Prevention

PCSK9 (Proprotein convertase subtilisin/kexin type 9) inhibitors: past, present, and the future

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Reduction in low-density lipoprotein cholesterol (LDL-C), mainly with statins, has decreased the risk of cardiovascular events over the last few decades. However, there are several patient populations that warrant further decrease in LDL-C by additional cholesterol-lowering therapy other than statins. Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors are a new class of drugs that have been shown to further decrease LDL-C by 50–70% when administered as a monotherapy or on a background therapy with statins. Proprotein convertase subtilisin/kexin type 9 inhibitors are also an excellent example of drug development in which discovery of gene mutations and its clinical effects have rapidly progressed into successful preclinical and clinical studies with multiple Phases 1–3 clinical trials completed or ongoing to date. This review summarizes the rapid evolution of the drug from genetic discovery to identification of targets for the drugs, to animal and human testing, and to large clinical outcomes trials, followed by discussion on foreseeable challenges of PCSK9 inhibitors.

Keywords
Proprotein convertase subtilisin/kexin type 9 inhibitors • Low-density lipoprotein cholesterol • Hypercholesterolaemia • Cardiovascular disease

Introduction

Cardiovascular disease accounts for the largest proportion in terms of the cause of death in advanced countries.1 Low-density lipoprotein cholesterol (LDL-C) has been identified as an independent and most potent modifiable risk factor for developing cardiovascular disease.2,3 The use of statins over past 20 years to reduce LDL-C has successfully decreased the risk of cardiovascular events,4,5 reinforcing the role of lowering LDL-C as a major means for diminishing cardiovascular morbidity and mortality.

However, despite statin therapy, there still exists an unmet need for an additional/alternative LDL-C-lowering therapy for further risk reduction. For example, some patients, especially with familial hypercholesterolaemia (FH), cannot achieve the goal LDL-C concentrations even with the maximal dose of highly potent statins.6 Moreover, some patients cannot tolerate statins at all or can only take a small dose of statins due to various reasons such as myalgia and rhabdomyolysis. Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors are a new class of drugs that appear promising as a novel agent for LDL-C reduction after being tested in several clinical trials. In this review, we will summarize the history and development as well as completed and ongoing clinical trials, and discuss some of the foreseeable challenges of PCSK9 inhibitors.

Genetics, discovery, and link to clinical outcomes

Genetics and molecular structure of proprotein convertase subtilisin/kexin type 9

Proprotein convertase subtilisin/kexin type 9 gene has the length of 3617 bp and expands over 12 exons encoding 692 amino acids for PCSK9.7,8 Expression of PCSK9 is particularly abundant in the liver, gastrointestinal system, kidney, and nervous system.8,9 Proprotein convertase subtilisin/kexin type 9 molecule consists of a signal sequence, a prodomain, a catalytic domain, and a C-terminal domain that contains abundant cysteine and histidine.10,11

Discovery of clinical importance of proprotein convertase subtilisin/kexin type 9 gene mutations

The clinical effects of PCSK9 were first recognized when a mutation in the gene was detected in French families in 2003.12 Subsequently, PCSK9 gene became the third gene after LDL receptor (LDL-R) gene

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and apolipoprotein B gene that was associated with autosomal-dominant form of FH, which is caused by a gain-of-function mutation in PCSK9 gene. Elevated LDL-C concentration, in turn, results in excessive risk of cardiovascular disease in these patients. Mutations in PCSK9 gene are reported to be responsible for ~10–25% of autosomal-dominant form of FH cases without mutations in LDL-R or apolipoprotein B.

**Clinical effects of loss-of-function mutation in proprotein convertase subtilisin/kexin type 9**

In contrast to the gain-of-function mutations, mutations that cause loss of function of PCSK9 have been reported to decrease in LDL-C concentrations in various patient populations. The Dallas Heart Study reported that individuals with nonsense mutation in PCSK9 gene had 28% lower LDL-C concentrations than general population. The Atherosclerosis Risk In Communities study showed reduced concentrations of LDL-C by 15 and 28% in 9523 Caucasian and 3363 African-American subjects, respectively, by loss of function in one of the two PCSK9 genes. Data from the same cohort of patients have shown that heterozygous loss-of-function mutations in PCSK9 gene are associated with reduced rates of cardiovascular events. The hazard ratios for development of coronary heart disease during 15-year follow-up were 0.50 [95% confidence interval (CI) (0.32–0.79)] among Caucasians and 0.11 [95% CI (0.02–0.81)] in African-Americans.

