Are PCSK9 Inhibitors the Next Breakthrough in the Cardiovascular Field?

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ABSTRACT

Proprotein convertase subtilisin/kexin type 9 (PCSK9) binds to the low-density lipoprotein receptor, escorting it to its destruction in the lysosome and thereby preventing the recirculation of the low-density lipoprotein receptor to the hepatocyte cell surface. Both gain-of-function mutations in PCSK9 (causing marked increases in low-density lipoprotein cholesterol [LDL-C] concentration and premature atherosclerosis) and loss-of-function mutations (causing modest LDL-C reduction with low rates of coronary heart disease) have been described. Several monoclonal antibodies to PCSK9 have achieved LDL-C reductions of 50% to 70% across various patient populations and background lipid therapies. Phase 2/3 trials have demonstrated good tolerability without clear drug-related toxicity, although the number and duration of patients treated to date is modest. Currently, 4 phase 3 trials involving >70,000 patients are testing whether these drugs reduce cardiovascular events. The U.S. Food and Drug Administration is currently reviewing the existing data to determine whether these agents could be made available prior to the completion of these cardiovascular endpoint trials expected in 2018. (J Am Coll Cardiol 2015;65:2638–51)

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Two separate lines of research—the first exploring the structure and function of a family of serine proteases, known as proprotein convertases, that activate a wide variety of proteins regulating several key cellular pathways in humans and other organisms (1), and the second investigating genetic causes of familial hypercholesterolemia (FH) (2), were the parents of a potent new class of low-density lipoprotein cholesterol (LDL-C)-lowering drugs known as the proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors. In 2001, scientists at Millennium Pharmaceuticals discovered PCSK9 during studies of cerebellar neuron apoptosis, and the gene was characterized shortly thereafter, in 2003 (3). In parallel, research by the French Network for Autosomal Dominant Hypercholesterolemia (4), and independently in Utah (5), identified a third FH locus (the first 2 mutation loci map to the low-density lipoprotein receptor [LDL-R] and apolipoprotein B genes). In 2003, Abifadel et al. (6) were the first to describe mutations in the PCSK9 gene as a cause of FH. Studies in families from Utah (7), Norway (8), and the United Kingdom (9) provided confirmation that PCSK9 mutations were responsible for FH.

These initial discoveries that gain-of-function mutations in PCSK9 could cause hypercholesterolemia were quickly followed by reports that loss-of-function mutations in PCSK9 caused a reduction in cholesterol (10). The modest (15% to 28%), but lifelong, lowering of LDL-C appeared to confer considerable protection for Autosomal Dominant Hypercholesterolemia (4), and independently in Utah (5), identified a third FH locus (the first 2 mutation loci map to the low-density lipoprotein receptor [LDL-R] and apolipoprotein B genes). In 2003, Abifadel et al. (6) were the first to describe mutations in the PCSK9 gene as a cause of FH. Studies in families from Utah (7), Norway (8), and the United Kingdom (9) provided confirmation that PCSK9 mutations were responsible for FH.

These initial discoveries that gain-of-function mutations in PCSK9 could cause hypercholesterolemia were quickly followed by reports that loss-of-function mutations in PCSK9 caused a reduction in cholesterol (10). The modest (15% to 28%), but lifelong, lowering of LDL-C appeared to confer considerable protection...
from the development of coronary heart disease (CHD) (11). Thus, the stage was set for the development of therapies that could inhibit PCSK9, lower LDL-C, and, hopefully, reduce atherothrombotic events.

**ROLE OF PCSK9 IN REGULATING LDL-R METABOLISM**

The principal route of clearance of circulating LDL-C from the blood is via hepatocyte endocytosis—a process mediated by binding of LDL-C to LDL-Rs on the hepatocyte cell membrane (Central Illustration). The typical LDL-R is able to recirculate back to the cell surface up to 150 times, with PCSK9 playing a critical role in LDL-R metabolism. The catalytic subunit of PCSK9 binds to the epidermal growth factor-like domain of the LDL-R and then escorts the receptor to its degradation within the lysosome. Given the counter-regulatory role played by PCSK9, gain-of-function mutations in PCSK9 resulting in its overexpression lead to fewer functioning LDL-Rs and higher levels of circulating LDL-C. Conversely, loss-of-function mutations in PCSK9 result in lower LDL-C levels. PCSK9 can bind other proteins; appears to play additional, lesser roles in lipid metabolism; and its expression can be modified by a number of factors (e.g., statins increase PCSK9 levels)—further details can be found elsewhere (1,2).

**THERAPEUTIC INHIBITION OF PCSK9**

Studies in PCSK9 knockout mice demonstrated a 2- to 3-fold increase in LDL-Rs and a 25% to 50% decrease in circulating cholesterol (12). This led to the exploration of a number of methods to reduce PCSK9 levels and/or inhibit its function, including both oral and parenteral therapies (2) (Central Illustration). Both antisense oligonucleotides and small interfering ribonucleic acids have been studied in pre-clinical and phase 1 human studies. Mimetic peptides, LDL-R antagonists, small molecules, and gene silencing approaches to modulate PCSK9 are in earlier stages of development. A number of approaches using novel small molecules have been described, including the use of epidermal growth factor-A mimetics to block PCSK9 binding of the LDL-R (13) and inhibitors of pro-PCSK9 autoprocessing and/or secretion (14); unfortunately, the PCSK9-LDL-R complex has a relatively flat surface that makes binding by a small molecule inhibitor challenging (15). However, parenteral monoclonal antibodies (MoAbs) have been the most successful strategy to date and are now in late-stage (phase 3 clinical trials) testing (Table 1); thus, they are the focus of this paper.

