PCSK9 inhibitors and reduction in cardiovascular events: Current evidence and future perspectives

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ABSTRACT

Proprotein convertase subtilisin/kexin type 9 (PCSK9) plays an important role in low-density lipoprotein (LDL) metabolism. Pharmacological PCSK9 inhibitors have been developed as a novel approach to treating dyslipidemia. This article reviews the spectrum of evidence implicating the role of PCSK9 in lipid metabolism and the clinical impact of PCSK9 inhibitors on lipid parameters and cardiovascular risk. Biochemical and genomic studies have established the role that PCSK9 plays in lipid metabolism and potential protection from cardiovascular disease observed in the setting of PCSK9 deficiency. This led to the development of inhibitory monoclonal antibodies (evolocumab, alirocumab) that produce dose-dependent lowering of LDL cholesterol up to 60%, with evidence of regression and stabilization of coronary atherosclerosis (GLAGOV, HUYGENS, PACMAN-AMI) and reduction in cardiovascular risk in large clinical outcomes trials (FOURIER, ODYSSEY Outcomes). More recent developments have witnessed alternative approaches to PCSK9 inhibition such as RNA interference (inclisiran), vaccines, and gene editing, which are currently undergoing clinical evaluation. PCSK9 inhibition has emerged as an important component of treatment approaches to lowering LDL cholesterol and plays an increasing role in preventive strategies.

Key words: cardiovascular risk, clinical trials, lipids, PCSK9, prevention

INTRODUCTION

Population and genetic studies have established the causal role of low-density lipoprotein (LDL) cholesterol in atherosclerotic cardiovascular disease [1]. The importance of LDL cholesterol was further emphasized by the results of numerous clinical outcomes trials that demonstrated lowering of cardiovascular risk with statins, directly proportional to the degree of lipid-lowering [2]. However, the finding that many cardiovascular events continue to occur despite using statin therapy highlights the importance of residual risk for many patients [3]. Analyses of these studies have demonstrated that LDL cholesterol may continue to provide a therapeutic target for efforts to reduce residual risk in patients treated with a statin. In addition, many patients cannot tolerate the doses of statins required to achieve guideline-mandated LDL cholesterol targets [4]. Based on these findings, there remains a need to develop new therapeutic strategies to lower LDL cholesterol levels more effectively.

PCSK9 AND LIPID METABOLISM

A key step in cholesterol homeostasis involves the uptake of circulating LDL particles by the liver after interaction with LDL receptors expressed on the hepatocyte surface. Within the hepatocyte, LDL dissociates from the LDL receptor and undergoes endosomal degradation while the receptor can shuttle back to the cell surface and continue to facilitate removal of LDL from the circulation. Biochemical studies have demonstrated that proprotein convertase subtilisin/kexin type 9 (PCSK9) plays an important role in the regulation of this process. When PCSK9 binds to the LDL particle/LDL receptor complex, it prevents intracellular dissociation within the hepatocyte. This results in degradation of the whole complex, which stops shuttling of the receptor back to the cell surface and limits hepatic uptake of LDL particles [5] (Figure 1).

Genetic studies have demonstrated the importance of PCSK9 in the regulation of LDL metabolism. Gain of function PCSK9 muta-

