Management of Severe Dyslipidaemia: Role of PCSK9 Inhibitors

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Abstract

Proprotein convertase subtilisin/kexin type 9 (PCSK9) plays an important role in regulation of LDL receptors on the hepatocyte surface and therefore is essential for effective removal of LDL particles from circulation. Genetic and biochemical studies have established that altered PCSK9 functionality influences both LDL cholesterol levels and cardiovascular risk. This has prompted development of inhibitory strategies targeting PCSK9. Study of monoclonal PCSK9 antibodies has progressed to the clinic, where they have been found to lower LDL cholesterol levels and reduce cardiovascular event rates in large, clinical outcome trials. The use of PCSK9 inhibitors in the setting of dyslipidaemia is reviewed.

Keywords

Atherosclerosis, cardiovascular risk, clinical trials, lipids, risk factors

Disclosure: Stephen J. Nicholls has received research support from AstraZeneca, Amgen, Anthera, Eli Lilly, Esperion, Novartis, Cerenis, The Medicines Company, Resverlogix, InfraReDx, Roche, Sanofi-Regeneron and LipoScience and is a consultant for AstraZeneca, Eli Lilly, Anthera, Omthera, Merck, Takeda, Resverlogix, Sanofi-Regeneron, CSL Behring, Esperion and Boehringer Ingelheim.

Received: 29 January 2018 **Accepted:** 15 May 2018 **Citation:** *European Cardiology Review* 2018; **13**(1):9–13. **DOI:** <https://doi.org/10.15420/ecr.2018.3.2>

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Therapeutic targeting of dyslipidaemia has been one of the major successes in cardiovascular medicine over the last three decades. On the basis of unequivocal evidence from animal models through to both population and genetic studies in humans, there is a clear association between increasing levels of LDL cholesterol (LDL-C) and incident cardiovascular risk.¹ This has prompted efforts to develop a range of therapeutic strategies that lower LDL-C levels. Seminal clinical trials have demonstrated that lowering LDL-C levels with statins reduces cardiovascular event rates in the setting of primary and secondary prevention.² More recently, addition of the cholesterol absorption inhibitor ezetimibe to a statin results in further reduction in cardiovascular risk.³ These studies contribute to large meta-analyses that have consistently demonstrated that each 1 mmol/l lowering of LDL-C is associated with an approximately 21 % reduction in the rate of cardiovascular events.² While these findings have been translated to clinical practice, with statins becoming a cornerstone of cardiovascular prevention strategies, there remains an ongoing need to develop additional lipid-lowering approaches.

Challenges with Statins

The findings of the statin cardiovascular outcome trials have supported the widespread use of statins in clinical practice as the first therapeutic option in prevention strategies. Recently, studies highlighting the importance of more intensive lipid lowering have led to calls for greater use of more potent statins in patients deemed to be at high cardiovascular risk.⁴ While these data are irrefutable, particularly for the very high-risk patient, many patients are either not treated, do not undergo appropriate dose escalation or stop taking this treatment.⁵ While clinical inertia contributes to the suboptimal prescription of statins, particularly at more potent doses, high discontinuation rates are driven by a range of factors, including inability to comply with long-term therapy, symptomatic myalgia and concerns regarding potential

associations with adverse effects such as new-onset diabetes and impaired cognitive function. While many patients do experience myalgia that prevents use of effective statin doses, the clinical implications of new-onset diabetes are uncertain and there is no evidence to clearly establish that statins have any objective impact on cognitive function.⁶

The additional challenge for statins is the inability of some patients to achieve guideline-mandated treatment goals.⁵ This is particularly problematic in patients with familial hypercholesterolaemia, in which the combination of very high baseline LDL-C levels and genetically altered lipid metabolism continues to expose many of these patients to unacceptably high LDL-C levels.⁷ This is likely to underscore a considerable high risk of cardiovascular events. Even when patients do achieve treatment targets with statin therapy, many cardiovascular events will continue to occur.⁸ This residual risk continues to support the need to develop additional lipid lowering strategies and to ask whether reducing LDL-C to very low levels will result in even greater cardiovascular protection.