**PCSK9 MONOCLONAL ANTIBODIES**

The first studies in humans in healthy volunteers (16,17) were conducted with the fully human PCSK9 MoAb REGN727 (hereafter alirocumab) and, shortly thereafter, with the fully human MoAb AMG145 (evolocumab [18]) and the humanized MoAb RN316 (bococizumab [19]). These studies demonstrated dose-dependent reductions in unbound PCSK9 levels beginning within hours after injection with top doses achieving unmeasurable PCSK9 levels for 2 weeks before returning to baseline >6 weeks following a single injection. Dose-dependent reduction in LDL-C (up to 70%), timing of nadir LDL-C (between 4 and 14 days), and delay in return to baseline LDL-C (2 to 8+ weeks) were observed with each of these MoAbs. More recently, data were presented with LY3015014, a humanized MoAb with a unique epitope that permits the normal proteolytic degradation of PCSK9 (unlike other MoAbs), thereby resulting in a more sustained lowering of LDL-C (20).

**PHASE 2 CLINICAL TRIALS**

Both alirocumab and evolocumab have been extensively evaluated in more than a dozen phase 2 trials exploring dose ranging and dose frequency, various patient populations, and adjunctive lipid-lowering therapies, with fewer studies available with bococizumab (Table 2). The top doses being developed of alirocumab (150 mg subcutaneously [SC] every 2 weeks) and evolocumab (140 mg SC every 2 weeks; 420 mg SC every 4 weeks) administered for 12 weeks reduce LDL-C by approximately 60% to 70% (75 to 140 mg/dl) at trough (17,18) and >90% (>100 mg/dl) at peak (21). The vast majority (70% to 90%) of patients with hyperlipidemia treated with statin therapy were able to achieve an LDL-C <70 mg/dl with alirocumab (22) and evolocumab (23,24), demonstrating the ability of these drugs to drive down levels of LDL-C to ranges not possible with existing therapies. A phase 2 trial with bococizumab in 351 patients with hypercholesterolemia reported LDL-C reductions of 53% (53 mg/dl) with 150 mg every 2 weeks and by 41% (45 mg/dl) with 300 mg every 4 weeks, adjusted for placebo (19). A phase 2 trial comparing LY3015014 with placebo in 527 patients with hypercholesterolemia treated with standard care (including statins) revealed reductions in LDL-C of up to 58% (~79 mg/dl) and 45% (~61 mg/dl) with administration every 4 and 8 weeks, respectively, adjusted for placebo (25).
In phase 2 studies, LDL-C was significantly and similarly lowered with alirocumab and evolocumab compared with placebo, whether patients were taking no, low-dose, or high-dose statins; taking ezetimibe; or had heterozygous FH. The findings appear consistent across major subgroups (e.g., age, sex, diabetes, risk level) with no significant treatment–subgroup interactions consistently reported. Longer-term follow-up (>1 year) demonstrated a persistent similar reduction in LDL-C as was observed in the 12-week studies.

In addition, evolocumab reduced LDL-C in the majority of patients with homozygous FH (26,27); the responders had partially functioning (2% to 25%) LDL-R. Genetic analyses in patients who did not respond to evolocumab demonstrated nonfunctioning LDL-Rs (<2% function) (26).

Both alirocumab and evolocumab also significantly reduce apolipoprotein B, total cholesterol, triglycerides, and non-high-density lipoprotein cholesterol (HDL); lipoprotein(a) (22,24,28,29), HDL, and
apolipoprotein A are minimally (if at all) increased (<10%), as would be expected given the mechanism of action of these drugs. No reduction in C-reactive protein has been reported, but it should be noted that the populations studied would be expected to have normal (or low) levels of C-reactive protein, and studies in patients post-acute coronary syndromes are ongoing.

No clear drug-related toxicities have been reported in the phase 2 studies, although the duration of therapy was generally short (12 weeks) and low-frequency, but clinically relevant signals cannot be excluded (30). One patient in an early phase 2 study of alirocumab developed a leukocytoclastic reaction (31); however, this has not been seen in subsequent trials. No neutralizing antibodies have been reported in the trials to date. A placebo-controlled study of evolocumab in patients who were intolerant of statins has shown no excess in myalgias or other serious adverse events compared with placebo (32). Other theoretical safety concerns (33) on the basis of other roles and targets of PCSK9 beyond LDL-R degradation include an increased risk for viral infections (because some LDL-Rs function as viral entry receptors), insulin resistance and glucose intolerance (reported in humans carrying the R46L PCSK9 loss-of-function-mutation (34)), and increased visceral adiposity, which is due to decreased free fatty acid clearance related to changes in other lipoproteins targeted by PCSK9 (35). Overall, across the phase 2 trials with a modest number of patient-years of follow-up, cardiovascular events were infrequent (30); longer-term safety experiences in a greater number of patients are discussed in the following section.

**PHASE 3 AND LONGER-TERM FOLLOW-UP STUDIES**

Multiple larger phase 3 studies with alirocumab and evolocumab evaluating lipid endpoints and longer-term follow-up studies have been published or presented (Table 3).

