeks × 12 weeks vs. ezetimibe 10 mg, both added to moderate-high intensity statins								
LDL-C lowering ability								
% at target (<70 mg/dl)								
Evolocumab 420 mg Q 4 weeks × 12 weeks vs. ezetimibe 10 mg: Low	1 RCT; Atorvastatin 10 mg group: evolocumab N=110 vs. placebo N=55 Atorvastatin 80 mg group: evolocumab N=110 vs. ezetimibe N=54	Medium	Direct	Unknown	Imprecise	Not detected	None	Higher for evolocumab: Atorvastatin 10 mg: 85.8% vs. 5.6%; EPC-calculated RR 5.22 (95% CI, 3.00 to 9.69) Atorvastatin 80 mg: 92.5% vs. 62.3%; EPC calculated RR 1.47 (95% CI, 1.23 to 1.88)

APPENDIX B Strength of Evidence (continued)

Strength of Evidence Grade	Study Design; No. Studies (N)	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Other Issues	Finding
% change in LDL at 12 weeks								
Evolocumab 420 mg Q 4 weeks × 12 weeks vs. ezetimibe 10 mg; Low	1 RCT; Atorvastatin 10 mg group: evolocumab N=110 vs. placebo N=55 Atorvastatin 80 mg group: evolocumab N=110 vs. ezetimibe N=54	Medium	Direct	Unknown	Imprecise	Not detected	None	Greater for evolocumab: % Change from baseline (95% CI): Atorvastatin 10 mg: -62.5% (95% CI, -66.1 to -58.9) vs. -19.0 (-24.0 to -13.9) Atorvastatin 80 mg: -65.1 (95% CI, -69.8 to -60.3) vs. -21.3 (95% CI, -28.0 to -14.5)
% change in HDL at 12 weeks								
Evolocumab 420 mg Q4 weeks × 12 weeks vs. ezetimibe 10 mg; Insufficient	1 RCT; Atorvastatin 10 mg group: evolocumab N=681110 vs. placebo N=55 Atorvastatin 80 mg group: evolocumab N=110 vs. ezetimibe N=54	Medium	Direct	Unknown	Imprecise	Not detected	None	Greater for evolocumab: % Change from baseline (95% CI): Atorvastatin 10 mg: 7.7 (95% CI, 5.0 to 10.4) vs. -0.9 (95% CI, -4.7 to 2.9) Atorvastatin 80 mg: 7.8 (95% CI, 5.2 to 10.4) vs. -0.6 (95% CI, -4.3 to 3.1)
Overall adverse events								
Evolocumab 420 mg Q 4 weeks × 12 weeks vs. ezetimibe 10 mg; Low	1 RCT; Atorvastatin 10 mg group: evolocumab N=110 vs. placebo N=55 Atorvastatin 80 mg group: evolocumab N=110 vs. ezetimibe N=54	Medium	Direct	Unknown	Imprecise	Not detected	None	No difference: Atorvastatin 10 mg: 30.9% vs. 40.0% Atorvastatin 80 mg: 39.1% vs. 35.2%
Withdrawals due to adverse events								
Evolocumab 420 mg Q4 weeks × 12 weeks vs. ezetimibe 10 mg; Insufficient	1 RCT; Atorvastatin 10 mg group: evolocumab N=110 vs. placebo N=55 Atorvastatin 80 mg group: evolocumab N=110 vs. ezetimibe N=54	Medium	Direct	Unknown	Imprecise	Not detected	None	No difference: Atorvastatin 10 mg: 1.8% vs. 0 Atorvastatin 80 mg: 1.8% vs. 1.9%
Serious adverse events								
Evolocumab 420 mg Q4 weeks × 12 weeks vs. ezetimibe 10 mg; Insufficient	1 RCT; Atorvastatin 10 mg group: evolocumab N=110 vs. placebo N=55 Atorvastatin 80 mg group: evolocumab N=110 vs. ezetimibe N=54	Medium	Direct	Unknown	Imprecise	Not detected	None	No difference; Atorvastatin 10 mg: 1.8% vs. 0 Atorvastatin 80 mg: 0.9% vs. 1.9%
Specific adverse events: potential injection-site reactions^b								
Evolocumab 420 mg Q4 weeks × 12 weeks vs. ezetimibe 10 mg; Insufficient	1 RCT; Atorvastatin 10 mg group: evolocumab N=110 vs. placebo N=55 Atorvastatin 80 mg group: evolocumab N=110 vs. ezetimibe N=54	Medium	Direct	Unknown	Imprecise	Not detected	None	No difference; Any statin + any evolocumab=1.3% vs. atorvastatin+ ezetimibe=0.9%; NR for individual ezetimibe or evolocumab groups

