Drug Class Review

Proprotein Convertase Subtilisin Kexin type 9 (PCSK9) Inhibitors

Expanded Scan Report

April 2017

Last Report: Original Report, July 2015

Last Preliminary Update Scan: Preliminary Scan Report #1

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Elena Inouye, PharmD (c)
Ryan Stoner, PhD
Ian Blazina, MPH
Marian McDonagh, PharmD

Drug Effectiveness Review Project
Marian McDonagh, PharmD, Principal Investigator

Pacific Northwest Evidence-based Practice Center
Roger Chou, MD, Director
Marian McDonagh, PharmD, Associate Director

Oregon Health & Science University

OBJECTIVE

The purpose of this expanded version of a preliminary updated literature scan is to provide an overview of the volume and nature of new research that has emerged subsequent to the previous full review, with some additional features to allow more insight into the potential impact of the new evidence (e.g. quality assessment and key findings).

In consultation with DERP participating organization representatives, methods and scope for this expanded scan were developed. This scan on proprotein convertase subtilisin kexin type 9 (PCSK9) inhibitors focuses on trials that fill evidence gaps present in the last report (July 2015). Emphasis is placed on head-to-head trials and health outcomes. Comprehensive review and synthesis of the new research presented in this report, along with previous evidence, would be included in a full update of the report.

Dates of Previous Reports

Original Report: July 2015 (searches through February 2015)

Dates of Previous Preliminary Update Scans

Scan #1: March 2017 (searches through February 2017)

Scope and Key Questions *(last report)*

1. What are the comparative benefits and harms of PCSK9 inhibitors in patients with heterozygous and homozygous familial hypercholesterolemia?

2. What are the comparative benefits and harms of PCSK9 inhibitors in patients with hypercholesterolemia who are unable to use statins due to intolerance or any other reasons?

3. What are the comparative benefits and harms of PCSK9 inhibitors in patients with non-familial hypercholesterolemia who have not achieved LDL-C <100 mg/dL or <70 mg/dL with their current lipid lowering regimen (e.g., statin, with or without ezetimibe, etc.)?

4. Do the comparative benefits and harms of PCSK9 inhibitors differ when used in different patient subgroups based on demographics, socioeconomic status, other medications, or comorbidities?

Inclusion Criteria *(last report)*

Populations

- Patients with heterozygous and homozygous familial hypercholesterolemia.
- Patients with hypercholesterolemia who are unable to use statins due to intolerance or any other reasons.
- Patients with non-familial hypercholesterolemia who have not achieved LDL-C <100 mg/dL or <70 mg/dL.

Interventions

Table 1. Included interventions

Generic Name	Trade Name	FDA Approval	Dose and Form
Alirocumab	Praluent™	7/24/2015	75 mg/mL, 150 mg/mL injection
Evolocumab	Repatha™	8/27/2015 7/11/2016	140 mg/mL injection 420 mg Pushtronex™ (on-body infuser with prefilled cartridge)

Outcomes

In the full report, the primary effectiveness outcomes included survival and health events (reduction in nonfatal myocardial infarction (MI), coronary heart disease (CHD), mortality (CHD and all-cause), stroke, and need for revascularization (including coronary artery bypass grafting, angioplasty, and coronary stents), LDL-C lowering ability, and HDL-C raising ability. Harms outcomes include overall adverse events, withdrawals due to adverse events, serious adverse events, and specific adverse events, including, but not limited to, serious hypocholesterolemia, neurocognitive dysfunction, injection site reactions, nasopharyngitis, gastrointestinal disturbance, etc.).

Methods for Expanded Scan

To identify new drugs, we searched the FDA website and CenterWatch. To identify relevant studies, we searched Ovid MEDLINE® from June 2016 through March 2017 for randomized controlled trials (RCTs) of the new PCSK9 inhibitors. Any trials of new drugs identified in prior scans were also included. We searched for relevant comparative effectiveness reviews using DERP standards.[1] We included primary publications of head-to-head RCTs, but for drugs without head-to-head evidence we included placebo-controlled trials. Secondary publications (e.g. subgroup analyses) were screened to identify any that resulted in strongly differing results compared to the overall trial. One reviewer assessed abstracts of citations identified from literature searches for inclusion, using the criteria described above. A single reviewer, using DERP methodology, assessed quality of included studies. A second reviewer reviewed any study rated poor quality, and any differences in judgment resolved through consensus. For fair- or good-quality trials, we abstracted key information, including:

- Proportion of participants achieving LDL-C goal (preferred) or change in calculated LDL-C from baseline. Cardiovascular (CV) outcomes were reported if available.
- Change in HDL-C from baseline
- Serious adverse events
- Withdrawals due to adverse events
- The author's conclusions statement

RESULTS

New Drugs or Formulations

Identified Since the Last Update Report

According to FDA documents, a new delivery mechanism of evolocumab, Pushtronex™ (evolocumab 420 mg delivered via an on-body infuser with prefilled cartridge) was approved in July 2016. No studies utilizing this new delivery system were identified in this scan.

New Serious Harms (Boxed Warnings)

Identified Since the Last Update Report

None.

New Comparative Effectiveness Reviews

Identified Since the Last Update Report

The Preliminary Update Scan in March 2017 identified 1 potentially relevant comparative effectiveness review from the Canadian Agency for Drugs and Technologies in Health (CADTH) published in December 2015. The review includes comparative evidence on lipid measures and adverse events of both alirocumab and evolocumab, but lacks data on long-term efficacy and safety.

New Evidence: Randomized Controlled Trials

We identified 10 RCTs that met our criteria. Two trials studied evolocumab and 8 trials studied alirocumab. The FOURIER evolocumab study is the first to assess health outcomes as primary outcomes. The remaining 9 RCTs provide data for populations with evidence gaps in the previous report. ODYSSEY MONO had 2 publications, both by the same author but in different years. Duplicate data was presented and only data from the original 2014 publication was abstracted for this expanded scan. ODYSSEY FH I and II were published in one publication. Although the two studies had similar study design and objectives, the data were not pooled. As such, each study is presented independently in this expanded scan. Table 2 highlights pertinent study characteristics. Further details on the assessments of study quality are available in Appendix A.

Table 2. Study Characteristics

Study	N Mean Age	Intervention Duration	Population	Overall Quality
Patients with Cardiovascular Risk and LDL-C ≥70 mg/dL				
Bays, 2015 ODYSSEY OPTIONS I	N=355 62.8 years	Alirocumab add-on 24 weeks	• Very high CVD risk and LDL-C ≥70 mg/dL • High CVD risk and LDL-C ≥100 mg/dL	Good
Farnier, 2016 ODYSSEY OPTIONS II	N=305 60.9 years	Alirocumab add-on 24 weeks	• Very high CVD risk and LDL-C ≥70 mg/dL • High CVD risk and LDL-C ≥100 mg/dL	Good

Study	N Mean Age	Intervention Duration	Population	Overall Quality
Roth, 2014 Roth, 2015 ODYSSEY MONO	N=103 60.2 years	Alirocumab 24 weeks	• Moderate CVD risk, defined by a 10-year risk of fatal CV events ≥ 1% and < 5% per European Systemic Coronary Risk Estimation	Good
Sabatine, 2017 FOURIER	N=27,654 62.5 years	Evolocumab add-on 48 weeks, 26 months follow-up	Clinically evident atherosclerotic CV disease and at least atorvastatin 20 mg daily with either: • Fasting LDL-C ≥70mg/dL OR • Non-HDL ≥100mg/dL	Good
Patients with Statin Intolerance				
Moriarty, 2015 ODYSSEY ALTERNATIVE	N=361 63.4 years	Alirocumab 24 weeks	Statin intolerance due to muscle symptoms and either: • Very high CVD risk and LDL-C ≥70 mg/dL OR • Moderate to high CVD risk and LDL-C ≥100 mg/dL	Fair
Nissen, 2016 GAUSS-3 (Phase B)	N=218 58.8 years	Evolocumab 24 weeks	LDL-C above target level for the appropriate CHD risk category[a] and either: • Intolerance to ≥3 statins OR • Intolerance to atorvastatin 10 mg + one other statin	Good
Patients with Heterozygous Familial Hypercholesterolemia (heFH)				
Ginsberg, 2016 ODYSSEY HIGH FH	N=107 50.6 years	Alirocumab add-on 24-78 weeks	• History of heFH with LDL-C ≥ 160 mg/dL on max-tolerated statin ± other lipid-lowering therapy	Poor
Kastelein, 2015 ODYSSEY FH I	N = 486 52.0 years	Alirocumab add-on 24 weeks	History of heFH on max-tolerated statin ± other lipid-lowering therapy with either: • History of CVD and LDL-C ≥ 70 mg/dL OR • No history of CVD and LDL-C ≥ 100 mg/dL	Good
Kastelein, 2015 ODYSSEY FH II	N = 249 53.2 years	Alirocumab add-on 24 weeks	History of heFH on max-tolerated statin ± other lipid-lowering therapy with either: • History of CVD and LDL-C ≥ 70 mg/dL OR • No history of CVD and LDL-C ≥ 100 mg/dL	Good
Mixed Patient Population				
Teramoto, 2016 ODYSSEY JAPAN	N=216 60.8 years	Alirocumab add-on 24-52 weeks	Stable daily statin ≥ 4 weeks and one of the following: • History of heFH and LDL-C ≥ 100 mg/dL OR • History of CAD and LDL-C ≥ 100 mg/dL OR • JAS[b] category III and LDL-C ≥ 120 mg/dL	Fair

