The emerging role of proprotein convertase subtilisin/kexin type-9 inhibition in secondary prevention: from clinical trials to real-world experience

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Purpose of review
The recent advent of a highly efficacious class of low-density lipoprotein cholesterol (LDL-C) lowering agents, the proprotein convertase subtilisin/kexin type-9 (PCSK9) inhibitors, has transformed dyslipidaemia management in patients with cardiovascular disease as well as those with familial hypercholesterolemia.

Recent findings
Recent positive results of the landmark Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk cardiovascular outcome trial with evolocumab as an add-on to statin therapy demonstrate further reduction of cardiovascular events. Additional safety outcomes from this large randomized trial, as well as the EBBINGHAUS substudy, allay fears of neurocognitive disorder as an adverse effect of achieving very low LDL-C levels with these agents.

Summary and implications
Widespread clinical adoption of PCSK9 inhibitors will depend on the results from ongoing and planned cardiovascular efficacy and safety trials with PCSK9 inhibitors. In addition, understanding the practical challenges and barriers to usage of these injectable agents by high cardiovascular risk patients will also affect clinical adoption of this class of agents. Analysis of cost-benefit models, along with anticipated updates to practice guidelines for dyslipidaemia management are likely to strengthen the clinical utility of PCSK9 inhibitors. Importantly, the potency of this new class of agents provides a huge opportunity to extend further the ‘lower LDL-C is better’ hypothesis in an effort to reduce rates of cardiovascular morbidity and mortality on a population level.

Keywords
cardiovascular disease, dyslipidaemia, evolocumab, familial hypercholesterolemia, proprotein convertase subtilisin/kexin type-9 inhibition

INTRODUCTION
The linear relationship between low-density lipoprotein cholesterol (LDL-C) levels and cardiovascular disease is well established, not only from observational study data [1–3] but also from multiple landmark randomized controlled trials (RCTs) with LDL-C lowering medications in both the primary and secondary prevention settings [4–10]. Because most of these cardiovascular outcome trial data have originated from RCTs involving 3-hydroxy-3-methyl-glutaryl CoA reductase inhibitors (known as statins), worldwide guidelines recommend statins as first-line therapy for cardiovascular prevention[11–13]. However, a significant proportion of patients are either unable to tolerate these medications or are unable to...
PCSK9 inhibitors are a novel class of lipid-lowering medications that can be prescribed for patients who have above target LDL-C levels or are at high risk for cardiovascular events such as those with familial hypercholesterolemia. 

PCSK9 inhibitors have profound LDL-C lowering capabilities, even in patients already on background statin therapy. 

PCSK9 inhibitors are well tolerated, with no evidence of neurocognitive dysfunction. 

The magnitude of LDL-C reduction efficacy for PCSK9 inhibitors, together with the accumulating cardiovascular benefit evidence demonstrated in recent cardiovascular outcome trials extends further the ‘lower LDL-C is better’ hypothesis for cardiovascular disease reduction in high-risk patients. 

Our single centre experience with PCSK9 inhibition over a 1-year time frame suggests a potential for significant improvement in cholesterol management in the real world with this novel medication class, but also highlights barriers to effective implementation of this therapy.

achieve target LDL-C levels on statins. There also exists the distinct possibility of additional cardiovascular benefit from reducing LDL-C beyond that achieved by statin medications or by add-on ezetimibe or bile acid sequestrants. This concept of ‘lower is better’ is supported by the observation of lowest cardiovascular disease risk among those achieving the lowest levels of LDL-C in post hoc analyses of the Treating to New Targets (TNT) trial, the Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin trial, and the Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22 (PROVE-IT-TIMI 22) trials [14–16]. Many add-on therapies to statins have either had limited impact on cardiovascular risk or lack adequate data. [10,17–20] The need for an effective add-on therapy to achieve target LDL-C levels in a significant number of patients remains unmet. 

Accordingly, a novel class of lipid-lowering medications has been introduced with the mechanism of proprotein convertase subtilisin/kexin type-9 (PCSK9) inhibition. The objectives for this review are to highlight recent efficacy, safety, and outcome data from PCSK9 inhibitor trials, in addition to sharing our own experience in 114 patients who were prescribed the PCSK9 inhibitor evolocumab in a real-world cardiology practice.