APPENDIX B Strength of Evidence *(continued)*

Strength of Evidence Grade	Study Design; No. Studies (N)	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Other Issues	Finding
Key Question 4. Statin Intolerant								
Evolocumab vs. ezetimibe over 12 weeks (GAUSS: evolocumab 280 mg, 350, or 420 mg given every 4 weeks vs. ezetimibe 10 mg; GAUSS-2: evolocumab 140 mg every two weeks or 420 mg once monthly to ezetimibe 10 mg)^{17,18}								
LDL-C: Low	2 RCTs, N = 434	Medium	Direct	Consistent	Imprecise	Undetected	None	Higher reduction for evolocumab: -26% (95% CI, -34.1% to -17.9%) for 280 mg every 4 weeks in GAUSS to -38% (95% CI, -43.7 to -32.4) for 140 mg every 2 weeks in GAUSS-2
HDL-C: Low	2 RCTs, N = 434	Medium	Direct	Consistent	Imprecise	Undetected	None	Evolocumab has a similar or better % change from baseline: Range = 3.6% (95% CI, -1.5 to 8.6) to 8.5% (P = 0.020)
Overall AE: Low	2 RCTs, N = 434	Medium	Direct	Consistent	Imprecise	Undetected	None	63% vs. 69%; RR 0.92 (95% CI, 0.80 to 1.06)
AE withdrawal: Low	2 RCTs, N = 434	Medium	Direct	Consistent	Imprecise	Undetected	None	3% vs. 12%; RR 0.29 (95% CI, 0.14 to 0.63)
Serious AE: Low	2 RCTs, N = 434	Medium	Direct	Consistent	Imprecise	Undetected	None	3% vs. 3%; RR 1.04 (95% CI, 0.34 to 3.15)
Neurocognitive dysfunction: Low	2 RCTs, N = 434	Medium	Direct	Consistent	Imprecise	Undetected	None	No events
Injection site: Insufficient	1 RCT, N = 307	Medium	Direct	Unknown	Imprecise	Undetected	None	No difference; 3% vs. 8%
Evolocumab 420 mg every 4 weeks plus ezetimibe 10 mg versus ezetimibe 10 mg alone × 12 weeks								
LDL-C: Low	1 RCT, N = 62	Medium	Direct	Unknown	Imprecise	Undetected	None	Greater reduction: (-47%; 95% CI, -53.7% to -40.8%)
HDL-C: Insufficient	1 RCT, N = 62	Medium	Direct	Unknown	Imprecise	Undetected	None	Greater increase: (12%; 95% CI, 3.9 to 20.1)
Overall AE: Insufficient	1 RCT, N = 62	Medium	Direct	Unknown	Imprecise	Undetected	None	67% vs. 59%
AE withdrawal: Insufficient	1 RCT, N = 62	Medium	Direct	Unknown	Imprecise	Undetected	None	3% vs. 6%
Serious AE: Insufficient	1 RCT, N = 62	Medium	Direct	Unknown	Imprecise	Undetected	None	No events
Neurocognitive dysfunction: Insufficient	1 RCT, N = 62	Medium	Direct	Unknown	Imprecise	Undetected	None	NR
Injection site: Insufficient	1 RCT, N = 62	Medium	Direct	Unknown	Imprecise	Undetected	None	NR
Long-term evidence in mixed populations (OSLER-1 and OSLER-2)¹⁶								
Evolocumab 420 mg q 4w (OSLER-1) or 140 mg q 2w or 420 mg q 4w (OSLER-2) + standard therapy vs. standard therapy alone × 48w								
LDL-C lowering ability								
Evolocumab + standard therapy vs. standard therapy alone: Moderate	RCT: 2 (4,465)	Medium	Direct	Consistent	Precise	Undetected	None	Evolocumab reduced LDL-C by 61% (95% CI, 59 to 63, P < 0.001) at 12w and by 58.4% (95% CI NR, P < 0.001) at 48w as compared to standard therapy

APPENDIX B Strength of Evidence (continued)