[a] National Cholesterol Education Project Adult Treatment Panel III
[b] Japan Atherosclerosis Society

Patients with Cardiovascular Risk and LDL-C ≥70 mg/dL

Cardiovascular Outcomes

The good-quality FOURIER trial (N=27,654) found that evolocumab reduced major cardiovascular (CV) events significantly more than placebo.[2] The composite of major CV events included cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, and coronary revascularization. Refer to Table 2 for a detailed summary of results. All patients received statin therapy throughout the trial, and rates of concurrent ezetimibe use were similar across treatment and placebo arms. This is the first trial to assess health outcomes of evolocumab as the primary efficacy endpoint. The magnitude of risk reduction with respect to major CV events increased over time, from 12% in the first year to 19% in the second year. Individual outcomes of myocardial infarction, stroke, and coronary revascularization were reduced in those treated with evolocumab. However, evolocumab had no observed effect on cardiovascular death or any other individual outcomes. There was no significant difference in the percentage of patients with serious adverse events or those withdrawing due to adverse events.

The effect of alirocumab on CV events is being assessed in the ODYSSEY OUTCOMES trial with an estimated completion date of December 2017.

Table 2. Summary of Results of the FOURIER Study

Study	Intervention	Benefit Outcomes	Harms Outcomes	Author's Conclusions
Sabatine, 2017 FOURIER N=27,654 48 weeks, 26 months follow-up	Evolocumab 140 mg Q2W or 420 mg QMO add-on vs. Placebo injection add-on	Evolocumab vs. placebo **Primary -** *Major CV events* 9.8% (1,344/13,784) vs. 11.3% (1,563/13,780) HR 0.85; 95% CI; 0.79 to 0.92 **Secondary -** *Composite of CV death, MI, or stroke* 5.9% (816/13,784) vs. 7.4% (1013/13,780) HR 0.80; 95% CI, 0.73 to 0.88	Evolocumab vs. placebo **Serious Adverse Events** 24.8% (3410/13,769) vs. 24.7% (3404/13,756) **Withdrawals due to Adverse Events** 4.6% (628/13,769) vs. 4.2% (581/13,756)	"inhibition of PCSK9 with evolocumab on a background of statin therapy lowered LDL cholesterol levels to a median of 30 [mg/dL] and reduced the risk of cardiovascular events. These findings show that patients with atherosclerotic cardiovascular disease benefit from lowering of LDL cholesterol levels below current targets."