**PCSK9 MONOTHERAPY.** Similar to the phase 2 trials discussed previously, larger phase 3 trials with these 2 PCSK9 inhibitors have demonstrated consistent reductions in LDL-C across a variety of patients and background therapies. Both evolocumab and alirocumab have been studied as monotherapies versus ezetimibe (36,37). In 614 patients with baseline LDL-C 100 to 190 mg/dl, evolocumab reduced LDL-C at 12 weeks by 55% to 57% (~80 mg/dl) on average compared with placebo, whereas ezetimibe achieved an 18% to 19% (~26 mg/dl) reduction (36). Similarly, in a study of alirocumab monotherapy versus ezetimibe in 103 patients with a 1% to 5% 10-year risk of fatal cardiovascular events, alirocumab reduced LDL-C by 47% (66 mg/dl) at 24 weeks, compared with only 16% (22 mg/dl) for ezetimibe (37).

**COMBINATION WITH STATIN.** In 316 patients with established CHD or CHD risk equivalents and hypercholesterolemia, alirocumab reduced LDL-C at 24 weeks by 46% (46 mg/dl) more than placebo, with 75% of patients achieving an LDL-C <70 mg/dl (compared with 9% with placebo) (38). In a similar population of patients who were taking maximally tolerated statins, alirocumab reduced LDL-C by 30% (21 mg/dl) more than ezetimibe, permitted more patients to achieve an LDL-C <70 mg/dl than ezetimibe (77% vs. 46%), and had a similar safety profile to ezetimibe (39).

Evolocumab was compared with placebo and with ezetimibe in 2,067 patients with an LDL-C ≥150 mg/dl, all of whom were treated with either moderate or intensive statin therapy (40). For patients on a high-intensity statin (atorvastatin 80 mg or rosuvastatin 40 mg), evolocumab reduced the mean LDL-C compared with placebo at 10 and 12 weeks by 66% to 75% (56 to 70 mg/dl) with 140 mg every 2 weeks and by 63% to 75% (51 to 66 mg/dl) with 420 mg every 4 weeks. In patients receiving moderate-dose statins

<table>
<thead>
<tr>
<th><strong>TABLE 1</strong> Trial Acronyms</th>
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<tbody>
<tr>
<td><strong>DESCARTES</strong></td>
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<td><strong>EBBINGHAUS</strong></td>
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<td><strong>FOURIER</strong></td>
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<td><strong>GAUSS</strong></td>
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<td><strong>LAPLACE</strong></td>
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<td><strong>MENDEL</strong></td>
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<td><strong>ODYSSEY LONG TERM</strong></td>
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<td><strong>OSLER</strong></td>
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<td><strong>PROFICIO</strong></td>
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<td><strong>RUTHERFORD</strong></td>
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<td><strong>SPIRE</strong></td>
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<td><strong>TESLA</strong></td>
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<td><strong>TIMI</strong></td>
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<td><strong>YUKAWA</strong></td>
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LDL-C = low-density lipoprotein cholesterol; PCSK9 = proprotein convertase subtilisin/kexin type 9.
**TABLE 2 Phase 2 Trial Results**

<table>
<thead>
<tr>
<th>Trial Name (Ref. #)</th>
<th>N</th>
<th>Baseline LDL-C (mg/dl)</th>
<th>Drug and Dosing (mg)</th>
<th>LDL-C Reduction vs. Placebo</th>
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<tbody>
<tr>
<td>In combination with statin</td>
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<tr>
<td>McKenney et al. (72)</td>
<td>183</td>
<td>≥100, 127</td>
<td>Ali 50-150 Q2W</td>
<td>35%-67% at week 12</td>
</tr>
<tr>
<td>Roth et al. (73)</td>
<td>92</td>
<td>&gt;100, 123</td>
<td>Ali 150 Q2W</td>
<td>56% at week 8</td>
</tr>
<tr>
<td>LAPPLACE-TIMI 57 (21)</td>
<td>631</td>
<td>≥100, 123</td>
<td>Evo 70-140 Q2W</td>
<td>42%-66% at week 12</td>
</tr>
<tr>
<td>YUKAWA (74)</td>
<td>310</td>
<td>≥116, 143</td>
<td>Evo 70-140 Q2W</td>
<td>53%-69% at week 12</td>
</tr>
<tr>
<td>Ballantyne et al. (75)</td>
<td>351</td>
<td>≥80, 109</td>
<td>Boco 50-150 Q2W</td>
<td>35%-53% at week 12</td>
</tr>
<tr>
<td>Kastelein et al. (25)</td>
<td>527</td>
<td>N/A, 135</td>
<td>LY3015014 20-300 Q4W</td>
<td>23%-58% at week 16</td>
</tr>
<tr>
<td>Monotherapy</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>MENDEL (76)</td>
<td>406</td>
<td>100-190, 143</td>
<td>Evo 70-140 Q2W</td>
<td>37%-47% at week 12</td>
</tr>
<tr>
<td>Statin intolerance</td>
<td></td>
<td></td>
<td>Evo 280-420 Q4W</td>
<td>44%-53% at week 12</td>
</tr>
<tr>
<td>GAUSS (32)</td>
<td>160</td>
<td>&gt;Goal, 193</td>
<td>Evo 280-420 Q2W</td>
<td>26%-36% at week 12</td>
</tr>
<tr>
<td>Heterozygous familial hypercholesterolemia</td>
<td></td>
<td></td>
<td>Evo 420 Q2W + ezetimibe 10 QD</td>
<td>47% at week 12</td>
</tr>
<tr>
<td>Stein et al. (16)</td>
<td>77</td>
<td>≥100, 155</td>
<td>Ali 150 Q2W</td>
<td>57% at week 12</td>
</tr>
<tr>
<td>RUTHERFORD (77)</td>
<td>169</td>
<td>≥100, 156</td>
<td>Ali 150-300 Q4W</td>
<td>18%-32% at week 12</td>
</tr>
<tr>
<td>Homozygous familial hypercholesterolemia</td>
<td></td>
<td></td>
<td>Evo 350-420 Q4W</td>
<td>44%-56% at week 12</td>
</tr>
</tbody>
</table>