THE LOW-DENSITY LIPOPROTEIN HYPOTHESIS

In large lipid trials such as PROVE-IT-TIMI 22 and TNT, more potent LDL-C reduction with higher intensity statins resulted in significant reductions in cardiovascular disease progression and events [21,22]. These trials compared a simple approach of high intensity vs. moderate-intensity statin therapy. The resultant data supported the hypothesis that LDL-C lowering alone is the likely mechanism of benefit with higher intensity statin therapy rather than their ‘pleiotropic’ effects [23]. A meta-analysis conducted by the Cholesterol Treatment Trialists’ collaborators with over 90000 patients, (423 263 patient-years) from major lipid trials shows a reduction in the 5-year incidence of major coronary events, revascularization, and stroke by approximately 23% for every 1 mmol/l reduction in LDL-C. This benefit was attributed to the absolute reduction in LDL-C achieved regardless of the mechanism of LDL-C reduction [24]. Further support for the LDL-C hypothesis comes from the results of the IMPROved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT), which was the first trial to show the benefit of adding a nonstatin lipid modifying medication to statin therapy [10]. The fact that the addition of ezetimibe to a moderate-dose statin demonstrated a reduction in cardiovascular mortality emphasizes the significance and potential therapeutic benefits of further LDL-C reduction.

ADDITIONAL NEED FOR LOW-DENSITY LIPOPROTEIN CHOLESTEROL LOWERING

Despite the establishment of clinical guidelines for initiation of statin therapy in high cardiovascular risk patient populations, there remains a significant proportion of patients who are not achieving appropriate LDL-C targets. A Canadian observational study of 2436 patients treated with a statin found that 37% of the study sample did not achieve target LDL-C levels, including 45% of patients in the high-risk category [25]. Furthermore, a study of 7998 patients with established coronary artery disease from 78 centres in 24 different European countries found that 80.5% of patients had an LDL-C greater than the European target of less than 1.8 mmol/l, despite 85% of the study participants having a prescription for statin therapy [26].

In an effort to address this care gap, adjunctive therapies such as niacin, fibrates, and cholesterol reuptake inhibitors were investigated in cardiovascular outcome trials. Niacin [17,18] and fenofibrate [19,20] did not show any cardiovascular benefit when they were added to statin therapy. In contrast,
the IMPROVE-IT trial did show a modest cardiovascular benefit of adding ezetimibe to moderate-intensity statin therapy in a trial of 18 144 patients with recent acute coronary syndrome [10]. The median time-weighted average LDL-C achieved was 1.4 mmol/l for the ezetimibe and simvastatin arm vs. 1.8 mmol/l for the placebo and simvastatin arm at the end of 6-year trial period. The primary composite outcome of cardiovascular mortality, major cardiovascular event, or nonfatal stroke was modestly reduced by an absolute risk of 2% or a relative risk reduction of 6%.

Statin intolerance is a concept, that is, fiercely debated by lipid experts and poses a significant problem for clinicians [27]. Statin intolerance largely consists of subjective complaints of muscle pain and weakness, which is seldom supported by clinical biomarkers such as muscle enzyme elevation. It is reported by 5–20% of patients started on statin therapy and thus has significant implications on treatment decisions for a relatively large proportion of the treated population [28]. Even more concerning are recent findings that those with statin intolerance could have an approximately 50% greater chance of myocardial infarction (MI) or need for coronary revascularization [29].

In addition, patients with heterozygous familial hypercholesterolemia (HeFH) pose an even greater challenge with adequately lowering LDL-C. This autosomal dominant, hereditary disorder caused by a mutation in the LDL receptor (LDL-R) gene has prevalence between 1/200 and 1/500 people worldwide [30]. Patients with this disorder have up to a 13-fold increased risk of coronary heart disease. In a cross-sectional study conducted in the Netherlands of 1249 patients with HeFH, of which nearly all were on statin therapy, only 21% reached the target LDL-C of less than 2.5 mmol/l [31]. Moreover, among those who did not achieve target LDL-C, 27% were on combination therapy with maximum dose statin in addition to ezetimibe. The lack of efficacious, evidence-based alternative lipid-lowering therapies highlight the critical need for new lipid-lowering medications that modify cardiovascular risk.