Lipid Outcomes

Three good-quality RCTs evaluated the lipid-lowering effects of alirocumab in patients with moderate, high, and very-high CVD risk. ODYSSEY OPTIONS I and II (N=355, N=305) compared alirocumab versus ezetimibe versus higher intensity statin in patients with current statin use. [3,4] These trials addressed the criticism of previous trials in which many patients in the control group had not been given truly intensive statin therapy. Compared to previous studies which allowed for concomitant statins in a range of dosages, ODYSSEY OPTIONS I and II set parameters for specific statin drug, dose, and duration prior to randomization. Refer to Table 3 for a detailed summary of treatment arms and results. Add-on alirocumab had higher proportions of patients achieving LDL-C goals compared to add-on ezetimibe or intensified statin therapy. However, for patients taking rosuvastatin 20 mg, the difference between add-on alirocumab and add-on ezetimibe was not significant. Add-on alirocumab also increased HDL-C levels, but this finding was not significant against all treatment arms. Alirocumab patients not meeting LDL-C goals at the Week 8 checkpoint experienced a dose increase to 150 mg every 2 weeks starting at

Week 12. In OPTIONS I, fewer patients in the atorvastatin 20 mg arm had a dose increase than the atorvastatin 40 mg arm. Study authors attributed this difference to the higher baseline LDL-C levels and greater proportion of patients with history of CVD in the atorvastatin 40 mg group. In OPTIONS II, data from the dose increase arms were pooled and study authors did not provide additional comment.

ODYSSEY MONO (N=103) compared *monotherapy* alirocumab 75 to 150 mg every 2 weeks with ezetimibe 10 mg daily in patients with moderate cardiovascular risk.[5,6] No additional lipid-lowering agents were allowed. Both the moderate CV risk population and monotherapy intervention are new since the last report. While alirocumab had a significant difference on lowering LDL-C levels, there was no significant difference in changes in HDL-C levels between alirocumab and ezetimibe monotherapies. Refer to Table 3 for a detailed summary of results. There was no difference in the percentage of patients with serious adverse events or those withdrawing due to adverse events for any of the three trials.

Evidence for evolocumab in this population was previously reported in the Original Report, and no new RCTs were identified.

Table 3. Summary of Results in Patients with Cardiovascular Risk

Study	Intervention	Benefit Outcomes	Harms Outcomes	Author's Conclusions
Bays, 2015 ODYSSEY OPTIONS I N=355	Entry statin of 20 mg atorvastatin Alirocumab 75 mg[b] Q2W vs. Ezetimibe 10 mg vs. Atorvastatin 40 mg Entry statin of 40 mg atorvastatin Alirocumab 75 mg[c] Q2W vs. Ezetimibe 10 mg vs. Atorvastatin 80 mg vs. Rosuvastatin 40 mg 24 weeks	Alirocumab vs. Ezetimibe vs. Double atorvastatin vs. Rosuvastatin **Proportion achieving LDL-C goal[a]** 20 mg atorvastatin: 87.2% (48/55) vs. 68.4% (36/53); p=0.028 vs. 34.5% (18/53); p<0.0001 vs. NA 40 mg atorvastatin: 84.6% (39/46) vs. 65.1% (30/46); p=0.0011 vs. 18.5% (9/47); p<0.0001 vs. 62.2% (28/45); p=0.0025 **Change in HDL-C** 20 mg atorvastatin: 4.8% vs. -0.1% vs. 1.9% vs. NA 40 mg atorvastatin: 7.7% vs. 2.0% vs. 4.7% vs. 5.7%	Pooled alirocumab vs. Pooled ezetimibe vs. Pooled statin only **Serious adverse events**: 3.8% (4/104) vs. 6.9% (7/101) vs. 5.4% (8/149); p=0.6036 **Withdrawals due to adverse events**: 6.7% (7/104) vs. 4.0% (4/101) vs. 5.4% (8/149); p=0.6950	"Adding alirocumab to atorvastatin provided significantly greater LDL-C reductions vs adding ezetimibe, doubling atorvastatin dose, or switching to rosuvastatin and enabled greater LDL-C goal achievement."