Similar findings were reported in two studies. In the Copenhagen Heart Study, the risk of developing coronary heart disease was reduced by 6–46% through reduction in LDL-C concentration by 11–15% in individuals with one loss-of-function mutation in PCSK9 gene. In the other study from Zimbabwe, the mean reduction in LDL-C concentration was 27% in African women. Patients who are heterozygous for PCSK9 gene were also found to be protected against peripheral artery disease and have lower carotid intima media thickness.

In healthy individuals with a nonsense mutation in each PCSK9 gene, LDL-C concentrations were as low as 14–16 mg/dL.

**Inhibitors that target proprotein convertase subtilisin/kexin type 9**

There are several PCSK9-directed therapies that are in various stages of development as summarized in Table 1. In this section, three categories of PCSK9 inhibitors are discussed: monoclonal antibody, small interfering RNA (siRNA), and antisense oligonucleotides (ASOs).

**Preclinical studies of monoclonal antibodies**

Monoclonal antibodies are the most common method of PCSK9 inhibition since the first discovery in 2009. These antibodies bind to the region on PCSK9 required for interaction with LDL-R, and inhibit interaction between PCSK9 and LDL-R. The first neutralizing anti-PCSK9 antibody increased LDL-R expressions on the hepatocytes and reduced LDL-C concentration by 30% in animals such as mice and primates. Several other monoclonal antibodies have been discovered with dose dependent 20–50% reductions in the LDL-C concentrations in monkeys. It was reported in animals that the effects last for more than a few weeks. Based on these results, several monoclonal antibodies against PCSK9 have undergone Phases 1–3 clinical trials as discussed later.

**Small interfering RNA**

Another method of inhibiting the activities of PCSK9 is to administer a single-strand siRNA that binds the messenger RNA of PCSK9. These siRNAs can be administered intravenously in small lipid nanoparticles. Administration of siRNA against PCSK9 messenger RNA in rats showed silencing of more than half of the messenger RNA, which led to reduction in the PCSK9 protein concentration in plasma, and in turn in LDL-C concentration by 30%. A study in primates showed that the reduction in plasma PCSK9 concentrations by a single administration of siRNA was rapid, durable, and reversible. In this study, LDL-C was reduced by 56–70% and the effects lasted for a few weeks. Promising results from a Phase 1 study were recently published regarding an siRNA; healthy volunteers who were given an siRNA had a 70% reduction in circulating PCSK9 concentrations and a 40% reduction in LDL-C from baseline.

**Antisense oligonucleotides**

Activities of messenger RNAs can be interfered with an ASO, which is a short nucleotide that binds to the messenger RNA. A study on an ASO reported that messenger RNA was reduced by 92% and the LDL-C concentration by 32%. Another study in monkeys showed that circulating PCSK9 concentration was reduced by 85% and

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**Table 1**

<table>
<thead>
<tr>
<th>Company</th>
<th>Drug</th>
<th>Agent</th>
<th>Indication</th>
<th>Phase</th>
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<tr>
<td>Sanofi/Regeneron</td>
<td>Alirocumab</td>
<td>Human monoclonal antibody</td>
<td>Hypercholesterolaemia</td>
<td>3 (published)</td>
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<tr>
<td>Amgen</td>
<td>Evolocumab</td>
<td>Human monoclonal antibody</td>
<td>Hypercholesterolaemia</td>
<td>3 (published)</td>
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<tr>
<td>Pfizer/Rinat</td>
<td>Bococizumab</td>
<td>Monoclonal antibody</td>
<td>Hypercholesterolaemia</td>
<td>3 (ongoing)</td>
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<tr>
<td>Novartis</td>
<td>LGT-209</td>
<td>Monoclonal antibody</td>
<td>Hypercholesterolaemia</td>
<td>2</td>
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<tr>
<td>Genentech</td>
<td>MPSK3169A, RG7652</td>
<td>Monoclonal antibody</td>
<td>Hypercholesterolaemia</td>
<td>2</td>
</tr>
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<td>Alnylam Pharmaceuticals/The Medicines Company</td>
<td>ALN-PCS02</td>
<td>siRNA oligonucleotide</td>
<td>Hypercholesterolaemia</td>
<td>1</td>
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<tr>
<td>Idera Pharmaceuticals</td>
<td>TBD</td>
<td>Antisense oligonucleotide</td>
<td>Hypercholesterolaemia</td>
<td>Preclinical</td>
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</table>

TBD: to be determined.
Modified from Urban et al.