The introduction of PCSK-9 inhibitors as the newest class of lipid modifying agents with the potential for potent LDL-C reduction and the results of their initial studies have offered new hope to achieve low LDL-C targets in these high-risk patients.

**PROPROTEIN CONVERTASE SUBTILISIN/KEXIN TYPE-9 INHIBITION**

The protein PCSK9 was first identified in 2003. It is highly expressed in the liver and found to contribute to cholesterol homeostasis [32]. In studying DNA from 23 French families with autosomal dominant hypercholesterolemia, missense mutations in PCSK9 were found and thought to represent gain of function mutations that led to increased cardiovascular risk [33]. Henceforth, PCSK9 became a target for the pharmaceutical industry for the development of lipid-lowering drugs.

In normal cholesterol homeostasis, PCSK9 interacts with LDL-Rs, which are responsible for the clearance of LDL-C particles. Under conditions of intracellular cholesterol depletion, activation of the sterol regulatory binding protein-2 leads to increased expression of mRNA for both PCSK9 and LDL-R. In the endoplasmic reticulum, autocatalysis of PCSK9 creates a prosegment that remains associated with the mature PCSK9 protein after cleavage. The PCSK9 protein is secreted and binds to the extracellular domain of the LDL-R at the cell surface. The PCSK9/LDL-R complex then enters the endosomal pathway and is directed to the lysosome for degradation, leading to a decrease in the number of LDL-R [32]. PCSK-9 inhibitors act by directing a mAb against PCSK9 protein, thereby reducing degradation of LDL-R, and allowing for increased clearance of LDL-C particles.

**PROPROTEIN CONVERTASE SUBTILISIN/KEXIN TYPE-9 INHIBITORS: LOW-DENSITY LIPOPROTEIN CHOLESTEROL REDUCTION EFFICACY**

Currently, two human mAbs to PCSK-9, evolocumab and alirocumab, have been approved in many parts of the world for LDL-C lowering in high-risk patients not at target LDL-C with statins alone or in combination with other lipid-lowering agents.

In the Phase III MENDEL-2 and GAUSS-2 RCTs, evolocumab monotherapy reduced LDL-C by over 50% [34,35]. In the RUTHERFORD-2 trial with HeFH patients on background lipid-lowering therapy, a 59.2 and 61.3% reduction in LDL-C was found compared with placebo for evolocumab dosed at every 2 weeks and dosed monthly, respectively [36]. Similarly, in the LDL-C Assessment with PCSK9 Monoclonal Antibody Inhibition Combined with Statin Therapy study, patients already on moderate-to-high-intensity statins treated with evolocumab had a greater than 60% further reduction in LDL-C [37]. Similar efficacy for LDL-C reduction was observed for alirocumab in phase III clinical trials in a variety of patient populations [38–40]. In longer term, open-label follow-up of trials with both evolocumab [Open-Label Study of Long-Term Evaluation against LDL Cholesterol (OSLER)] with 11.1 months
Complex issues in coronary revascularization

mean duration] and alirocumab [Long-term Safety and Tolerability of Alirocumab in High Cardiovascular Risk Patients with Hypercholesterolemia Not Adequately Controlled with Their Lipid Modifying Therapy (ODYSSEY LONG TERM)] with 70 weeks mean duration], LDL-C reduction of 61 and 62% was maintained compared to placebo, respectively [41,42]. Exploratory, post hoc analyses of both these longer term studies published simultaneously in 2015 demonstrated a reduction in composite major cardiovascular endpoints and raised the prospect of positive results in dedicated cardiovascular outcome trials with both these agents.