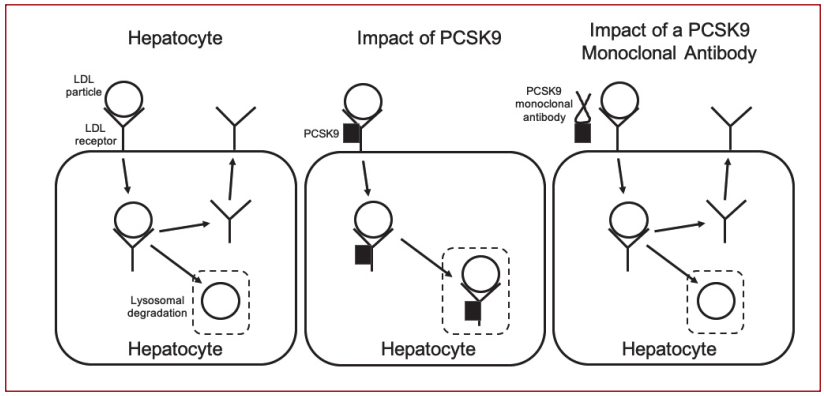

Figure 1. Schematic of low-density lipoprotein (LDL) uptake by hepatocytes (left panel) and impact of both proprotein convertase subtilisin/ /kexin type 9 (PCSK9) (central panel) and inhibitory monoclonal antibodies (right panel). The left panel demonstrates binding of LDL particles to the receptor on the hepatocyte surface, and the complex internalized into the cell followed by dissociation of the LDL particle and receptor. This permits recycling of the LDL receptor to the cell surface for more LDL uptake and degradation of intracellular LDL. The binding of PCSK9 to this complex prevents intracellular dissociation and leads to degradation of both LDL particle and receptor. This process is inhibited by PCSK9 monoclonal antibodies, permitting ongoing recycling of the LDL receptor

tions have been demonstrated to associate with elevated LDL cholesterol levels and have been identified as the third genetic locus underscoring familial hypercholesterolemia, in addition to those influencing the LDL receptor directly and expression of apolipoprotein B (apoB) [6]. Additional studies have shown that individuals with polymorphisms associated with reductions in PCSK9 also demonstrate lower levels of LDL cholesterol [7, 8]. A small number of individuals who have homozygous PCSK9 deficiency, associated with very low LDL cholesterol levels but are otherwise healthy and fertile, has been identified [9]. Mendelian randomization studies have demonstrated that loss of function PCSK9 polymorphisms is associated with lower rates of cardiovascular disease, directly proportional to lower levels of apoB [10]. Additional analyses demonstrate that loss of function polymorphisms of both hydroxy-methyl glutaryl coenzyme reductase A (the target of statins) and PCSK9 is associated with incremental protection from cardiovascular disease [10]. These findings suggest that addition of a PCSK9 inhibitor should provide clinical benefits in statin-treated patients.

DEVELOPMENT OF PCKS9 MONOCLONAL ANTIBODIES

The first foray into clinical development of PCSK9 inhibitors involved manufacturing of monoclonal antibodies. This therapeutic approach was facilitated by advances in antibody technology that witnessed an evolution from fully mouse to chimeric (~30% mouse), humanized (~5%–10% mouse) and ultimately fully human generations. This development enabled administration of antibodies with a significant reduction in immunogenicity, with major implications for tolerability, and potentially lower likelihood of developing neutralizing antibodies. Early clinical studies of these monoclonal antibodies demonstrated dose-dependent lowering of LDL cholesterol by up to 60% when administered by subcutaneous injection either every two weeks or once a month. Administration was well tolerated by patients, with reports of relatively mild injection-site reactions and a greater incidence of nasopharyngitis [11–16].

These lipid-lowering effects were similarly observed when the PCSK9 inhibitor was administered as monotherapy [11–13] or in combination with statin therapy [14–16]. The observation that PCSK9 levels increase with statin therapy [17] highlights the potential for inhibitory monoclonal antibodies to be efficacious when used in combination. The finding that these antibodies are effective lipid-lowering agents is further reinforced by the observation that a higher proportion of patients achieve treatment targets [14–16]. These agents have also been demonstrated to be of clinical utility in patients with heterozygous familial hypercholesterolemia [18, 19] and those with documented statin intolerance [13]. This is important as the two scenarios often involve a large number of patients who cannot achieve effective lipid lowering with statin monotherapy. Studies performed in the setting of homozygous familial hypercholesterolemia also demonstrate a reduction in LDL cholesterol levels by up to 30% and a reduced requirement for LDL apheresis [20], with the degree of benefit directly proportional to the presence of functional LDL receptor expression [21]. In patients with documented statin intolerance, administration of evolocumab produced more robust reductions in LDL cholesterol levels compared with ezetimibe, suggesting that more patients can achieve more effective lipid lowering despite their inability to tolerate statins [13]. These lipid studies have also demonstrated modest reductions in levels of triglycerides and lipoprotein (a) [Lp(a)] [11–16]. As a result, it is clear that PCSK9 monoclonal antibodies exert favorable effects on circulating levels of atherogenic lipid parameters in the blood.