Trials appear in order of publication date; abstracts/presentations are listed after publications. *Change for baseline (no placebo group was tested).

Ali = alirocumab; Boco = bococizumab; Evo = evolocumab; LDL-C = low-density lipoprotein cholesterol; NA = not available (entry criteria specified diagnosis of high cholesterol); QD = daily; Q2W = biweekly; Q4W = every 4 weeks; Q8W = every 8 weeks; other abbreviations as in Table 1.

(atorvastatin 10 mg, rosuvastatin 5 mg, or simvastatin 40 mg), the corresponding reductions were 67% to 70% (75 to 84 mg/dl) and 63% to 69% (78 to 80 mg/dl) with evolocumab dosed every 2 and 4 weeks, respectively. Reductions with ezetimibe were less than one-half of that achieved with evolocumab, regardless of the background statin. On a background of high-intensity statin, the mean achieved LDL-C with evolocumab was 33 to 38 mg/dl, with >90% achieving an LDL-C <70 mg/dl.

**COMBINATION WITH EZETIMIBE.** In a 52-week placebo-controlled randomized trial of evolocumab in 901 patients with hypercholesterolemia treated with diet alone, atorvastatin 10 mg, atorvastatin 80 mg, or atorvastatin 80 mg + ezetimibe 10 mg (background therapy dependent upon Adult Treatment Panel 3 risk level), evolocumab reduced LDL-C by 57% (57 mg/dl) on average compared with placebo (range 49% to 62% across the various background therapies) after 52 weeks of therapy (41). The mean achieved LDL-C at week 52 ranged from 45 to 64 mg/dl with evolocumab, and the LDL-C was reduced <70 mg/dl in 82% of patients (compared with 6% with placebo). Among 189 patients who received atorvastatin 80 mg + ezetimibe 10 mg, the mean LDL-C values fell from 117 to 64 mg/dl with evolocumab versus 120 to 115 mg/dl with placebo, and 67% and 11% had an LDL-C <70 mg/dl at week 52, respectively.

**PATIENTS WITH STATIN INTOLERANCE.** Two phase 3 trials (42,43) in statin-intolerant patients have demonstrated the efficacy and tolerability of PCSK9 inhibitors in this challenging population. In a randomized placebo-controlled trial of 307 patients intolerant to 2 or more statins whose LDL-Cs were not at goal as defined by Adult Treatment Panel 4, both evolocumab 140 mg every 2 weeks and 420 mg every 4 weeks reduced LDL-C at 12 weeks by 53% to 56% (99 to 106 mg/dl) compared with 15% to 18% (30 to 36 mg/dl) for ezetimibe (42). Preliminary results of a placebo-controlled study of 314 patients with baseline LDL-C averaging 190 mg/dl who were intolerant of 2 or more statins (of which 1 was at a low dose) due to myalgia randomized to alirocumab (75 mg every 2 weeks with optional up-titration to 150 mg every 2 weeks), ezetimibe 10 mg daily, or atorvastatin 20 mg daily were reported at the 2014 American Heart...
**TABLE 3 Phase 3 and Long-Term Extension Trial Results**