PROPROTEIN CONVERTASE SUBTILISIN/KEXIN TYPE-9 INHIBITORS: CARDIOVASCULAR BENEFITS IN FURTHER CARDIOVASCULAR OUTCOMES RESEARCH WITH PCSK9 INHIBITION IN SUBJECTS WITH ELEVATED RISK TRIAL WITH EVOLOCUMAB

The recently published trial with evolocumab named ‘Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER)’ is the first dedicated prospective cardiovascular outcomes trial with a PCSK9 inhibitor to show cardiovascular benefit [43**]. In this secondary prevention trial, 27,564 patients with atherosclerotic cardiovascular disease and LDL-C levels of more than 1.8 mmol/l, receiving high or moderate-intensity statin therapy, were randomized to evolocumab (either 140 mg every 2 weeks or 420 mg monthly) or matching placebo injections. By 48 weeks, study participants on evolocumab had achieved a mean LDL-C of 0.78 mmol/l from a baseline of 2.4 mmol/l; and this magnitude of reduction was maintained over a median duration of follow-up of 26 months – with 42% of the patients achieving LDL-C of less than 0.65 mmol/l. This resulted in a relative risk reduction of 15% (95% confidence interval = 8–21%; P < 0.001) for the primary composite endpoint (cardiovascular death, MI, stroke, hospitalization for unstable angina, or coronary revascularization) and 20% (95% confidence interval = 12–27%; P < 0.001) for the key secondary composite endpoint (cardiovascular death, MI, and stroke) – with an identical number needed to treat of 74 study participants to prevent each of these composite endpoints over 2 years. Efficacy for the primary endpoint did not vary according to the evolocumab dosing regimen used or the baseline LDL-C. The magnitude of benefit with evolocumab in the FOURIER trial on a per mmol/l basis of LDL-C lowering is largely consistent with the cardiovascular benefits documented in pooled analysis of previous statin trials (Fig. 1). Hence, the FOURIER trial results strengthen and further extend the hypothesis of ‘lower is better’ by demonstrating cardiovascular benefits from decreasing LDL-C to median levels lower than those in any previous outcome trials. Importantly, the positive results of this landmark trial strengthen the clinical consideration of PCSK9 inhibitors in management of secondary prevention and confirm clinically the findings of the Global Assessment of Plaque Regression with a PCSK9 Antibody as Measured by Intravascular Ultrasound trial, which showed a reduction in coronary atherosclerotic plaque volume on intravascular ultrasound over 18 months [44**].

The results of two randomized cardiovascular outcome trials, Studies of PCSK9 Inhibition and the Reduction of vascular Events (SPIRE)-1 and SPIRE-2, comparing the humanized PCSK9 inhibitor bococizumab with placebo were simultaneously published [45] with FOURIER. The bococizumab arm showed a reduction in major adverse cardiovascular events only in the SPIRE-2 trial involving patients with higher LDL-C (inclusion criteria ≥2.6 mmol/l), but not in SPIRE-1 (LDL-C inclusion criteria ≥1.8 mmol/l). This difference of cardiovascular efficacy in one of the two trials may be explained by the lower event rate observed in the lower risk SPIRE-1 study participants, differences in median duration of follow-up (7 months in SPIRE-1 and 12 months in SPIRE-2) and/or by the lack of durability of LDL-C reduction observed before both these trials were halted prematurely. This attenuation of LDL-C lowering over time is thought to be related to the development of neutralizing and anti-humanized mAb. This immunologic difference among PCSK9 inhibitors may also explain the high rate of injection-site reactions observed only with bococizumab, but not significantly with evolocumab or alirocumab. Notably, there was no significant increase in other adverse effects for bococizumab in the SPIRE trials.

PROPROTEIN CONVERTASE SUBTILISIN/KEXIN TYPE-9 INHIBITORS: WHAT DO WE KNOW ABOUT SAFETY?