PCSK9 INHIBITORS AND CORONARY ATHEROSCLEROSIS

Serial intravascular ultrasound (IVUS) imaging within the coronary vasculature has been employed in clinical trials of medical therapies to evaluate their impact on plaque progression. Studies of increasingly intensive statin therapy have demonstrated slowing of disease progression and ultimately plaque regression, directly proportional to the degree of lipid lowering [22–24]. Addition of the cholesterol absorption inhibitor, ezetimibe, to statin therapy has also been demonstrated to produce greater plaque regression [25]. The Global Assessment of Plaque Regression with a PCSK9 Antibody as Measured by Intravascular Ultrasound (GLAGOV) study compared the effects of treatment with evolocumab 420 mg monthly and placebo for 18 months in patients with coronary disease who had been treated with a stable dose of statin therapy for at least 4 weeks. Achieving lower LDL cholesterol levels with evolocumab (36 mg/dl vs. 92 mg/dl) was associated with plaque regression on serial IVUS imaging, with a higher proportion of patients demonstrating any degree of regression (63% vs. 48%). Individual patient analysis demonstrated a direct relationship between achieved LDL cholesterol levels down to 20 mg/dl and the rate of disease progression [26]. Subsequent radiofrequency analyses of the ultrasound backscatter revealed that evolocumab treatment resulted in modest reductions in fibrous and fibrofatty components and a larger proportional increase in plaque calcium [27]. This complemented prior observations on high-intensity statin therapy and suggested that plaque regression and calcification resulted from intensive lipid lowering [28].

The High-Resolution Assessment of Coronary Plaques in a Global Evolocumab Randomized Study (HUYGENS) aimed to compare the effects of treatment with evolocumab 420 mg monthly and placebo for 12 months in patients following a non-ST-segment elevation myocardial infarction and evidence of vulnerable plaque features in a non-culprit artery. Patients underwent serial imaging with both IVUS and optical coherence tomography (OCT) catheters, the latter enabling evaluation of plaque composition. In the setting of intensive statin therapy following acute coronary syndrome, evolocumab-treated patients demonstrated lower levels of LDL cholesterol (27 mg/dl vs. 87 mg/dl), with a higher proportion achieving treatment targets of 70 mg/dl (93.9% vs. 29.2%). The primary endpoint of the study, the change in minimum fibrous cap thickness at any point along the length of the vessel, increased to a greater degree in the evolocumab-treated patients (+42.7 μm vs. +21.5 μm). Evolocumab treatment also resulted in a higher increase in the average minimum fibrous cap thickness on all measured images along the vessel (+62.3 μm vs. +29.8 μm) and a decrease in both the maximum lipid arc (–57.5° vs. –31.4°) and macrophage index (–3.35 mm vs. –1.43 mm). Similar benefits were observed in favor of evolocumab treatment in regions containing lipid-rich plaque at baseline. A direct association was observed between the intensity of lipid lowering and thickening of the fibrous cap. In patients undergoing serial IVUS imaging, greater plaque regression was observed in patients treated with evolocumab [29]. In fact, the degree of regression achieved with evolocumab in HUYGENS was more than two-fold greater than that observed in GLAGOV (–2.29% vs. –0.95%), highlighting heightened modifiability of plaque in patients with acute coronary syndrome [29].

The Effects of the PCSK9 Antibody Alirocumab on Coronary Atherosclerosis in Patients with Acute Myocardial Infarction (PACMAN-AMI) study employed serial multimodality imaging to compare the effects of alirocumab 150 mg every two weeks and placebo treatment for 12 months in patients following myocardial infarction. Patients treated with alirocumab similarly achieved lower LDL cholesterol levels at 12 months (23.6 mg/dl vs. 74.4 mg/dl). Serial imaging of patients demonstrated that alirocumab-treated patients had a higher reduction in percent atheroma volume (–2.13% vs. –0.92%) on IVUS, higher reduction in maximum lipid core burden index (–79.4 vs. –37.6) on near-infrared spectroscopy, and a higher increase in minimum fibrous cap thickness (+62.7 μm vs. +33.2 μm) and decrease in macrophage angle (–26.0° vs. –16.0°) on OCT [30]. While the findings of these studies were demonstrated after 12 months of treatment, a small observational study reported early increases in fibrous cap thickness and decreases in the lipid arc when patients underwent follow-up imaging with OCT after 4 weeks of treatment with evolocumab [31]. The changes observed in these studies demonstrate the importance of intensive lipid lowering on both plaque burden and composition. Importantly, the studies performed in patients following acute coronary syndrome demonstrated a greater degree of plaque regression, suggesting the presence of more modifiable plaques (Table 1).