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LDL-C concentration by 50%. However, a Phase 1 clinical trial was terminated prematurely and there is currently no ongoing trial on ASO for PCSK9.

**General mechanism of reduction in low-density lipoprotein cholesterol by proprotein convertase subtilisin/kexin type 9 inhibition**

**Physiological function of proprotein convertase subtilisin/kexin type 9**

Secreted PCSK9 has two possible destinations: the first is to be secreted and immediately get bound to LDL-R in the liver, and the second is to enter the systemic circulation. The PCSK9/LDL-R complex gets endocytosed and becomes internalized into the lysosome to undergo degeneration. Presence of PCSK9 enhances degradation of LDL-R, therefore leading to fewer number of LDL-R present on the cell surface. Proprotein convertase subtilisin/kexin type 9 circulating in the plasma can bind to LDL-R in various organ systems such as the liver, intestines, kidneys, lungs, pancreas, and adipose tissue. This mechanism explains an inverse relationship between PCSK9 concentrations in plasma and LDL-R. Increase in the plasma PCSK9 concentration results in an elevated LDL-C concentration because uptake of LDL-C becomes reduced due to a decreased number of LDL-R on the cell surface (Figure 1A). There are more complicated interactions between PCSK9, LDL-R, LDL-C, and statins, which is beyond the perspective of this review and has recently been published elsewhere.

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**Figure 1** (A) Regulation of hepatic LDL receptor expression by proprotein convertase subtilisin/kexin type 9. (B) Mechanism of low-density lipoprotein cholesterol reduction by proprotein convertase subtilisin/kexin type 9 inhibition. (Adopted from Dadu et al. [70]).
Effects of proprotein convertase subtilisin/kexin type 9 inhibition on low-density lipoprotein cholesterol concentration

When the activity of PCSK9 is inhibited, a larger number of LDL-R returns to the cell surface instead of being degraded in the lysosome. A consequence is increased uptake of LDL-C from the bloodstream. PCSK9 inhibitors decrease LDL-C concentrations through this mechanism (Figure 1B).

Clinical studies on proprotein convertase subtilisin/kexin type 9 inhibition

Pharmacokinetics and pharmacodynamics of proprotein convertase subtilisin/kexin type 9 inhibitors

The pharmacokinetics of PCSK9 inhibitor is represented in Figure 2. Prior to administration of a PCSK9 inhibitor, PCSK9 molecules are freely circulating in plasma (or already bound to the LDL-C receptor). Immediately after an injection of anti-PCSK9 antibody, the antibody binds free PCSK9, and plasma free PCSK9 gets rapidly depleted. Because free PCSK9 concentrations are reduced, fewer LDL-R become degraded in the lysosomal compartments. This results in a larger number of LDL-R on the cell surface, and in turn, more LDL particles become bound to LDL-R. Low-density lipoprotein cholesterol concentration gets subsequently reduced. As PCSK9 antibody gets metabolized and its concentration lowered with time, increase in concentration of plasma free PCSK9 occurs followed by recovery of LDL-C concentrations, because more LDL-R become bound to PCSK9 leading to increased degeneration of LDL-R in the lysosomal compartment. This effect of PCSK9 inhibition on LDL-C has been confirmed in a Phase 1 study with healthy volunteers.42

Completed clinical trials

Effects on low-density lipoprotein cholesterol

Table 2 summarizes results from the published Phase 3 trials. Proprotein convertase subtilisin/kexin type 9 inhibitors significantly reduced LDL-C compared with the active comparator or placebo in each PCSK9 inhibitor, patient population, background treatment, and treatment arm. This effect on LDL-C appears to be dose dependent as shown in Figure 3.43,44 The effects of PCSK9 inhibition in LDL-C are not affected by age, gender, region, body mass index, and LDL-C concentrations.