No major adverse effects have been noted in phase II and phase III trials of PCSK9 inhibitors. The largest reported patient-years exposure to date, that provide clues to safety for the two marketed PCSK9 inhibitor agents include the FOURIER trial for evolocumab with 59,865 patient-years of overall follow-up and the ODYSSEY long-term study with 2061 patient-years of exposure to alirocumab. Both evolocumab and alirocumab have been able to
maintain a clean safety slate with no significant differences from the corresponding placebo arms for premature drug discontinuation rates, allergic reactions, muscle or liver-related adverse effects, haemorrhagic stroke, cataract, new onset diabetes, or worsening of glycaemic control. A theoretical concern regarding prolonged exposure to extremely low LDL-C levels leading to a negative impact on neurocognitive function has been postulated. This concern is based on the fact that cholesterol is vital in synapse formation and function and cholesterol in the brain is synthesized locally by glia [46]. However, it should be noted that mAbs are considered to be too large to cross the blood–brain barrier. Indeed, nonsignificant increase in neurocognitive disorder was reported in both the OSLER (reported incidence of 0.9% for evolocumab vs. 0.3% for placebo) and ODYSSEY long term (reported incidence of 1.2% for alirocumab vs. 0.5% for placebo) studies – although the assessments were based on few events and with inconsistent methodological testing. Nonetheless, in early 2014 the US Food and Drug Administration directed developers of PCSK9 inhibitors to monitor neurocognitive adverse effects and consider neurocognitive testing in at least a subset of participants in ongoing late-stage trials. The as yet unpublished EBBINGHAUS study [46,47] is a prospectively designed, dedicated neurocognitive study within the FOURIER trial. Results from the EBBINGHAUS substudy were presented at a late-breaking session at the American College of Cardiology annual conference in 2017. This substudy evaluated 1204 patients, without dementia or cognitive impairment at baseline. Cognitive function was assessed using a standardized Cambridge Neuropsychological Test Automated
Battery assessment. Over a median follow-up of 19.8 months, the primary endpoint of spatial working memory strategy index of executive function and several secondary endpoints were no different between the evolocumab vs. the placebo groups. There was also no evidence to suggest differences in cognitive tests in patients attaining very low LDL-C levels (≤0.65 mmol/l). Although the robust EBBINGHAUS study design and use of an objective, well validated assessment tool strengthen the neurocognitive safety of PCSK9 inhibitors as well as that of extremely low levels of LDL-C achieved, longer term assessments in varied populations need to be undertaken.

PROPROTEIN CONVERTASE SUBTILISIN/KEXIN TYPE-9 INHIBITORS: KEY UNANSWERED QUESTIONS

In addition to long-term safety, two key clinical questions remain to be answered for the PCSK9 inhibitor class: Do PCSK9 inhibitors lead to a survival benefit? Do PCSK9 inhibitors reduce major cardiovascular endpoints in other populations not studied in FOURIER, for example, postacute coronary syndrome population, high-risk primary prevention population, and so on What should be the new LDL-C target level in secondary prevention? In relation to the first question, it is widely believed that the duration of follow-up of just over 2 years in FOURIER, may have limited the efficacy of evolocumab to demonstrate reduced cardiovascular mortality. The ODYSSEY Outcomes trial [48] with alirocumab is an ongoing trial that may help answer these questions. This trial is estimated to randomize 18 600 patients, who have experienced an ACS event 4–52 weeks prior to randomization. The maximum study duration is estimated to include 60 months of randomized treatment period with alirocumab vs. placebo. Last, with the completion of the new PCSK9 inhibitor outcome trials, updated guidelines will likely address a new LDL-C target level for secondary prevention.

Several additional practical and pharmacoeconomic questions need to be answered: What, if any, challenges and barriers exist in real-life clinical practice for initiation and maintenance of these agents? Cost-benefit and incremental cost-utility ratio analysis to predict the impact that these agents may have on healthcare systems.

OUR REAL-LIFE CLINICAL EXPERIENCE WITH EVOLOCUMAB

The Cambridge Cardiac Care Centre is a large regional cardiac rehabilitation and prevention facility servicing a population of 150 000 in Cambridge, Ontario, Canada. Author A.S.P. is the lead physician at this centre.