Additional studies have attempted to evaluate the impact of PCSK9 inhibition on atherosclerotic plaque using different imaging modalities. Non-randomized data demonstrate a reduction in carotid intima-medial thickness with evolocumab treatment [32]. The Effect of Evolocumab on Carotid Plaque Composition in Asymptomatic Carotid Artery Stenosis (EVOCAR-1) study evaluated the impact of PCSK9 inhibition using serial carotid magnetic resonance imaging (MRI) [33]. The Effects of Proprotein Convertase Subtilisin/Kexin Type 9 Inhibition on Arterial Wall Inflammation in Patients with Elevated Lipoprotein (a) (ANITSCHKOW) study evaluated the impact of evolocumab on carotid plaque inflammatory activity using serial positron emission tomography (PET) imaging with fluorodeoxyglucose (FDG) in patients with elevated Lp(a) levels at baseline. While both LDL cholesterol and Lp(a) levels were reduced with evolocumab, a significant reduction in carotid FDG activity was not observed [34].

Table 1. Major trials of monoclonal antibody PCSK9 inhibitors to date

Study	Clinical setting	Study evaluation	Finding
GLAGOV	Evolocumab vs. placebo in statin-treated patients with CAD	Serial IVUS imaging of coronary plaque progression	Incremental plaque regression with evolocumab directly proportional to LDL-C lowering
HUYGENS	Evolocumab vs. placebo in statin-treated patients following an ACS	Serial OCT/IVUS imaging of coronary plaque progression and composition	Incremental plaque regression, fibrous cap thickening, and decrease in plaque lipid and macrophages with evolocumab
PACMAN-AMI	Alirocumab vs. placebo in statin-treated patients following an ACS	Serial OCT/IVUS/NIRS imaging of coronary plaque progression and composition	Incremental plaque regression, fibrous cap thickening, and decrease in plaque lipid and macrophages with alirocumab
FOURIER	Evolocumab vs. placebo in statin-treated patients with stable ASCVD	Clinical outcomes trial	15% reduction in MACE
ODYSSEY outcomes	Alirocumab vs. placebo in statin-treated patients following an ACS	Clinical outcomes trial	15% reduction in MACE
SPIRE	Bococizumab vs. placebo in statin-treated patients with high CV risk	Clinical outcomes trial	No clinical benefit and development of neutralizing antibodies

Abbreviations: ACS, acute coronary syndrome; ASCVD, atherosclerotic cardiovascular disease; CAD, coronary artery disease; CV, cardiovascular; IVUS, intravascular ultrasound; LDL-C, low-density lipoprotein cholesterol; MACE, major adverse cardiovascular events; NIRS, near-infrared spectroscopy; OCT, optical coherence tomography

PCSK9 INHIBITORS AND CARDIOVASCULAR EVENTS

Some early evidence suggested that administration of PCSK9 inhibitors should translate to reductions in cardiovascular risk in statin-treated patients. Mendelian randomization analyses demonstrated an additive protective effect of polymorphisms resulting in reductions in both HMG-CoA reductase and PCSK9, suggesting the potential for therapeutic combination [10]. Post-hoc analyses of early phase 2 studies of both evolocumab and alirocumab demonstrated fewer cardiovascular events in patients treated with the PCSK9 inhibitor compared with placebo [35, 36].

The Further Cardiovascular Outcomes Research with PCSK9 Inhibition Subjects with Elevated Risk (FOURIER) study compared the effects of evolocumab 140 mg every two weeks or 420 mg monthly or placebo on cardiovascular events in 27 564 statin-treated patients with atherosclerotic cardiovascular disease and LDL cholesterol levels of at least 70 mg/dl. Patients treated with evolocumab achieved lower levels of LDL cholesterol (30 mg/dl vs. 92 mg/dl). After a median follow-up duration of 2.2 years, the risk of major adverse cardiovascular events was decreased by 15% in the patients treated with evolocumab. A linear relationship was observed between the achieved LDL cholesterol levels and the rate of major adverse cardiovascular events [37]. An embedded substudy that evaluated neurocognitive function found no adverse effect in the evolocumab-treated patients [38].

The ODYSSEY Outcomes study compared the effects of treatment with alirocumab 75–150 mg every two weeks or placebo in 18 924 statin-treated patients who had acute coronary syndrome 1–12 months earlier with either LDL cholesterol higher than 70 mg/dl, non-HDL cholesterol higher than 100 mg/dl, or apoB higher than 80 mg/dl. This study directed investigators to down titrate therapy if patients who achieved LDL cholesterol levels below 15 mg/dl. On treatment, LDL cholesterol levels were lower in the alirocumab group (40–66 mg/dl at different points throughout the study compared with 92 mg/dl in the placebo group). After a median follow-up duration of 2.8 years, the rate of major adverse cardiovascular events was similarly reduced by 15%. A finding of fewer deaths in the alirocumab group (3.5% vs. 4.1%) was observed although this was not statistically significant. These findings extended the benefits of PCSK9 inhibition to patients with recent acute coronary syndrome [39].