PCSK9 and Lipid Homeostasis

Proprotein convertase subtilisin/kexin type 9 (PCSK9) was discovered in 2003 and plays an important role in the regulation of lipid metabolism.⁹ PCSK9 is a factor, synthesised within the hepatocyte and secreted into the circulation, where it binds to the complex between LDL particles and the LDL receptor. Within the hepatocyte, the presence of PCSK9 prevents dissociation of the LDL particle from the receptor, which directs both to lysosomal degradation. This process prevents ongoing shuttling of the free LDL receptor back to the hepatocyte surface, where it continues to remove LDL particles and their cholesterol content from circulation. Gain-of-function PCSK9 mutations have been identified as the third autosomal dominant locus underlying familial

hypercholesterolaemia.¹⁰ In addition, a number of polymorphisms have been identified that result in reduced PCSK9 and are associated with both lower LDL-C levels and lower rates of cardiovascular events.^{11,12} Mendelian randomisation studies have provided further evidence linking low levels of PCSK9 activity with both lower lipid levels and cardiovascular risk.¹³ These data have supported the rapid expansion of efforts to develop inhibitory approaches to PCSK9 inhibition as a potential cardioprotective agent.

PCSK9 Monoclonal Antibodies and Lipid Levels

Advances in monoclonal antibody technology permit development of fully human antibodies targeting PCSK9. A large number of lipid studies have demonstrated that the agents evolocumab and alirocumab produce dose-dependent lowering of LDL-C by up to 60 %. In addition, PCSK9 inhibitors have been demonstrated to lower triglyceride levels by up to 20 % and lipoprotein(a) by 25–30 % and to modestly raise HDL cholesterol (HDL-C) levels. These findings are observed when these agents are administered either as monotherapy^{14–16} or in combination with statins.^{17–19}

Given their ability to produce robust LDL-C lowering, these agents have been extensively evaluated in patients with familial hypercholesterolaemia, with evidence of substantial lipid lowering in both heterozygous (–60 %) and homozygous (–30 %) patients.^{20–22} The finding of LDL-C lowering in homozygous familial hypercholesterolaemia suggests that some of these patients have some level of functioning LDL receptor activity. In fact, further analyses demonstrated LDL-C lowering in those patients with functional LDL receptors, while there was no activity in patients with no functioning LDL receptors.²² The ability to achieve effective lipid lowering as monotherapy has permitted the evaluation of PCSK9 inhibitors in patients with statin intolerance. The lipid efficacy is balanced by the finding of no excess in myalgia rates compared with ezetimibe treatment in these patients.¹⁶ The observation of similar lipid lowering in statin-treated patients would be anticipated, given that statins are associated with an increase in PCSK9 levels.²³ In general, these agents were well tolerated, with no concerning signs of adverse events.

PCSK9 Monoclonal Antibodies and Clinical Outcomes

Clinical trials have transitioned queries regarding the impact of PCSK9 inhibitors on circulating lipid levels to atherosclerotic plaque within the artery wall and subsequently cardiovascular events.

Evolocumab

The Global Assessment of plaque reGression with a PCSK9 antiBody as measured by intraVascular ultrasound (GLAGOV) study employed serial intravascular ultrasound imaging to determine the impact of the PCSK9 inhibitor evolocumab on progression of coronary atherosclerosis in patients already treated with a statin, who had presented for a clinically indicated coronary angiogram.²⁴ The combination of evolocumab and statin produced a lower LDL-C than statin monotherapy (0.95 mmol/l versus 2.4 mmol/l). This translated to a beneficial impact on the change in percentage total atheroma volume (–0.95 % versus 0.05 %) and a greater percentage of patients demonstrating any degree of disease regression (64 % versus 47 %). A direct relationship was observed between achieved LDL-C levels and the rate of disease progression, demonstrating no loss of incremental benefit at lower LDL-C levels. Patients with baseline LDL-C levels less than 1.8 mmol/l demonstrated even greater

reductions in percentage atheroma volume (–1.97 %) and a greater percentage of patients with regression (81 %). This may reflect the need for additional risk factors for study entry in these patients and the fact that their lower LDL-C did not protect them from the need for coronary angiography, thus potentially identifying patients with more modifiable disease. Subsequent analyses have revealed that ongoing progression, despite treatment with evolocumab, was observed in patients with additional risk factors and that regression was accompanied by an increase in plaque calcium, further supporting a role in plaque stabilisation.