Effects of background therapy with statins

As PCSK9 inhibitors would be used concomitantly with statins in most cases, a question arises as to whether PCSK9 inhibitors have different effects depending on background statin use. When evolocumab was administered in 56 healthy volunteers and 57 individuals on statin, there was no difference in the amplitude of LDL-C reduction.45 Similarly, in a Phase 2 study with alirocumab, reduction in LDL-C concentrations were not affected by the dose of atorvastatin (10–40 mg daily).43 Another alirocumab study showed no difference in effects between the arm treated with atorvastatin 10 and 80 mg.46 The DESCARTES trial provides further insights; the mean reduction in LDL-C in the evolocumab group was similar between patients taking no statin, atorvastatin 10 mg and atorvastatin 80 mg.47 Likewise, there was no significant difference in the LDL-lowering effects of the LAPLACE-2 study between different background statin intensity and doses (Figure 4).48

Frequency of administration

There have been several Phase 2 trials that assessed LDL-C lowering by PCSK9 inhibitors in different administration frequencies; the effects were similar between 2- and 4-week injection intervals (Figure 4). As shown in Figure 5, however, administration of alirocumab...
<table>
<thead>
<tr>
<th>Trial name</th>
<th>PCSK9 inhibitor</th>
<th>Population and study design</th>
<th>Number of patients</th>
<th>Study duration</th>
<th>LDL-C</th>
<th>ApoB</th>
<th>Non-HDL-C</th>
<th>TG</th>
<th>HDL-C</th>
<th>Lp(a)</th>
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<tr>
<td>ODYSSEY Mono</td>
<td>Alirocumab</td>
<td>Patients with hypercholesterolaemia on no statins, compared with ezetimibe</td>
<td>103</td>
<td>24 weeks</td>
<td>−31.6</td>
<td>−25.8</td>
<td>−25.5</td>
<td>−1.2</td>
<td>4.4</td>
<td>−4.4</td>
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<td>ODYSSEY COMBO I</td>
<td>Alirocumab</td>
<td>Hypercholesterolaemia not adequately controlled (with maximum dose of a statin with or without other lipid-modifying therapy), and high CVD risk</td>
<td>311</td>
<td>24 weeks</td>
<td>−45.9</td>
<td>−35.8</td>
<td>−37.5</td>
<td>−0.6</td>
<td>7.3</td>
<td>−14.6</td>
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<td>ODYSSEY COMBO II</td>
<td>Alirocumab</td>
<td>Hypercholesterolaemia not adequately controlled with current lipid-modifying therapy, and high CVD risk</td>
<td>707</td>
<td>24 weeks</td>
<td>−29.7</td>
<td>−22.4</td>
<td>−22.9</td>
<td>−0.3</td>
<td>8.1</td>
<td>−21.7</td>
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<td>ODYSSEY LONG TERM</td>
<td>Alirocumab</td>
<td>Hypercholesterolaemia not adequately controlled with current lipid-modifying therapy, and high CVD risk</td>
<td>2341</td>
<td>24 weeks</td>
<td>−61.9</td>
<td>−54.0</td>
<td>−52.3</td>
<td>−17.3</td>
<td>4.6</td>
<td>−25.6</td>
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<td>DESCARTES</td>
<td>Evolocumab</td>
<td>Patients with hyperlipidaemia 420 mg Q4W added to diet alone or to diet plus atorvastatin or to diet plus atorvastatin plus ezetimibe</td>
<td>901</td>
<td>52 weeks</td>
<td>−57.0</td>
<td>−44.2</td>
<td>−50.3</td>
<td>−11.5</td>
<td>5.4</td>
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<td>LAPLACE-2</td>
<td>Evolocumab</td>
<td>Patients with hypercholesterolaemia, 140 mg Q2W or 420 mg Q4W added to moderate- or high-intensity statin therapy, compared with ezetimibe or placebo</td>
<td>2067</td>
<td>12 weeks</td>
<td>−59.2</td>
<td>−70.6</td>
<td>−61.4</td>
<td>−54.9</td>
<td>66.6</td>
<td>−9.3</td>
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<td>GAUSS-2</td>
<td>Evolocumab</td>
<td>Patients with statin intolerance, 140 mg Q2W or 420 mg Q4W compared with ezetimibe</td>
<td>307</td>
<td>12 weeks</td>
<td>−68.8</td>
<td>−69.7</td>
<td>−32.9</td>
<td>−33.1</td>
<td>3.6</td>
<td>4.8</td>
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<td>MENDEL-2</td>
<td>Evolocumab</td>
<td>Patients with hypercholesterolaemia on no statins, 140 mg Q2W or 420 mg Q4W compared with ezetimibe</td>
<td>614</td>
<td>12 weeks</td>
<td>−54.8</td>
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<td>−47.8</td>
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<td>RUTHERFORD-2</td>
<td>Evolocumab</td>
<td>Patients with heFH, 140 mg Q2W or 420 mg Q4W</td>
<td>329</td>
<td>12 weeks</td>
<td>−59.2</td>
<td>−61.3</td>
<td>−49.1</td>
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<td>−54.8</td>
<td>55.0</td>
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<td>OSLER-2</td>
<td>Evolocumab</td>
<td>Hypercholesterolaemia or mixed dyslipidaemia; completion of previous evolocumab study (no specification regarding statin therapy)</td>
<td>4465</td>
<td>12 weeks</td>
<td>−61</td>
<td>−47.3</td>
<td>−52.0</td>
<td>−12.6</td>
<td>7.0</td>
<td>−25.5</td>
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<tr>
<td>TESLA Part B</td>
<td>Evolocumab</td>
<td>Patients with hoFH, not on apheresis, 420 mg Q4W</td>
<td>49</td>
<td>12 weeks</td>
<td>−30.9</td>
<td>−23.1</td>
<td>0.3</td>
<td>−0.1</td>
<td>−11.8</td>
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</table>