Study	Intervention	Benefit Outcomes	Harms Outcomes	Author's Conclusions
Farnier, 2016 ODYSSEY OPTIONS II N=305	Entry statin of 10 mg rosuvastatin Alirocumab 75 mg[d] Q2W vs. Ezetimibe 10 mg vs. Rosuvastatin 20 mg Entry statin of 20 mg rosuvastatin Alirocumab 75 mg[d] Q2W vs. Ezetimibe 10 mg vs. Rosuvastatin 40 mg 24 weeks	Alirocumab vs. Ezetimibe vs. Double rosuvastatin **Proportion achieving LDL-C goal[a]** 10 mg rosuvastatin: 84.9% (41/48) vs. 57.2% (27/47); p=0.0007 vs. 45.0% (22/48); p<0.0001 20 mg rosuvastatin: 66.7% (35/53) vs. 52.2% (26/50); p=0.1177 vs. 40.1% (21/52); p=0.0022 **Change in HDL-C** 10 mg rosuvastatin 9.1% vs. 4.0%; p=0.1491 vs. 1.7%; p=0.0311 20 mg rosuvastatin 7.2% vs. -1.8%; p=0.0072 vs. 1.5%; p=0.0866	Pooled alirocumab vs. Pooled ezetimibe vs. Pooled double rosuvastatin **Serious adverse events**: 5.8% (6/103) vs. 7.9% (8/101) vs. 7.9% (8/101) **Withdrawals due to adverse events**: 4.9% (5/103) vs. 7.9% (8/101) vs. 5.0% (5/101)	"The addition of alirocumab to rosuvastatin provided incremental LDL-C lowering versus adding ezetimibe or doubling the rosuvastatin dose."
Roth, 2014 Roth, 2015 ODYSSEY MONO N=103	Alirocumab 75 mg[e] Q2W vs. Ezetimibe 10 mg/d 24 weeks	Alirocumab vs. Ezetimibe **Change in LDL-C** -47.2% vs. -15.6%; p<0.0001 **Change in HDL-C** 6.0% vs. 1.6%; p=0.1116	Alirocumab vs. Ezetimibe **Serious adverse events**: 1.9% (1/52) vs. 2.0% (1/51) **Withdrawals due to adverse events**: 9.6% (5/52) vs. 7.8% (4/51)	"Alirocumab demonstrated significantly greater LDL-C lowering versus ezetimibe after 24 weeks with the lower 75 mg Q2W dose sufficient to provide ≥50% LDL-C reduction in the majority of the patients. Adverse events were comparable between groups."

[a] Goals defined as LDL-C <70 mg/dL or <100 mg/dL for very high risk or high risk patients, respectively
[b,c,d,e] Dose increased to 150 mg Q2W in [b]8.0% and [c]20.9% of patients; [d]17 patients of pooled group; [e]14 patients

Patients with Statin Intolerance

Cardiovascular Outcomes

No studies identified.

Lipid Outcomes

Two RCTs, one for alirocumab and one for evolocumab, assessed the efficacy and safety in patients with statin intolerance.[7,8] Each study had unique definitions for statin intolerance in attempt to address criticism of prior studies that the definition of statin intolerance was too broad. Both studies showed that PCSK9 inhibitor therapy had a statistically significant difference in improving LDL-C levels without significant differences in serious adverse events or withdrawals due to adverse events compared with ezetimibe. Alirocumab was also compared to a statin re-challenge with atorvastatin for adverse events. Detailed results of each study are summarized in Table 4. The fair-quality ODYSSEY ALTERNATIVE (N=361) is the first trial of alirocumab in the statin-intolerance population.[7] The study defined statin intolerance as inability to tolerate 2 or

more statins due to muscle symptoms with 1 of the statins having been discontinued at the lowest-approved daily starting dose. A placebo run-in period prior to randomization excluded 6.4% of patients with non-statin-related muscle symptoms. Alirocumab was compared to ezetimibe or atorvastatin re-challenge. Lipid data was collected for the atorvastatin arm, but not reported. The study was assessed as fair-quality due to its overall 29.6% attrition rate without explanation. However, similar rates of adverse events and withdrawals due to adverse events were seen across all three treatment arms.

The good-quality GAUSS-3 trial defined statin intolerance as experiencing muscle-related adverse effects while taking atorvastatin only.[8] During the 20 week placebo crossover statin re-challenge Phase A (N=491), 17.3% of patients tolerated the statin re-challenge without muscle-related symptoms, 26.5% of patients had symptoms with placebo but not atorvastatin, and 9.8% of patients had symptoms with both placebo and atorvastatin. Patients included in Phase B (N=218) had to have had muscle-related adverse effects while taking atorvastatin but none while taking placebo. GAUSS-3 provides additional evidence for evolocumab in the statin-intolerant population; this study was longer in duration (24 weeks vs. 12 weeks) than previous studies, GAUSS and GAUSS-2, which were presented in the original report.