The Further cardiovascular Outcomes Research with PCSK9 Inhibition in subjects with Elevated Risk (FOURIER) study was the first large clinical outcomes trial to evaluate the impact of adding evolocumab to existing statin therapy in patients with a prior history of MI, stroke or peripheral arterial disease and LDL-C ≥ 1.8 mmol/l.²⁵ Similar to GLAGOV, patients had generally been on optimised regimens prior to study entry, with more than 60 % receiving the highest intensity statin therapy prior to the study. Mean LDL-C reduced in the evolocumab/statin group by 2.4 mmol/l versus 0.78 mmol/l in the placebo group. This was associated with a reduction in the risk of cardiovascular events for patients in the evolocumab/statin group, with a 15 % reduction in the risk for the primary composite end point (cardiovascular mortality, non-fatal MI, non-fatal stroke, coronary revascularisation and hospitalisation for unstable angina, and a 20 % reduction in the risk of secondary end point events (cardiovascular death, non-fatal MI and non-fatal stroke). While this study was large (27,654 patients), the median treatment exposure was only 26 months, with many taking the study drug for only 12 months. Given that the event curves did not begin to separate for at least 6 months, the limited treatment exposure in many patients may have led to a potential underestimate of event reduction with evolocumab. Prespecified landmark analyses revealed a greater proportional reduction in cardiovascular events with evolocumab in patients treated in the second year and beyond. Subsequent analyses demonstrated a direct association between achieved LDL cholesterol levels and cardiovascular event rates, further extending the lower-is-better concept.

Evolocumab was well tolerated, with no excess in the rate of adverse events compared with placebo. In particular, there was no excess in the rate of injection-site reactions or adverse events that are often raised in relation to statins (new-onset diabetes, myalgia, cataracts, cognitive decline).²⁵ While a prior pooled analysis of evolocumab-treated patients in longer-term lipid studies signalled a potential excess rate of investigator-reported neurocognitive adverse events,²⁶ this was not observed in FOURIER.²⁵ Furthermore, a large substudy that evaluated executive cognitive function using well-validated assays failed to demonstrate any impairment with either evolocumab treatment or achievement of very low LDL-C levels.²⁷

A number of subgroup analyses have been subsequently reported providing further insight into the efficacy and safety profile of evolocumab therapy. These findings included:

- Similar event reductions in patients with a baseline LDL-C < 1.8 mmol/l.²⁸
- Similar event reductions in patients with and without diabetes, with no worsening of glycaemic control or in the incidence of new-onset diabetes.²⁹
- Similar event reductions in patients with and without prior stroke.³⁰

- Greater event reductions in patients with prior MI and high-risk features (<2 years from index MI, at least two prior MIs, multivessel coronary artery disease).³¹
- Greater proportional reductions with evolocumab were observed in patients with an established history of peripheral arterial disease, compared to those without. In addition to the reduction in coronary and cerebrovascular events, evolocumab administration resulted in a significant reduction in the incidence of major adverse limb events (acute limb ischaemia, major amputation or urgent peripheral revascularisation for ischaemia) in both patients with and without established peripheral arterial disease.³²

Bococizumab

Bococizumab is a humanised monoclonal antibody targeting PCSK9. While preliminary lipid studies were favourable with similar findings to that observed with both evolocumab and alirocumab, two large clinical outcome trials were stopped prematurely due to the incidence of neutralising antibodies, resulting in a loss of LDL-C lowering in many patients. The presence of neutralising antibodies with the humanised agent bococizumab, but not the fully human antibodies evolocumab and alirocumab, seems most likely to explain the loss of LDL-C lowering in patients treated with this agent alone. However, the Studies of PCSK9 Inhibition and the Reduction of vascular Events 2 (SPIRE-2) study of bococizumab in patients with higher baseline lipid levels at entry (LDL-C ≥ 2.59 mmol/l or non-HDL-C > 3.36 mmol/l) demonstrated a significant reduction in event rates, despite accruing a relatively small number of clinical events.^{33,34} This supports the benefits of novel lipid lowering agents in patients with higher baseline LDL-C levels.