ApoB, apolipoprotein B; HDL-C, high-density lipoprotein cholesterol; heFH, heterozygous familial hypercholesterolaemia; hoFH, homozygous familial hypercholesterolaemia; Lp(a), lipoprotein(a); Q2W, every 2 weeks; Q4W, every 4 weeks; TG, triglycerides. Results are expressed as percent treatment difference from baseline adjusted for placebo or active comparator. Results are expressed as a range when multiple comparisons were reported within one trial. Modified from Gouni-Berthold et al. 72
Figure 3  Dose–response relationship between proprotein convertase subtilisin/kexin type 9 inhibitors and mean percent change in low-density lipoprotein cholesterol concentrations with alirocumab (modified from McKenney et al.).

![Dose–response relationship between proprotein convertase subtilisin/kexin type 9 inhibitors and mean percent change in low-density lipoprotein cholesterol concentrations with alirocumab.](image)

Figure 4  Low-density lipoprotein-lowering effects of proprotein convertase subtilisin/kexin type 9 inhibitor by different statin potency and doses (modified from Robinson et al.).

![Low-density lipoprotein-lowering effects of proprotein convertase subtilisin/kexin type 9 inhibitor by different statin potency and doses.](image)
every 4 weeks resulted in a larger fluctuation of LDL-C concentrations than every 2 weeks.43

Safety of proprotein convertase subtilisin/kexin type 9 administration
In terms of the safety with PCSK9 inhibitors, 36–75% of the patients on PCSK9 inhibitors in Phase 3 trials had adverse events and 2–6% had serious adverse events.47–49 Adverse events leading to the discontinuation of the study drug occurred in 2–10%. These numbers were similar to the comparator in each study. Elevation of liver aminotransferase concentrations 3 times of the upper normal limit in patients receiving PCSK9 inhibitor was observed in <2% of the patients. Abnormal elevation of creatinine kinase concentrations was similarly rare. No neutralizing anti-drug antibody, which may impact pharmacokinetics of PCSK9 inhibitors, effects on LDL-C concentrations or safety, was reported in any of the Phase 3 trials.