Table 4. Summary of Results in Patients with Statin Intolerance

Study	Intervention	Benefit Outcomes	Harms Outcomes	Author's Conclusions
Moriarty, 2015 ODYSSEY ALTERNATIVE N=361	Alirocumab 75 mg[b] Q2W Ezetimibe 10 mg Atorvastatin 20 mg 24 weeks	Alirocumab vs. Ezetimibe **Proportion achieving LDL-C goal[a]** 41.9% (52/126) vs. 4.4% (5/122); p<0.0001 **Change in HDL-C** 7.7% vs. 6.8%; p=0.70	Alirocumab vs. Ezetimibe vs. Atorvastatin **Serious adverse events**: 9.5% (12/126) vs. 8.1% (10/124) vs. 11.1% (7/63) **Withdrawals due to adverse events**: 18.3% (23/126) vs. 25.0% (31/124) vs. 25.4% (16/63)	"Alirocumab produced greater LDL-C reductions than ezetimibe in statin-intolerant patients, with fewer skeletal-muscle adverse events vs. atorvastatin."
Nissen, 2016 GAUSS-3 (Phase B) N=218	Evolocumab 420 mg QMO vs. Ezetimibe 10 mg/d 24 weeks	Evolocumab vs. Ezetimibe **Change in LDL-C** -52.8% vs. -16.7% (adjusted p<0.001) **Change in HDL-C** 7.4% vs. 2.9% (adjusted p=0.008)	Evolocumab vs. Ezetimibe **Total muscle-related events**: 20.7% (30/145) vs. 28.8% (21/73) **Withdrawals due to adverse events (muscle symptoms)**: 8.3% (12/145) vs. 6.8% (5/73)	"Among patients with statin intolerance related to muscle-related adverse effects, the use of evolocumab compared with ezetimibe resulted in a significantly greater reduction in LDL-C levels after 24 weeks. Further studies are needed to assess long-term efficacy and safety."

[a] Goals defined as LDL-C <70 mg/dL or <100 mg/dL for very high risk or moderate-high risk patients, respectively
[b] Dose increased to 150 mg Q2W in 54 patients

Patients with Heterozygous Familial Hypercholesterolemia

Cardiovascular Outcomes

No studies identified.

Lipid Outcomes

Four placebo-controlled RCTs assessing the efficacy and safety of add-on alirocumab treatment in patients with heterozygous familial hypercholesterolemia were identified since the original

report.[9-11] Compared to previous studies in this population, these trials were significantly larger in size (N>100 vs. N<80) and longer in duration (24-78 weeks vs. 12 weeks). Of the patients on alirocumab, 41.0% to 96.7% of patients reached their LDL-C goal compared to only 2.4% to 10.2% of patients on placebo. There were no significant differences in serious adverse effects or withdrawals due to adverse effects. The effect of alirocumab on HDL-C levels was significant in some studies, but nonsignificant in others. This result is consistent with previous findings. Detailed results of each study are summarized in Table 5. ODYSSEY FH series (HIGH FH, FH I, and FH II) had similar study designs.[12] All patients had concomitant statins at the maximum-tolerated dose. Additional lipid lowering therapies were allowed and percentages of patients taking additional therapies did not differ between the alirocumab and placebo groups. Good-quality ODYSSEY FH I (N=486) and FH II (N=249) were identical in design and only differed on their geographical location of sites. FH II was performed in Europe, whereas FH I encompassed sites in North America, Europe, and South Africa.[10] Results of both were published in the same publication, but were not pooled. Fair-quality ODYSSEY JAPAN (N=216) provides new evidence for the Japanese sub-population. Unlike the other new studies which focused solely on patients with heFH, ODYSSEY JAPAN had a broader scope of patients, including non-heFH patients with high CV risk.[11] ODYSSEY HIGH FH (N=107) was rated poor quality because of important differences at baseline following randomization, particularly the percentage of patients also taking ezetimibe (19.4% vs. 34.3%), and an unusually high attrition rate (35.5% overall).[9] The attrition was in part due to the closure of three sites due to serious breach of compliance with Good Clinical Practice, but the reporting of attrition was unclear and inconsistent throughout the manuscript.

Evidence for evolocumab in this population was previously reported in the Original Report, and no new RCTs were identified.