Strength of Evidence Grade	Study Design; No. Studies (N)	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Other Issues	Finding
LDL-C lowering ability: % patients with LDL $\leq$ 100 or $\leq$ 70 at 12 weeks								
Evolocumab + standard therapy vs. standard therapy alone: Low	RCT: 2 (4,465)	Medium	Direct	Unknown	Precise	Undetected	None	% patients with LDL reduced to 100 mg/dL or lower (90.2% vs. 26.0%) or 70 mg/dL (73.6% vs. 3.8%)
HDL-C raising ability								
Evolocumab + standard therapy vs. standard therapy alone: Low	RCT: 2 (4,465)	Medium	Direct	Unknown	Precise	Undetected	None	Change from baseline in HDL-C at 12w was 8.7% in evolocumab group vs. 1.7% in standard therapy alone group ($P < 0.001$)
Overall adverse events								
Evolocumab + standard therapy vs. standard therapy alone: Low	RCT: 2 (4,465)	Medium	Direct	Unknown	Precise	Undetected	None	Any AEs occurred in 69.2% of evolocumab group and 64.8% of standard therapy alone group
Withdrawals due to adverse events								
Evolocumab + standard therapy vs. standard therapy alone: Insufficient	RCT: 2 (4,465)	Medium	Direct	Unknown	Imprecise	Undetected	None	2.4% of patients in evolocumab group prematurely discontinued study drug due to AEs (NA for standard therapy group)
Serious adverse events								
Evolocumab + standard therapy vs. standard therapy alone: Low	RCT: 2 (4,465)	Medium	Direct	Unknown	Precise	Undetected	None	No difference in % of patients with SAEs (7.5% for both groups)
Specific adverse events: neurocognitive events								
Evolocumab + standard therapy vs. standard therapy alone: Insufficient	RCT: 2 (4,465)	Medium	Direct	Unknown	Imprecise	Undetected	None	0.9% in evolocumab group vs. 0.3% in standard therapy group
Specific adverse events: injection-site reactions								
Evolocumab + standard therapy vs. standard therapy alone: Insufficient	RCT: 2 (4,465)	Medium	Direct	Unknown	Imprecise	Undetected	None	4.3% of patients in evolocumab group (NA for standard therapy group)
Specific adverse events: gastroenteritis								
Evolocumab + standard therapy vs. standard therapy alone: Insufficient	RCT: 2 (4,465)	Medium	Direct	Unknown	Imprecise	Undetected	None	1.5% of patients in evolocumab group vs. 0.8% in standard therapy group

APPENDIX B Strength of Evidence (continued)

Strength of Evidence Grade	Study Design; No. Studies (N)	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Other Issues	Finding
Specific adverse events: cardiovascular events								
Evolocumab + standard therapy vs. standard therapy alone: Insufficient	RCT: 2 (4,465)	Medium	Direct	Unknown	Imprecise	Undetected	None	CV events at 1 year reduced from 2.18% in standard therapy group vs. 0.95% in evolocumab group (HR evolocumab, 0.47; 95% CI, 0.28 to 0.78)

Note: Numbered footnotes refer to citations listed in References at the end of the appendices.

^aIncludes delirium (including confusion), cognitive and attention disorders and disturbances, dementia and amnesic disorders, disturbances in thinking and perception, and mental impairment disorders.

^bIncludes injection-site rash, inflammation, pruritus, reaction, or urticaria.

AE = adverse events; CI = confidence interval; CV = cardiovascular; EPC = Evidence-based Practice Center; GI = gastrointestinal; HDL-C = high-density lipoprotein cholesterol; HR = hazard ratio; LDL-C = low-density lipoprotein-cholesterol; NA = not available; NR = not reported; NS = not sufficient; RCT = randomized controlled trial; RR = relative risk.