Tolerability
In the ODYSSEY MONO trials, injection site reaction was observed in 1 of 52 patients who received alirocumab compared with 2 of 51 in placebo at 24 weeks.49 In the OSLER trial with a 52-week follow-up, only 1 of 38 patients who experienced injection-site reaction discontinued evolocumab.50 Similarly, the DESCARTES study reported that 34 of 599 patients (5.7%) in the evolocumab group and 15 of 302 (5.0%) in the placebo group had injection-site reactions, and only 1 patient discontinued evolocumab.47 In the ODYSSEY COMBO II study, ~85% of patients were still taking study medication (or placebo) at 1 year, indicating good acceptance and tolerability of parenteral LDL-C-lowering therapies.51

Target patient populations
Familial hypercholesterolaemia
Heterozygous FH is one of the most common genetic diseases (prevalence 1/200–1/500) and characterized by extremely high LDL-C concentrations. This results in development of atherosclerosis and cardiovascular disease in younger age.52 The mean age of onset of cardiovascular disease was 42–46 years in men and 51–52 years in women.53,54 Homozygous FH is a more severe form of FH, and these patients develop cardiovascular disease at mean age of 20 years.55 The treatment goal for adult patients with heterozygous FH who also have coronary heart disease or diabetes is 70 mg/dL.52 However, ~80% of adult patients with heterozygous FH on lipid-lowering treatment do not reach the LDL-C goal of 100 mg/dL.56 Therefore, FH patients appear to be a good target population for PCSK9 inhibitors.57

Patients who cannot reach low-density lipoprotein cholesterol goals with high-dose statins
Patients with severe non-FH and FH sometimes cannot achieve adequately low LDL-C concentrations despite maximum dose of highly potent statins. As a number of studies have shown that the incidence of cardiovascular events directly correlates with LDL-C concentrations,58 those with high LDL-C despite maximum statin therapy is at increased risk of developing cardiovascular events. The guidelines do not make recommendations as to which additional lipid-lowering agents should be chosen for these patients. Proprotein convertase subtilisin/kexin type 9 inhibitors are known to reduce LDL-C concentrations even when added to background statin therapy, and may offer additional protective effects against cardiovascular complications. This would probably have a substantial clinical impact as the IMPROVE-IT study demonstrated achieving lower LDL-C targets than the conventional goal, from 70 to 54 mg/dL, resulted in a significant reduction in adverse cardiovascular events.59

Statin intolerance
Statins are most often the first line treatment for hypercholesterolaemia, and have been shown to reduce LDL-C concentrations and cardiovascular complications. However, some patients cannot tolerate statin therapy because of various reasons such as myalgia,
Table 3  Selected Phase 3 trials on monoclonal antibody against proprotein convertase subtilisin/kexin type 9 that are (A) ongoing and (B) completed and presented but not published as a full manuscript