Table 5. Summary of Results in Patients with Familial Hypercholesterolemia

Study	Intervention	Benefit Outcomes	Harms Outcomes	Author's Conclusions
Kastelein, 2015 ODYSSEY FH I N = 486	Alirocumab 75 mg[c] Q2W add-on vs. Placebo injection add-on 24 – 78 weeks	Alirocumab vs. Placebo **Proportion achieving LDL-C goal[a]** **24 weeks:** 72.2% vs. 2.4%; p<0.0001 **Change in HDL-C** **24 weeks**: 8.8% vs. 0.8%; p<0.0001	Alirocumab vs. Placebo **Serious Adverse Events** 13.7% (44/322) vs. 13.5% (22/163) **Withdrawals due to Adverse Events** 4.0% (13/322) vs. 6.1% (10/163)	"In patients with heFH and inadequate LDL-C control at baseline despite maximally tolerated statin ± other LLT, alirocumab treatment resulted in significant LDL-C lowering and greater achievement of LDL-C target levels and was well tolerated."
Kastelein, 2015 ODYSSEY FH II N = 249	Alirocumab 75 mg[d] Q2W add-on vs. Placebo injection add-on 24 – 78 weeks	Alirocumab vs. Placebo **Proportion achieving LDL-C goal[a]** **24 weeks:** 81.4% vs. 11.3%; p<0.0001 **Change in HDL-C** **24 weeks**: 6.0% vs. -0.8%; p<0.05	Alirocumab vs. Placebo **Serious Adverse Events** 9.0% (15/167) vs. 9.9% (8/81) **Withdrawals due to Adverse Events** 3.6% (6/167) vs. 1.2% (1/81)	"In patients with heFH and inadequate LDL-C control at baseline despite maximally tolerated statin ± other LLT, alirocumab treatment resulted in significant LDL-C lowering and greater achievement of LDL-C target levels and was well tolerated."

Study	Intervention	Benefit Outcomes	Harms Outcomes	Author's Conclusions
Ginsberg, 2016 ODYSSEY HIGH FH N=107	Alirocumab 150 mg Q2W add-on vs. Placebo injection add-on 24 – 78 weeks	Alirocumab vs. Placebo **Proportion achieving LDL-C goal[a]** **24 weeks:** 41.0% vs. 5.7%; p=0.0016 **Change in HDL-C** **24 weeks:** 7.5% vs. 3.9%; p=0.2745	Alirocumab vs. Placebo **Serious Adverse Events** 13.9% (10/72) vs. 11.4% (4/35) **Withdrawals due to Adverse Events** 4.2% (3/72) vs. 5.7% (2/35)	"In patients with heFH and very high LDL-C baseline levels despite maximally tolerated statin ± other LLT, alirocumab 150 mg Q2W demonstrated significant reductions in LDL-C levels with 41% of patients achieving predefined LDL-C goals. Alirocumab was generally well tolerated."
Teramoto, 2016 ODYSSEY JAPAN N=216	Alirocumab 75 mg[e] Q2W add-on vs. Placebo injection add-on 24 weeks, 52 weeks for adverse events	Alirocumab vs. Placebo **Proportion achieving LDL-C goal[b]** **24 weeks:** 96.7% vs. 10.2%; p<0.0001 **Change in HDL-C** **24 weeks:** 7.9% vs. 2.1%; p=0.0020	Alirocumab vs. Placebo **Serious Adverse Events** 7.0% (10/143) vs. 12.5% (9/72) **Withdrawals due to Adverse Events** 4.9% (7/143) vs. 5.6% (4/72)	"In high-risk Japanese patients with hypercholesterolemia on stable statin therapy, alirocumab markedly reduced LDL-C vs. placebo and was well tolerated over 52 weeks."

[a] Goals defined as LDL-C <70 mg/dL or <100 mg/dL for with or without prior CV events, respectively
[b] Goals defined as LDL-C <100 mg/dL for heFH and CAD patients, <120 mg/dL for JAS category III patients
[c,d,e] Dose increased to 150 mg Q2W in [c]135 patients; [d]61 patients; [e]2 patients

SUMMARY

In this expanded scan, we identified 9 fair-and good-quality RCTs (N=30,054) of PCSK9 inhibitors, ranging in duration from 24 weeks to 26 months, which included new evidence on cardiovascular outcomes, new evidence of lipid outcomes in populations not previously studied, and additional evidence supplementing lipid outcomes in patients with statin-intolerance.