<table>
<thead>
<tr>
<th>Trial Name</th>
<th>N</th>
<th>Baseline LDL-C Entry Criteria, Median (mg/dl)</th>
<th>Drug and Dosing (mg)</th>
<th>LDL-C Reduction vs. Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Monotherapy</strong></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>MENDEL-2 (36)</td>
<td>614</td>
<td>100-190, 143</td>
<td>Evo 140 Q2W</td>
<td>57% and 39%* at 10-12 weeks†</td>
</tr>
<tr>
<td>ODYSSEY MONO (78)</td>
<td>103</td>
<td>100-190, 140</td>
<td>Ali 75 Q2W</td>
<td>32%* at week 24</td>
</tr>
<tr>
<td><strong>In combination with statin</strong></td>
<td></td>
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<tr>
<td>LAPLACE-2 (40)</td>
<td>2,067</td>
<td>⩾ 150, 109</td>
<td>Evo 140 Q2W</td>
<td>66%-75% and 44%-46%* at weeks 10-12†</td>
</tr>
<tr>
<td>ODYSSEY COMBO I (39)</td>
<td>720</td>
<td>⩾ 70, 108</td>
<td>Ali 75 Q2W</td>
<td>30%* at week 12</td>
</tr>
<tr>
<td>ODYSSEY COMBO II (38)</td>
<td>316</td>
<td>⩾ 70, 97</td>
<td>Ali 75 Q2W</td>
<td>46% at week 24</td>
</tr>
<tr>
<td>YUKAWA-2 (79)</td>
<td>404</td>
<td>⩾ 100, N/A</td>
<td>Evo 140 Q2W</td>
<td>74%-75% at weeks 10-12; 75%-70% at week 12</td>
</tr>
<tr>
<td><strong>In addition to diet alone, statin, or statin + ezetimibe</strong></td>
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<tr>
<td>DESCARTES (41)</td>
<td>901</td>
<td>⩾ 75, 104</td>
<td>Evo 420 Q4W</td>
<td>49%-62% at week 52</td>
</tr>
<tr>
<td>ODYSSEY CHOICE I (80)</td>
<td>803</td>
<td>&gt; Goal, 122</td>
<td>Ali 75 Q2W</td>
<td>52%-59% at week 24</td>
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<tr>
<td><strong>Statin intolerance</strong></td>
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<tr>
<td>GAUSS-2 (42)</td>
<td>307</td>
<td>&gt; Goal, 193</td>
<td>Evo 140 Q2W</td>
<td>38%* at week 12; 38%* at weeks 10-12†</td>
</tr>
<tr>
<td>ODYSSEY ALTERNATIVE (44)</td>
<td>314</td>
<td>&gt; Goal, 191</td>
<td>Ali 75 Q2W</td>
<td>30%* at week 24</td>
</tr>
<tr>
<td>ODYSSEY CHOICE II (80)</td>
<td>233</td>
<td>&gt; Goal, 158</td>
<td>Ali 75 Q2W</td>
<td>56% at week 24</td>
</tr>
<tr>
<td>RUTHERFORD-2 (45)</td>
<td>331</td>
<td>⩾ 100, 154</td>
<td>Evo 140 Q2W</td>
<td>59% at 12 weeks; 60% at weeks 10-12†</td>
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<tr>
<td>ODYSSEY FH I and II (47)</td>
<td>735</td>
<td>⩾ 160, 141</td>
<td>Ali 75 Q2W</td>
<td>51%-58% at week 24</td>
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<tr>
<td><strong>Heterozygous familial hypercholesterolemia</strong></td>
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<tr>
<td>TESLA Part B (27)</td>
<td>50</td>
<td>⩾ 130, 347</td>
<td>Evo 420 Q4W</td>
<td>31% at week 12</td>
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<tr>
<td><strong>Homozygous familial hypercholesterolemia</strong></td>
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<tr>
<td><strong>Long-term extension studies</strong></td>
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<tr>
<td>OSLER-1 (48)</td>
<td>1,359</td>
<td>⩾ 100, 120</td>
<td>Evo 420 Q4W</td>
<td>52% at week 52 (vs. standard of care)</td>
</tr>
<tr>
<td>ODYSSEY LONG TERM (22)</td>
<td>2,341</td>
<td>⩾ 70, 122</td>
<td>Ali 150 Q2W</td>
<td>62% at week 24</td>
</tr>
</tbody>
</table>

Trials appear in order of publication date; abstracts/presentations are listed after publications. See Table 1 for some trial acronyms. *Versus ezetimibe 10 mg QD. †Mean of the reductions at weeks 10 and 12. ‡Dose adjusted to 150 mg Q2W if LDL-C not at target (target either < 70 or < 100 mg/dl, depending on risk) at week 12. §Dose adjusted to 75 mg if LDL-C < 25 mg/dl at weeks 8-12.

**ODYSSEY ALTERNATIVE** = Study of Alirocumab in Patients With Primary Hypercholesterolemia and Moderate, High, or Very High Cardiovascular (CV) Risk, Who Are Intolerant to Statins; **ODYSSEY CHOICE** = Study to Evaluate the Efficacy and Safety of an Every Four Weeks Treatment Regimen of Alirocumab in Patients With Primary Hypercholesterolemia; **ODYSSEY COMBO** = Efficacy and Safety of Alirocumab Versus Placebo on Top of Lipid-Modifying Therapy in Patients With High Cardiovascular Risk and Hypercholesterolemia; **ODYSSEY FH** = Efficacy and Safety of Alirocumab Versus Placebo on Top of Lipid-Modifying Therapy in Patients With Heterozygous Familial Hypercholesterolemia Not Adequately Controlled With Their Lipid-Modifying Therapy; **ODYSSEY MONO** = Efficacy and Safety of Alirocumab Versus Ezetimibe in Patients With Primary Hypercholesterolemia; other abbreviations as in Tables 1 and 2.

Association Scientific Sessions (44). Alirocumab not only was significantly more effective in reducing LDL-C (absolute decline of 84 mg/dl compared with 33 mg/dl for ezetimibe), but also had the lowest rate of muscle-related adverse events (33% vs. 41% ezetimibe [p = 0.10] vs. 46% atorvastatin [p = 0.04]).

**FAMILIAL HYPERCHOLESTEROLEMIA.** Evolocumab has completed separate phase 3 trials in patients with heterozygous (45) and with homozygous FH (27); alirocumab has been studied in patients with heterozygous FH in phase 3 (46). A placebo-controlled trial of 331 patients with heterozygous FH taking statin + additional lipid-lowering agents demonstrated that both evolocumab 140 mg every 2 weeks and 420 mg every 4 weeks significantly reduced LDL-C by approximately 60% (90 to 95 mg/dl) compared with placebo (45). Similar preliminary findings were reported with alirocumab at the European Society of Cardiology Congress in 2014 (47). Analyses of 2 trials, enrolling a total of 732 patients with heterozygous FH on a maximally-tolerated dose of statin ± other lipid-lowering therapy, showed 51% to 58% (66 to 85 mg/dl) reductions in LDL-C at 24 weeks with alirocumab compared with placebo. The only phase 3 trial conducted in patients with homozygous FH enrolled 50 patients with ≥4 weeks of a stable lipid regimen and demonstrated a 31% relative (93 mg/dl absolute) further reduction from
the baseline LDL-C with evolocumab compared with placebo (27).