A third cardiovascular outcomes trial was conducted evaluating the impact of a PCSK9 inhibitory monoclonal antibody. The SPIRE studies were conducted in 27 438 high-cardiovascular-risk patients with entry LDL cholesterol levels greater than 70 or 100 mg/dl, respectively, who were randomized to treatment with bococizumab or placebo. The trials were stopped prematurely due to observing the development of neutralizing antibodies, a gradual diminution of LDL cholesterol lowering over time, and a combined lack of significant reduction in cardiovascular event rates. In the trial of patients with baseline LDL cholesterol levels higher than 70 mg/dl, there was no difference in cardiovascular event rates between the groups. In the trial of patients with baseline LDL cholesterol higher than 100 mg/dl, fewer cardiovascular events were observed in the bococizumab-treated patients [40]. In contrast to other agents, bococizumab is a humanized monoclonal antibody, which is likely to underscore the development of neutralizing antibodies and greater incidence of injection-site reactions. Accordingly, the development of this agent was terminated.

Additional substudies of the FOURIER and ODYSSEY Outcomes studies provided further insights into the most effective approaches to using PCSK9 inhibitors in clinical practice. Posthoc analyses demonstrated the lowest cardiovascular event rates in patients achieving the lowest LDL cholesterol levels, with no increase in adverse events [41]. Analyses of patients with recurrent clinical events, multivessel coronary disease, poly-vascular disease, diabetes, and the presence of multiple risk factors identified higher event rates and a greater absolute risk reduction with the use of PCSK9 inhibitors [10, 42, 43]. While the primary composite

endpoints of these studies focused on events attributable to the coronary and cerebral circulations, additional investigation demonstrated that the use of PCSK9 inhibitors reduced the rate of lower limb ischemic clinical events, regardless of whether patients had manifest peripheral arterial disease at baseline [10]. Longer-term administration produced greater reductions in cardiovascular risk, with the emergence of a statistically significant reduction in cardiovascular death [44]. Administration of a PCSK9 inhibitor not only reduced the risk of a first cardiovascular event, the typical focus of large outcomes trials, but also reduced the risk of subsequent and recurrent events [45]. While the benefits of PCSK9 inhibitors were directly proportional to the degree of LDL cholesterol lowering, additional investigations demonstrated that Lp(a) lowering with these agents was independently associated with their clinical benefit [46, 47] (Table 1).

RNA TARGETED APPROACHES TO PCSK9 INHIBITION

Therapeutic monoclonal antibodies target PCKS9 in the circulation, require administration at least every two weeks and are associated with injection-site reactions and nasopharyngitis. Technological advances in RNA inhibitory therapeutics now permit targeted delivery within the hepatocyte with the potential to inhibit PCSK9 synthesis with greater durability and tolerability. Inclisiran is a double-stranded small interfering RNA, conjugated with triantennary N-acetylgalactosamine (GalNAc), which permits selective uptake by hepatocytes [48–50]. Early studies have demonstrated that administration of inclisiran produces LDL cholesterol lowering in the range of 50%, with good durability (38% LDL cholesterol lowering at 6 months). The agent is well tolerated, apart from an increase in injection-site reactions, but provides the opportunity for twice-yearly dosing [48–51]. Pooled data from early studies in patients at high cardiovascular risk demonstrated that inclisiran-treated patients experienced fewer cardiovascular events [52] although this finding will require validation in a dedicated randomized clinical trial. Inclisiran is currently undergoing evaluation for its effects on cardiovascular outcomes and longer-term safety and tolerability in large clinical outcomes trials conducted in patients with and without clinically manifest atherosclerotic cardiovascular disease.