- Evolocumab treatment significantly reduced the composite risk of major CV events and reduced the composite risk of cardiovascular death, myocardial infarction, or stroke in patients with CVD. (1 trial, N=27,654, 26 months)
- Alirocumab is effective in lowering LDL-C levels as monotherapy or add-on therapy compared to ezetimibe or intensified statin therapy in patients with moderate to very high risk of CVD. Results confirm findings from previous studies with less intensive lipid-lowering comparators. (3 trials)
- Alirocumab and evolocumab are effective in lowering LDL-C for patients with statin-intolerance. Definitions of statin-intolerance were more precise and trials included a statin re-challenge. (2 trials)
    - Alirocumab trial was the first trial in statin-intolerant patients.
    - Evolocumab trial confirmed findings from previous trials, but with more accurately defined statin intolerance.
- New evidence in larger studies confirms findings of smaller studies that alirocumab significantly reduces LDL-C in patients with heterozygous familial hypercholesterolemia. (4 trials)

APPENDIX A. QUALITY ASSESSEMENT

All studies had blinded clinicians, outcome assessors, and patients. All studies analyzed with intention-to-treat.

Author, Year Study name	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Acceptable level of *overall* attrition (≤20%)?	Acceptable level of *differential* attrition (<10%)?	Overall quality
Bays, 2015 ODYSSEY OPTIONS I	Yes; IVRS/IWRS	Yes; IVRS/IWRS	Yes; some differences in age and % with CHD history, but similar LDL and HDL	Yes	Yes	Good
Farnier, 2016 ODYSSEY OPTIONS II	Yes; IVRS/IWRS	Yes; IVRS/IWRS	Yes; some differences in % with CHD history and % with T2DM history, but similar LDL and HDL	Yes	Yes For most comparisons between arms	Good
Ginsberg, 2016 ODYSSEY HIGH FH	Yes; IVRS/IWRS	Yes; IVRS/IWRS	No; baseline differences between alirocumab and placebo with respect to ezetimibe use (19.4% vs. 34.3%), male gender (48.6% vs. 62.9%) and coronary heart disease history (43.1% vs. 62.9%)	No. Only 73.6% alirocumab and 77.1% placebo completed the double-blind period (at least 76 week of exposure and visit week 78 performed)	Unclear	Poor
Kastelein, 2015 ODYSSEY FH I	Yes; IVRS/IWRS	Yes; IVRS/IWRS	Yes; Alirocumab had slightly less % of smokers and patients with T2DM but similar baseline LDL levels	Yes; >20% but majority were due to last visit outside of protocol visit window. Primary endpoint taken at 24 weeks, which was not the last visit so likely had negligible effect on primary outcomes	Yes	Good
Kastelein, 2015 ODYSSEY FH II	Yes; IVRS/IWRS	Yes; IVRS/IWRS	Yes; Alirocumab had slightly higher % patients with CVD risk factors but similar baseline LDL levels.	Yes	Yes	Good
Moriarty, 2015 ODYSSEY ALTERNATIVE	Yes	Unclear	Yes; some differences in CV risk levels of ezetimibe, but similar LDL and HDL	No, >20% attrition and minimal explanation reported	Yes	Fair
Nissen, 2016 GAUSS-3	Yes; IVRS/IWRS	Yes; IVRS/IWRS	Unclear; Ezetimibe had higher % of patients with 2 or more CV risk factors (60.3% vs. 41.4%) and higher % of women, but similar LDL, HDL, and history of statin intolerance	Yes	Yes	Good
Roth, 2014 ODYSSEY MONO	Yes; computerized	Yes	Yes	Yes	Yes	Good
Sabatine, 2017 FOURIER	Yes; IVRS/IWRS	Yes; IVRS/IWRS	Yes	Yes	Yes	Good
Teramoto, 2016 ODYSSEY JAPAN	Unclear	Unclear	Yes; Alirocumab had less % of patients with other CAD and higher % of diabetic patients, but similar baseline LDL and HDL	Yes	Yes	Fair

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