**LONGER-TERM TREATMENT.** Larger and longer-term studies provide further information regarding the durability of lipid-lowering effects and safety of PCSK9 inhibitors. In the OSLER I (Open-Label Study of Long-Term Evaluation against LDL Cholesterol) study (48), 1,104 patients who completed 1 of 4 phase 2 studies with evolocumab entered an open-label controlled study comparing evolocumab 420 mg every 4 weeks plus standard of care (SOC) to SOC alone. The LDL-C reduction with evolocumab + SOC, as compared with SOC alone, remained constant at approximately 52% (~73 mg/dl) for the entire 52-week period. More patients receiving evolocumab achieved LDL-C <100 mg/dl (96% vs. 32%), <70 mg/dl (83% vs. 4%), <50 mg/dl (56% vs. 0.5%), and <25 mg/dl (12% vs. 0%) (p < 0.001 for each comparison with SOC alone). The tolerability of longer-term evolocumab was good (only 3.7% developed adverse events that led to discontinuation of evolocumab), and serious adverse events occurred in a similar number of patients who received evolocumab + SOC (7.1%) as with SOC alone (6.3%). Adverse events were not increased among the 98 patients receiving evolocumab who achieved an LDL-C <25 mg/dl compared with those achieving higher LDL-C levels or compared with patients receiving SOC only.

A pre-specified combined analysis of 4,465 patients who completed 1 of 12 phase 2 or 3 studies of evolocumab and who were then randomized to either evolocumab plus SOC versus SOC alone in an open-label extension study over an average of 11 months, was conducted across the OSLER 1 and 2 studies (24). Evolocumab 420 mg every 4 weeks reduced the average LDL-C by 61% from 120 to 48 mg/dl at 12 weeks. Adverse events (the primary study endpoint) occurred in 69% of patients treated with evolocumab versus 65% in the SOC group, with no difference in the rate of serious adverse events (7.5% in each group). Only 2.4% of patients in the evolocumab group stopped treatment due to an adverse event. Neurocognitive events were reported more frequently with evolocumab (0.9% vs. 0.3%), with no apparent relationship to the achieved LDL-C. The ongoing EBBINGHAUS (Evaluating PCSK9 Binding antiBody Influence on CoGnitive HeAlth in High cardiovascuLar Risk Subjects) study (NCT02207634) is prospectively evaluating this issue in a subgroup of patients with apparently normal cognitive function enrolled in a phase 3 cardiovascular outcomes study with evolocumab (49). The pre-specified composite of death, myocardial infarction, hospitalization for unstable angina, coronary revascularization, stroke, transient ischemic attack, and hospitalization for heart failure was reduced by 53% (95% confidence interval: 22% to 72%; p = 0.003) (Figure 1). Although promising, the modest number of cardiovascular events (n = 60), an exploratory, albeit adjudicated, endpoint in this analysis, requires confirmation in an adequately-powered trial.

In the ODYSSEY LONG TERM (Long-term Safety and Tolerability of Alirocumab in High Cardiovascular Risk Patients with Hypercholesterolemia Not Adequately Controlled With Their Lipid Modifying Therapy) placebo-controlled trial in 2,341 patients with hyperlipidemia on maximally tolerated statin who were at high risk for CHD, alirocumab reduced LDL-C by 62% at 24 weeks compared with placebo (achieved mean LDL-C 119 mg/dl with placebo vs. 48 mg/dl with alirocumab) (22). More patients achieved an LDL-C <70 mg/dl at week 24 with alirocumab compared with placebo (79% vs. 8%; p < 0.001). Patients in the alirocumab group had higher rates of injection-site reactions (5.9% vs. 4.2%), myalgia (5.4% vs. 2.9%), neurocognitive events (1.2% vs. 0.5%), and ophthalmologic events (2.9% vs. 1.9%) over a period of 78 weeks. As was observed with evolocumab, rates of adverse events among 575 (37%) patients who...
achieved an LDL-C <25 mg/dl on at least 2 consecutive readings was similar to the overall alirocumab group. In a post-hoc analysis of selected cardiovascular events with alirocumab, the time to first adjudicated major cardiovascular event (a composite of CHD death, myocardial infarction, ischemic stroke, or unstable angina requiring hospitalization) was less frequent with alirocumab than with placebo (hazard ratio: 0.52; 95% confidence interval: 0.31 to 0.90). Confirmation of these findings in a prospectively designed cardiovascular outcomes trial is needed, given the small number of events (n = 53) in this post-hoc analysis.