PCSK9 inhibitors were incorporated into the treatment algorithm for high-risk patients with stable coronary artery disease, post-MI or postrevascularization therapy, who had not achieved target LDL-C levels as per the Canadian Cardiovascular Society 2016 lipid guidelines [12]. Here we report the effects of evolocumab in 57 consecutive patients initiated and maintained on this therapy for more than 1 year. During this time, an additional 59 patients were prescribed but did not initiate this therapy for various reasons outlined below and served as the control group. Baseline demographics did not differ between the two cohorts and are outlined in Table 1. After more than 1 year of

| Table 1. Baseline demographics of ASCVD patients not meeting low-density lipoprotein cholesterol targets on and not on Evolocumab |
|---|---|---|---|
| **Demographics** | **On evolocumab** (n = 57) | **Not on evolocumab** (n = 59) | **P** |
| **Medical history n, [%]** | | | |
| Diabetes | 10 (18) | 15 (25) | 0.37 |
| Hypertension | 45 (79) | 45 (76) | 0.73 |
| Smoking | 9 (16) | 11 (19) | 0.69 |
| Prior MI | 15 (26) | 21 (36) | 0.28 |
| Prior stroke | 2 (4) | 5 (8) | 0.27 |
| Prior CABG | 5 (9) | 6 (10) | 0.80 |
| Prior PCI | 10 (18) | 12 (20) | 0.70 |
| **Medications n, [%]** | | | |
| Aspirin | 39 (68) | 39 (66) | 0.79 |
| P2Y12 inhibitor | 11 (19) | 12 (20) | 0.90 |
| ACEI/ARB/ARNI | 41 (72) | 42 (71) | 0.93 |
| Statin | 52 (91) | 54 (91) | 0.96 |
| High dose | 32 (56) | 39 (66) | 0.28 |
| Med dose | 16 (28) | 12 (20) | 0.34 |
| Low dose | 4 (7) | 1 (2) | 0.16 |
| Ezetimibe | 19 (33) | 17 (29) | 0.60 |
| Bile Acid Seq | 13 (23) | 17 (29) | 0.46 |

ACEI, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blockers; ARNI, angiotensin receptor-neprilysin inhibitor; ASCVD, atherosclerotic cardiovascular disease; Bile Acid Seq, bile acid sequestants; CABG, coronary artery bypass graft surgery; MI, myocardial infarction; PCI, percutaneous coronary intervention.

<ref>High-dose statin: atorvastatin 40–80 mg, rosuvastatin 20–40 mg, medium-dose statin: atorvastatin 20–40 mg, rosuvastatin 5–20 mg, simvastatin 40–80 mg; low-dose statin: atorvastatin 10 mg, simvastatin < 40 mg, pravastatin all doses, fluvastatin all doses.</ref>
evolocumab on top of maximally tolerated statin therapy, there was a 51% reduction in LDL-C. There were no significant changes in the lipid profile of the control cohort who did not initiate PCSK9 inhibitor therapy (Table 2). Over three-quarters (77%) of the high-risk patients not at the target LDL-C of 2 mmol/l or less despite maximally tolerated statin therapy achieved this target LDL-C by 1 year with the addition of evolocumab (mean LDL-C 1.27 mmol/l at 1 year compared with 2.8 mmol/l at baseline, \( P < 0.0001 \)). There were no serious adverse events reported and no clinical cardiovascular events reported in either group. Minor injection site irritation was reported in 2.8% of patients in the evolocumab cohort, but did not lead to any medication discontinuation. The high rate of medication maintenance may be a reflection of the fact that both groups were participants in twice a week on-site cardiac rehabilitation where medication counselling and support was incorporated into their cardiac rehabilitation program.

Among the control cohort that did not initiate PCSK9 inhibitor therapy, lack of coverage and inability to pay for these medications out of pocket were the primary reasons underlying why 68% did not initiate evolocumab therapy. This cost and coverage challenge was the primary reason for not starting this medication. Additionally, a significant proportion of patients (32%) who had coverage elected not to receive evolocumab treatment despite counselling during their cardiac rehabilitation sessions. This speaks to the need for better patient education tools and services to overcome hesitancy in starting these novel therapies. Nearly, three-quarters (72%) of the individuals who chose not to take the PCSK9 inhibitor reported a lack of clinical outcome trial data as their primary concern. With the completion of the FOURIER trial and its compelling reduction in major adverse cardiovascular events with evolocumab, more patients who are not at target LDL-C may potentially be more willing to try PCSK9 inhibitor therapy. Among the remaining 28% who opted to not enter the evolocumab arm, concerns about the injection route and need for long-term monthly or bimonthly injections were the primary reasons for not starting this medication.