REFERENCES FOR APPENDICES A AND B

- Cannon CP, Cariou B, Blom D, et al. Efficacy and safety of alirocumab in high cardiovascular risk patients with inadequately controlled hypercholesterolaemia on maximally tolerated doses of statins: the ODYSSEY COMBO II randomized controlled trial. *Eur Heart J*. 2015;36(19):1186-94.
- Kereiakes DJ, Robinson JG, Cannon CP, et al. Efficacy and safety of the proprotein convertase subtilisin/kexin type 9 inhibitor alirocumab among high cardiovascular risk patients on maximally tolerated statin therapy: the ODYSSEY COMBO I study. *Am Heart J*. 2015;169(6):906-15.e913.
- McKenney JM, Koren MJ, Kereiakes DJ, Hanotin C, Ferrand A-C, Stein EA. Safety and efficacy of a monoclonal antibody to proprotein convertase subtilisin/kexin type 9 serine protease, SAR236553/REGN727, in patients with primary hypercholesterolemia receiving ongoing stable atorvastatin therapy. *J Am Coll Cardiol*. 2012;59(25):2344-53.
- Robinson JG, Farnier M, Krempf M, et al. Efficacy and safety of alirocumab in reducing lipids and cardiovascular events. *N Engl J Med*. 2015;372(16):1489-99.
- Roth EM, McKenney JM, Hanotin C, Asset G, Stein EA. Atorvastatin with or without an antibody to PCSK9 in primary hypercholesterolemia. *N Engl J Med*. 2012;367(20):1891-900.
- Stein EA, Gipe D, Bergeron J, et al. Effect of a monoclonal antibody to PCSK9, REGN727/SAR236553, to reduce low-density lipoprotein cholesterol in patients with heterozygous familial hypercholesterolaemia on stable statin dose with or without ezetimibe therapy: a phase 2 randomised controlled trial. *Lancet*. 2012;380(9836):29-36.
- Stein EA, Mellis S, Yancopoulos GD, et al. Effect of a monoclonal antibody to PCSK9 on LDL cholesterol. *N Engl J Med*. 2012;366(12):1108-18.
- 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):1809-19.
- Giugliano RP, Desai NR, Kohli P, et al. Efficacy, safety, and tolerability of a monoclonal antibody to proprotein convertase subtilisin/kexin type 9 in combination with a statin in patients with hypercholesterolaemia (LAPLACE-TIMI 57): a randomised, placebo-controlled, dose-ranging, phase 2 study. *Lancet*. 2012;380(9858):2007-17.
- Desai NR, Giugliano RP, Zhou J, et al. AMG 145, a monoclonal antibody against PCSK9, facilitates achievement of national cholesterol education program-adult treatment panel III low-density lipoprotein cholesterol goals among high-risk patients: an analysis from the LAPLACE-TIMI 57 trial (LDL-C assessment with PCSK9 monoclonal antibody inhibition combined with statin therapy-thrombolysis in myocardial infarction 57). *J Am Coll Cardiol*. 2014;63(5):430-33.
- Hirayama A, Honarpour N, Yoshida M, et al. Effects of evolocumab (AMG 145), a monoclonal antibody to PCSK9, in hypercholesterolemic, statin-treated Japanese patients at high cardiovascular risk—primary results from the phase 2 YUKAWA study. *Circ J*. 2014;78(5):1073-82.
- Raal F, Scott R, Somaratne R, et al. Low-density lipoprotein cholesterol-lowering effects of AMG 145, a monoclonal antibody to proprotein convertase subtilisin/kexin type 9 serine protease in patients with heterozygous familial hypercholesterolemia: the Reduction of LDL-C with PCSK9 Inhibition in Heterozygous Familial Hypercholesterolemia Disorder (RUTHERFORD) randomized trial. *Circulation*. 2012;126(20):2408-17.
- Raal FJ, Stein EA, Dufour R, et al. PCSK9 inhibition with evolocumab (AMG 145) in heterozygous familial hypercholesterolaemia (RUTHERFORD-2): A randomised, double-blind, placebo-controlled trial. *Lancet*. 2015;385(9965):331-40.
- Raal FJ, Honarpour N, Blom DJ, et al. Inhibition of PCSK9 with evolocumab in homozygous familial hypercholesterolaemia (TESLA Part B): A randomised, double-blind, placebo-controlled trial. *Lancet*. 2015;385(9965):341-50.
- Robinson JG, Nedergaard BS, Rogers WJ, et al. Effect of evolocumab or ezetimibe added to moderate- or high-intensity statin therapy on LDL-C lowering in patients with hypercholesterolemia: the LAPLACE-2 randomized clinical trial. *JAMA*. 2014;311(18):1870-82.
- Sabatine MS, Giugliano RP, Wiviott SD, et al. Efficacy and safety of evolocumab in reducing lipids and cardiovascular events. *N Engl J Med*. 2015;372(16):1500-09.
- Stroes E, Colquhoun D, Sullivan D, et al. Anti-PCSK9 antibody effectively lowers cholesterol in patients with statin intolerance: the GAUSS-2 randomized, placebo-controlled phase 3 clinical trial of evolocumab. *J Am Coll Cardiol*. 2014;63(23):2541-48.
- Sullivan D, Olsson AG, Scott R, et al. Effect of a monoclonal antibody to PCSK9 on low-density lipoprotein cholesterol levels in statin-intolerant patients: the GAUSS randomized trial. *JAMA*. 2012;308(23):2497-506.