It is of interest to compare the reduction in cardiovascular events observed, given the degree of LDL-C reduction obtained with PCSK9 inhibitors, in these 2 recent analyses in the context of the relationship between LDL-C reduction and major vascular events reported in the CTT (Cholesterol Treatment Trialists) meta-analysis (50). The latter analysis demonstrated a 22% reduction in major vascular events for each 1 mmol/l reduction in LDL-C in an analysis of >170,000 patients from 27 randomized trials of cholesterol lowering—a relationship that remained consistent across a broad range of baseline LDL-C values. Given the LDL-C reduction (70 to 72 mg/dl or 1.8 to 1.9 mmol/l) observed in the OSLER 1 and 2 and ODYSSEY LONG-TERM analyses, the CTT meta-analysis would have predicted a reduction of just over 40% in major vascular events—a value that falls well within the confidence interval of the observed results. Ongoing phase 3 trials that are adequately powered to examine cardiovascular events are ongoing.

**PHASE 3 CLINICAL OUTCOME TRIALS**

There are 4 ongoing large, placebo-controlled phase 3 trials in >70,000 patients investigating whether PCSK9 inhibitors on a background of statin reduce cardiovascular events (Figure 2). In the ODYSSEY Outcomes trial (51), 18,000 patients 1 to 12 months post-acute coronary syndrome treated with maximally-tolerated atorvastatin or rosuvastatin are being randomized to subcutaneous alirocumab or placebo every 2 weeks. All patients must have either an LDL-C ≥70 mg/dl, non-HDL total cholesterol ≥100 mg/dl, or apolipoprotein B ≥80 mg/dl. The initial dose of alirocumab is 75 mg, with drug discontinuation for LDL-C <15 mg/dl on repeated measurements, and up-titration to 150 mg for LDL-C ≥50 mg/dl.

In the FOURIER (Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk) trial (52), 27,500 stable patients with prior MI, ischemic stroke, or peripheral arterial disease treated with optimal-dose statin are being randomized to SC evolocumab or placebo. All patients must have either an LDL-C >70 mg/dl or non-HDL total cholesterol of ≥100 mg/dl. The dose of evolocumab is 140 mg every 2 weeks or 420 mg every 4 weeks; these 2 regimens achieve similar reductions of LDL-C over time (43). No adjustment of the dose of evolocumab is permitted on the basis of LDL-C values, although patients may select whether they prefer the every 2-week or every 4-week regimen.

Two placebo-controlled phase 3 trials (53,54) in patients at high risk for cardiovascular events are assessing whether bococizumab 150 mg SC every 2 weeks reduces cardiovascular events. The entry criteria are similar, except that SPIRE-1 (Studies of PCSK9 Inhibition and the Reduction of vascular Events-1) (53) is enrolling 17,000 patients with LDL-C between 70 and 100 mg/dl, whereas in SPIRE-2 (54), 9,000 patients with LDL-C ≥100 mg/dl are being enrolled.

Completion of these 4 trials is projected for late 2017. In the interim, the U.S. Food and Drug Administration is currently evaluating both alirocumab and evolocumab on the basis of phase 2 and 3 studies completed through mid-2014. Thus, while we await the results from the ongoing phase 3 outcomes trials, it is possible that PCSK9 inhibitors may be available before then for use in selective high-risk patients who are not able to achieve the desired LDL-C level (e.g., FH, statin-intolerant).

**CLINICAL IMPLICATIONS FOR INDIVIDUAL PATIENTS**

Given the consistent effects on LDL-C that have been reported with MoAbs to PCSK9 in a wide variety of clinical scenarios, the most obvious benefit to individual patients is that a dramatically lower LDL-C level can be achieved, with a high likelihood of reaching <70 mg/dl. A remarkable feature of the MoAb to PCSK9 is that the LDL-C reduction is sustained for 2 to 8 weeks after a single SC injection, depending on the dose and the MoAb binding it.

Patients with FH (recent estimates in the general population are 1 in 200 for heterozygous FH [55] and as many as 1 in 160,000 for homozygous FH [56]) typically do not achieve recommended levels of LDL-C with currently available oral therapies (57); thus, FH patients stand to benefit the most from treatment with a PCSK9 inhibitor. In addition, patients with hypercholesterolemia who are intolerant to high doses of statin or have a less than expected
response to statin would have a very high likelihood (>90% in some studies) of achieving an LDL-C <70 mg/dl. Only the rare patient with homozygous FH and <2% LDL-R activity (so-called null mutations) have shown a lack of response to PCSK9 inhibitors; in such patients, other treatments (e.g., therapies that target hepatic secretion of apolipoprotein B) are needed.
A second added benefit of PCSK9 inhibitors is the ability to lower the lipoprotein(a) concentration and, hopefully, thereby also reduce the independent residual risk associated with elevated lipoprotein(a) levels that has been demonstrated even among patients who have low LDL-C on statin therapy (58). Statins and other commonly used oral lipid-lowering therapies (other than nicotinic acid, which itself does not reduce cardiovascular events when added to a statin (59,60)) do not significantly affect lipoprotein(a). Because lipoprotein(a) is not thought to be cleared by the LDL-R but is mainly regulated by hepatic secretion (61), further work is needed to elucidate the mechanism through which PCSK9 inhibitors reduce lipoprotein(a). In addition, ongoing studies may provide additional insight as to whether the reduction in lipoprotein(a) obtained with PCSK9 inhibitors will translate into added clinical benefit, above and beyond that attributable to achieving a lower LDL-C.