<table>
<thead>
<tr>
<th>Name of study</th>
<th>Monoclonal antibody</th>
<th>Patient population</th>
<th>Study objectives and follow-up period</th>
<th>Target completion date</th>
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<tbody>
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<td>(A)</td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>GLAGOV</td>
<td>Evolocumab</td>
<td>Coronary heart disease; clinical indication for coronary catheterization; and LDL-C level ≥ 80 mg/dL or, with additional risk factors, ≥ 60 and &lt;80 mg/dL (no specification regarding statin therapy)</td>
<td>To determine the effects of evolocumab every 4 weeks on atherosclerotic disease burden (per cent atheroma volume measured by intravascular ultrasonography), at 72 weeks</td>
<td>November 16</td>
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<tr>
<td>FOURIER</td>
<td>Evolocumab</td>
<td>Clinical CVD, high risk of recurrent CVD event, and LDL-C level ≥ 70 mg/dL or non-HDL-C ≥ 100 mg/dL (no specification regarding statin therapy)</td>
<td>To assess the effect of evolocumab every 2 or 4 weeks plus a statin vs. placebo plus a statin on major CVD events (CVD death, nonfatal myocardial infarction, unstable angina requiring hospitalization, stroke, or coronary revascularization), at 5 years</td>
<td>February 18</td>
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<tr>
<td>TAUSSIG</td>
<td>Evolocumab</td>
<td>Homozygous FH or PCSK9 mutations; LDL-C level above ATP III target or receiving apheresis and completion of previous evolocumab study (no specification regarding statin therapy)</td>
<td>To assess the long-term safety and efficacy of evolocumab every 2 or 4 weeks on LDL-C level in patients with severe FH, at 5 years</td>
<td>January 20</td>
</tr>
<tr>
<td>SPIRE-HF</td>
<td>Bococizumab</td>
<td>Heterozygous FH; high or very high CVD risk; LDL-C level &gt; 70 mg/dL and Tg level ≤ 400 mg/dL (with statin therapy)</td>
<td>To compare the effect of bococizumab and a statin vs. placebo on LDL-C level in patients with heterozygous FH, at 12 weeks</td>
<td>May 16</td>
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<tr>
<td>SPIRE-HR</td>
<td>Bococizumab</td>
<td>High or very high CVD risk; LDL-C level &gt; 70 mg/dL and Tg level ≤ 400 mg/dL (with statin therapy)</td>
<td>To compare the effect of bococizumab and a statin vs. placebo on LDL-C level, at 12 weeks</td>
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<td>SPIRE-LDL</td>
<td>Bococizumab</td>
<td>High or very high CVD risk; LDL-C level &gt; 70 mg/dL and Tg level ≤ 400 mg/dL (with statin therapy)</td>
<td>To compare the effect of bococizumab and a statin vs. placebo on LDL-C level, at 12 weeks</td>
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<td>SPIRE-1</td>
<td>Bococizumab</td>
<td>High CVD risk; LDL-C level ≥ 70 mg/dL and &lt;100 mg/dL or non-HDL-C level ≥ 100 mg/dL and &lt;130 mg/dL, with lipid-lowering therapy (no specification regarding statin therapy)</td>
<td>To compare the effect of bococizumab vs. placebo on reducing the occurrence of major cardiovascular events, including cardiovascular death, myocardial infarction, stroke, and unstable angina requiring urgent revascularization, at 5 years</td>
<td>August 17</td>
</tr>
<tr>
<td>SPIRE-2</td>
<td>Bococizumab</td>
<td>High CVD risk; LDL-C level ≥ 100 mg/dL or non-HDL-C level ≥ 130 mg/dL, with lipid-lowering therapy (no specification regarding statin therapy)</td>
<td>To compare the effect of bococizumab vs. placebo on reducing the occurrence of major cardiovascular events, including cardiovascular death, myocardial infarction, stroke, and unstable angina requiring urgent revascularization, at 5 years</td>
<td>August 17</td>
</tr>
<tr>
<td>ODYSSEY OUTCOMES</td>
<td>Alirocumab</td>
<td>Recent (in the past 4–16 weeks) acute coronary syndrome event requiring hospitalization</td>
<td>To compare the effect of alirocumab vs. placebo on CVD events (cardiovascular death, nonfatal myocardial infarction, fatal and non-fatal ischaemic stroke, and unstable angina requiring hospitalization), for up to 64 months</td>
<td>January 18</td>
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<tr>
<td>ODYSSEY ALTERNATIVE</td>
<td>Alirocumab</td>
<td>Statin intolerance; primary hypercholesterolaemia (heterozygous FH or non-FH); and moderate, high, or very high CVD risk (no statin therapy)</td>
<td>To evaluate the efficacy and safety of alirocumab vs. ezetimibe and vs. atorvastatin, after 24 weeks of treatment</td>
<td>Completed; preliminary results presented at AHA Scientific Sessions 2014</td>
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elevated liver enzymes, and rhabdomyolysis. The exact prevalence of statin intolerance is unknown and largely depends on how intolerance is defined. However, it has been reported that 12% of patients started on statin had to discontinue the therapy, within which 62% was due to adverse effects.60 Patients who cannot tolerate statins remain at high risk of developing cardiovascular events. Nevertheless, monotherapy with other lipid-lowering therapies is not shown to remain at high risk of developing cardiovascular events. Nevertheless, monotherapy with other lipid-lowering therapies is not shown to reduce hard clinical endpoints such as coronary artery disease or cardiovascular death. Proprotein convertase subtilisin/kexin type 9 inhibitors are expected to offer an alternative treatment option for these patients with statin intolerance.

### Ongoing clinical trials

A number of Phase 3 clinical trials are being conducted for PCSK9 inhibitors such as evolocumab, bococizumab, and alirocumab. Table 3 summarizes the patient population, information on background statin therapy, active comparator vs. placebo, duration of the study and estimated completion time of selected Phase 3 trials that are either ongoing or completed. The primary and secondary endpoints are presented at AHA or ESC Congress 2014. The results of the GLAGOV trial are currently ongoing to assess the effects of PCSK9 inhibition onto the progression or regression of coronary atherosclerosis by utilizing coronary imaging techniques. In this context, the GLAGOV trial is currently ongoing to assess change in per cent atheroma volume as determined by intravascular ultrasound at 78 weeks post-randomization (https://clinicaltrials.gov/ct2/show/NCT01813422).