EMERGING APPROACHES TO PCSK9 INHIBITION

With evidence that PCSK9 inhibition produces favorable effects on atherogenic lipid parameters in the circulation, atherosclerotic burden and composition on imaging, and cardiovascular events in large clinical trials, there is ongoing interest in developing novel approaches to targeting PCSK9 in high-risk patients. While clinical evaluation of RNA interference with inclisiran is ongoing, there are additional therapeutic approaches in development to reduce PCSK9 activity. While most efforts in the PCSK9 field have focused on the development of injectable biologics, there has been some interest in the potential to develop a daily oral therapeutic. Early clinical trials of an oral tricyclic macrocycle PCSK9 inhibitor with good bioavailability demonstrated similar efficacy to injectables with reductions in PCSK9 by 90% and LDL cholesterol by up to 65% and evidence of good tolerability [53].

While this agent requires ongoing clinical evaluation, it might provide an alternative clinical model in comparison to injectable delivery. In parallel, other programs are attempting to reduce PCSK9 using less frequent injectable technologies. The use of vaccine technology is being employed to target PCSK9. Early mouse studies of an immunogenic fused PCSK9-tetanus have been incorporated onto the surface of negatively charged nanoliposomes as a vaccine delivery system. Long-term administration in mice demonstrated reductions in PCSK9 by 58% and LDL cholesterol by more than 40% [54]. PCSK9 has also been employed as the therapeutic targeting approach for gene editing, with evidence of sustainable reductions in LDL cholesterol by more than 50% in non-human primates and with development progressing to early human studies [55]. The development of these latter technologies provides the opportunity for either yearly or potentially once-in-a-lifetime administration of a PCSK9 inhibitor. The ability of these agents to demonstrate longer-term efficacy and patient tolerability will be essential for them to advance to clinical practice.

IMPLICATIONS FOR CLINICAL PRACTICE

The development of PCSK9 inhibitors has provided a greater opportunity to achieve more effective lipid control in high-cardiovascular-risk patients. Given that more than 50% of high-risk patients fail to achieve LDL cholesterol treatment goals with statin monotherapy, there is increasing support for the concept that many patients will require combination lipid-lowering therapy — in a similar fashion to that observed in hypertension and type 2 diabetes mellitus. The evidence that using PCSK9 inhibitors in combination with maximally tolerated statin therapy results in more than 90% of patients achieving treatment targets suggests that this combination can be effective at achieving more substantial reductions in cardiovascular risk. This is particularly important for patients with statin intolerance or genetic dyslipidemia, where many will fail to achieve effective lipid lowering with statin monotherapy.

In parallel, the PCSK9 inhibitor trials have offered the opportunity to evaluate cardiovascular efficacy and safety at very low LDL cholesterol levels. Given that the achieved LDL cholesterol levels in these studies are typically below 1 mmol/L, we now have substantial experience with patients achieving very low LDL cholesterol levels. What has been observed is greater regression and stabilization of coronary atherosclerosis and greater reductions in cardiovascular event rates. Importantly, there appear to be no

safety signals in patients achieving LDL cholesterol levels of less than 0.5 mmol/l. As many patients will achieve comparable LDL cholesterol levels in clinical practice, there is no rationale for back titration of either statin or PCSK9 inhibitor therapy.

The biggest challenge in the field involves access to these therapies. Concerns regarding costs [56, 57] have stimulated research to identify those patients who are most likely to derive clinical benefits. Further cost reductions will lead to greater availability of PCSK9 inhibitors in clinical practice. The appearance of additional approaches to PCSK9 inhibition, such as RNA interference, gene editing, and vaccines, opens up opportunities to not only provide alternative clinical models for lipid management but also introduce greater competition in the field. The same can be said for bempedoic acid and cholesteryl ester transfer protein (CETP) inhibitors, which also reduce LDL cholesterol and may either become alternatives to PCSK9 inhibitors or may be useful in patients who cannot tolerate PCSK9 inhibitors [58]. It is likely that in the future, many more patients will be treated with combination lipid-lowering therapy, which includes a PCSK9 inhibitor. As this occurs, it will remain essential that real-world studies offer the opportunity to continue to monitor long-term safety and tolerability of these approaches.

CONCLUSION

In the last two decades, the PCSK9 field has rapidly advanced from early genetic studies implicating PCSK9 in lipid metabolism and dyslipidemia to the clinical development of therapeutic PCSK9 inhibitors that have come into clinical practice. Increasing efforts should be undertaken to overcome the barriers to access to these agents as combination approaches to optimal lowering of LDL cholesterol become the cornerstone of lipid management. Ongoing clinical development programs have the potential to introduce a range of alternative therapeutics that will give patients and healthcare professionals a greater choice in the shared decision-making on targeting their cardiovascular risks.

Article information

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