**IMPLICATIONS FOR POPULATION HEALTH**

Atherosclerotic cardiovascular disease remains the leading cause of morbidity and mortality in developed countries, while rates are rapidly increasing in developing regions. In the United States, the prevalence of CHD is 15.5 million (6.2%) in adults age ≥20 years, with an estimated 635,000 new CHD events occurring annually (62). In addition, there are nearly 60 million Americans estimated to have an LDL-C ≥160 mg/dl (63)—a level at which high-intensity statin may be necessary to achieve the desired 50% reduction in LDL-C. Yet even among patients with established atherosclerosis, an analysis in 2012 from a large U.S. managed-care database demonstrated that only 26% of patients were receiving a high-intensity statin (64). This likely explains why only about one-third of very high-risk patients achieve an LDL-C <70 mg/dl in surveys conducted both within (65) and outside of the United States (66). Whether the underutilization of high-intensity statins is due to intolerance (which is estimated to be only 10% to 20% of patients) and/or patient or physician preference, the acceptance of high-dose statin therapy has been slow over the decade since the PROVE IT TIMI 22 (Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis In Myocardial Infarction 22) study first established its superiority over moderate-intensity statin therapy in high-risk patients (67).

Whether the safety and tolerability profile of the PCSK9 MoAbs will continue to be as favorable as reported in the phase 2 and early phase 3 studies remains to be seen. However, their introduction into clinical practice could result in a major shift in the LDL-C population distribution (Figure 3) and has the potential to have a large effect on future atheroembolic events. As seen in the Mendelian randomization studies of loss-of-function mutations
In the LAPLACE-TIMI 57 (LDL-C Assessment with Proprotein Convertase Subtilisin Kexin Type 9 Monoclonal Antibody Inhibition Combined with Statin Therapy-Thrombolysis In Myocardial Infarction 57) trial, the mean LDL-C among stable, high-risk patients with hypercholesterolemia was 123 mg/dl, a value that is similar to the average reported in several surveys of the U.S. general population (23). With administration of 140 mg every 2 weeks of evolocumab, the average LDL-C was reduced to a mean of 47 mg/dl, with >90% of patients achieving an LDL-C <70 mg/dl. The majority of patients thus achieved an LDL-C of 25 to 60 mg/dl, a range labeled as physiological for humans by Brown and Goldstein in their 1985 Nobel Lecture. HDL-C = high-density lipoprotein cholesterol; revasc = revascularization; other abbreviations as in Figures 1 and 2.

In PCSK9, even a modest (15% to 28%) lifelong reduction in LDL-C translates into a large (47% to 88%) reduction in CHD events (11). This raises the possibility of a dramatic alteration in the population burden of atherosclerosis if potent PCSK9 inhibition could be safely and economically (e.g., at a price similar to other currently available lipid therapies) initiated earlier in life (i.e., primary prevention). Although event rates in a primary prevention population are considerably lower than in secondary prevention, the CTT meta-analysis (50) of more intensive LDL-C lowering observed a 25% reduction in major vascular events for each 1 mmol/l (38.7 mg/dl) reduction in LDL-C in patients without vascular disease. Moreover, among individuals at apparently low risk clinically, genetics and other novel risk factors could be used to identify subsets with higher risk (68). If the relationship between LDL-C reduction and clinical benefit observed in the primary prevention trials with statins holds true for PCSK9 inhibitors (50), a 36% reduction in major vascular events would be expected with PCSK monotherapy, compared with placebo. This is comparable to the decline in rates of CHD death or first MI reported in a survey of 4 U.S. communities over a 10-year period (69), a trend that has been attributed to reduced rates of smoking, wider use of aspirin, and better control of CHD risk factors, in particular more frequent use of statins. However, the authors wish to caution against excessive exuberance pending the results of the ongoing cardiovascular outcome trials. Furthermore, given increasing constraints on health care spending and higher bars being set by the Centers for Medicare and Medicaid Services for coverage determination of novel therapies (70), we anticipate the availability of MoAbs to PCSK9 will be limited initially to those patients who are at high cardiovascular risk, with an LDL-C that is not well controlled despite intensive therapy with statin + ezetimibe, or who cannot tolerate statin therapy.

**SUMMARY**

In the 12 years since mutations in the PCSK9 gene were identified as the third locus for FH, dozens of clinical trials have demonstrated that potent reduction in LDL-C is possible with MoAbs directed against the PCSK9 protein. In addition, these therapies reduce a number of other atherogenic lipoproteins, including apolipoprotein B, non-HDL total cholesterol, and lipoprotein(a). The safety and tolerability profile of the 2 most extensively studied MoAbs (alirocumab, evolocumab) for periods of up to 2 years appears promising; however, longer exposure is necessary to more completely evaluate potentially delayed adverse effects, such as neurocognitive impairment and cancer. Given the reduction in LDL-C observed in phase 2 and 3 trials to date and the analyses of cardiovascular events in longer-term studies, major vascular events could be reduced by 40% to 50% in high-risk patients if the benefits follow a similar relationship as that observed with statins. This degree of clinical benefit ought to be easily within the reach of ongoing phase 3 cardiovascular outcome studies with 3 PCSK9 MoAbs in a total of >70,000 patients. Although the annals of clinical trials are rife with “can’t miss” therapies that subsequently proved to be failures, the notion that both statins and PCSK9 MoAbs result in an increase in LDL-R activity on the hepatocyte surface (71) leads us to conclude that PCSK9 inhibitors are well positioned to become 1 of the next major breakthroughs in cardiovascular therapeutics.

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**KEY WORDS** cholesterol, lipids, low-density lipoprotein