#### Challenges

### Cost effectiveness

The cost of a cardiovascular event is high; the total first year cost after an acute coronary event is ~$22 529 (~19 800 euros). Among patients without FH, high-dose statins have shown to be cost effective for reducing cardiovascular disease in long term.65 No prior study has performed cost-effectiveness analysis in terms of PCSK9 inhibitor compared with previously existing treatment for hyperlipidaemia. There appears to be a specific target for PCSK9 inhibitors to be cost-effective; among patients with FH who require LDL apheresis, the treatment is limited by the high cost that can reach between $45 000 and $100 000 (~39 600–88 000 euros) per year.66 Especially, in this high-risk population with large health-care costs, PCSK9 inhibitors may prove to be cost effective. The cost-effectiveness of PCSK9 inhibitors would also depend on the marketing price and the patient’s baseline risk of cardiovascular events.67

### Compliance with injections

Compliance issues associated with injectable medications do not often get addressed by randomized controlled trials, but could pose a significant limitation in daily clinical practice when utilizing
PCSK9 inhibitors. There are mainly two characteristics of PCSK9 inhibitors that can significantly affect patient compliance. First, practically speaking, subcutaneous self-injections would be challenging for some of the patients; however, if the patient cannot perform injection at home, the patient would have to visit the clinic at least monthly. Second, the amount of medication to be injected is rather large; for example, 6 mL of evolocumab needed to be injected monthly in the clinical trials. 47 Although this could be divided into 3 mL injection twice or 2 mL injection three times, pain associated with subcutaneous injection of this amount of liquid can be substantial. The positive news is that several Phase 3 trials reported that most patients are tolerating subcutaneous injection of the study drug (or placebo) at 52 weeks. 51 A post-marketing registry data would help understand what proportion of patients can actually remain compliant with monthly self-injections in the real world.

Long-term safety

Safety of PCSK9 inhibitors in longer term than 12 weeks has been reported only in three published clinical trials. The first trial, ODYSSEY MONO, was a medium-sized trial (~50 patients in each arm) and reported no significant increase in adverse events in the PCSK9 inhibitor arm. The second trial, DESCARTES study, was a larger trial with longer follow-up period of 52 weeks involving 900 patients. The rates of adverse events were similar in the evolocumab arm and the placebo arm. 47 The third was the OSLER trial. 50 At 52 weeks, adverse events were observed in 81% of patients who received evolocumab compared with 73% in the standard of care group. In the evolocumab arm, 3.7% had adverse events leading to discontinuation of the drug. Regarding safety and tolerability in >1 year, alirocumab was tolerated well without a significant increase in adverse effects attributable to the study drug according to the data from the ODYSSEY LONG TERM trial. 48 A number of Phase 3 trials with planned follow-up period >1 year are ongoing, such as the ODYSSEY OUTCOMES (https://clinicaltrials.gov/ct2/show/NCT01663402), GLAGOV (https://clinicaltrials.gov/ct2/show/NCT01813422), FOURIER (https://clinicaltrials.gov/ct2/show/NCT01764633), TAUSIG (https://clinicaltrials.gov/ct2/show/NCT01624142), and SPIRE 1/2 trials (https://clinicaltrials.gov/ct2/show/NCT01975389?term=SPIRE-2&rank=1), (https://clinicaltrials.gov/ct2/show/study/NCT01975376?term=SPIRE-1&rank=1).

Conclusions

In summary, PCSK9 has experienced a rapid evolution from genetic discovery, to drug target, to animal, then human testing, and now to large clinical outcomes trials. It has provided new biologic insights and a potent natural pharmacologic mechanism to further lower LDL-C. If outcomes of the ongoing trials are positive, they would shift the guidelines for treatment of hypercholesterolaemia, and may result in adding back of the LDL-based treatment decisions in the guidelines. With 50–70% further reduction in LDL-C, PCSK9 inhibitors appear to be a promising pharmacologic intervention for patients with difficult-to-treat hypercholesterolaemia.

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References