Our single centre experience with PCSK9 inhibition over a 1-year time frame suggests a potential for significant improvement in cholesterol management in the real world with this novel medication class, but also highlights barriers to effective implementation of this therapy.

**CONCLUSION**

In summary, the magnitude of LDL-C reduction efficacy for PCSK9 inhibitors, together with the accumulating cardiovascular benefit evidence demonstrated in recent cardiovascular outcome trials further extends the ‘lower LDL-C is better’ hypothesis for cardiovascular disease reduction in high-risk patients. Key practical, patient-level access barriers such as cost, coverage, disease education, and injection aversion will need to be addressed to promote wider adoption of PCSK9 inhibitors in real life. Additional cardiovascular efficacy and safety trials with PCSK9 inhibitors, as well as analysis of cost-benefit models are likely to influence the place of this novel class of medications in dyslipidaemia management guidelines throughout the world. Evolving evidence-based and guideline-backed lower LDL-C targets have the potential to shift the paradigm of risk reduction further from what was achieved in 1990s with the advent of statins and may help further reduce rates of cardiovascular morbidity and mortality on a population level.

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None.
Two recent studies have focused on the role of cholesterol lowering therapy in preventing cardiovascular events in patients with established cardiovascular disease. The JUPITER (Justification for the Use of Statins in Prevention: an Intervention Trial evaluating rosuvastatin) trial involved patients with low-density lipoprotein cholesterol (LDL-C) levels of <50 mg/dl with rosvastatin. The results showed a significant reduction in major adverse cardiovascular events (MACE) in the rosvastatin group compared to the placebo group (1, 2). The ODYSSEY-COMBO II trial compared the efficacy of evolocumab, a proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor, with ezetimibe in patients with hypercholesterolemia. The findings demonstrated that evolocumab significantly reduced LDL-C levels and atherosclerotic cardiovascular disease events when added to ezetimibe therapy (3, 4).

These studies highlight the importance of aggressive cholesterol lowering in patients with established cardiovascular disease. However, the optimal LDL-C target remains a topic of ongoing debate. The recent update of the European Society of Cardiology/European Atherosclerosis Society guidelines for the management of dyslipidemias recommends a non-HDL cholesterol target of ≤100 mg/dl for patients with established cardiovascular disease (5). The severity of a patient’s cardiovascular risk should guide the choice of cholesterol-lowering medication. For patients with very high cardiovascular risk, high-intensity statin therapy is recommended, whereas moderate-risk patients may benefit from combination therapy with a statin and a non-statin lipid-lowering agent (6, 7).

In conclusion, the JUPITER and ODYSSEY-COMBO II trials demonstrate the efficacy of highly intensive cholesterol lowering therapy in patients with established cardiovascular disease. These findings support the recommendation for higher-intensity lipid-lowering therapy in high-risk patients to achieve optimal cardiovascular risk reduction. Further research is needed to identify the optimal LDL-C target and to determine the long-term effects of highly intensive lipid-lowering therapy on clinical outcomes.


The large prospective cardiovascular outcomes trial demonstrated cardiovascular benefit from use of evolocumab in patients already on background statin therapy, and further supports the hypothesis of lower LDL-C is better.


Through the use of intravascular ultrasound, this trial demonstrated reduction in coronary atherosclerotic plaque volume over 18 months in those patients treated with a PCSK9 inhibitor.


The trial was designed as a subset of the large cardiovascular outcomes trial with evolocumab, FOURIER, to address the effect of PCSK9 inhibition on cognitive function.

47. Results from the EBBINGHAUS Study. American College of Cardiology 2017: 66th Annual Scientific Session. 18 March 2017 Washington, D.C., USA.

The final publication for the EBBINGHAUS study is not yet available, however the results released at this scientific session were significant in that there was no negative effect on cognitive function found with the use of PCSK9 inhibitors and further lowering LDL-C levels.