Alirocumab

The primary results of the ODYSSEY Outcomes trial were reported at the 2018 Scientific Sessions of the American College of Cardiology.³⁵ This study evaluated the impact of addition of alirocumab to background statin therapy in patients who have experienced an acute coronary syndrome in the preceding 4–52 weeks.³⁶ This study differed from FOURIER from the perspective that it aimed for a target LDL-C of 0.65–1.3 mmol/l. This required backtitration of alirocumab dose for patients with LDL-C < 0.39 mmol/l. From an intention-to-treat perspective, alirocumab produced lower LDL-C levels than placebo (1.72 mmol/l versus 2.67 mmol/l), which was associated with a 15 % reduction in the primary composite endpoint of coronary heart disease death, non-fatal MI, ischaemic stroke or unstable angina requiring hospitalisation. On nominal, non-hierarchical testing, a reduction in all-cause mortality was observed in alirocumab-treated patients (3.5 % versus 4.1 %). While the benefit appeared to be largely observed in those patients with a baseline LDL-C greater than 2.59 mmol/l, further supporting findings from SPIRE and FOURIER, patients at lower baseline levels were more likely to undergo backtitration of alirocumab dose. Reassuring data were observed for safety and tolerability, providing additional information that intensive lowering of LDL-C can be beneficial for high-risk patients.

Use of PCSK9 Monoclonal Antibodies in Clinical Practice

These trials have now translated the benefits of PCSK9 monoclonal antibodies from their effects on circulating lipid parameters in the blood to plaque within the artery wall and ultimately cardiovascular events. As predicted, incremental lowering of LDL-C produces clinical benefit, extending prior observations of a direct association between these parameters. In fact, the early studies with evolocumab now

demonstrate both cardiovascular efficacy and overall safety in patients achieving very low LDL-C levels. The question will now involve how to translate these findings to clinical practice. It would appear that there are a number of groups in whom use of a PCSK9 inhibitor should be considered.

Familial hypercholesterolaemia is common and, left untreated, is a major driver of premature atherosclerotic cardiovascular disease. Many patients with this genetic disorder continue to demonstrate unacceptably high LDL-C levels, despite use of maximally tolerated lipid-lowering agents.⁷ Accordingly, there is a need to develop novel approaches to achieve more effective lipid lowering. Clinical studies performed in these patients have demonstrated that administration of a PCSK9 inhibitor can provide a useful adjunctive therapy in both heterozygous and homozygous states.^{20–22} The clinical utility of this benefit is further evidenced by a reduction in need for LDL apheresis in those patients with the most refractory forms of dyslipidaemia.³⁷ The evolution of PCSK9 inhibitors has provided an important stimulus to increase awareness of familial hypercholesterolaemia, which should result in greater use of cascade screening of relatives and early initiation of effective lipid lowering.

Statin intolerance is increasingly recognised in clinical practice. This results in poor adherence and discontinuation of therapy, with consequent higher lipid levels. Clinical studies in patients with documented statin intolerance have demonstrated effective lipid lowering, without reproducing symptomatic myalgia in these patients.^{14–16} While clinical outcome trials of PCSK9 inhibitors have not been directly performed in this patient cohort, the ability to achieve more effective lipid lowering is likely to result in cardiovascular protection worth considering in the patient at very high risk of cardiovascular events.

The fundamental importance of very high LDL-C levels in driving cardiovascular risk highlights that these individuals should be considered for therapy, regardless of the presence of either familial hypercholesterolaemia or statin intolerance. A patient with very high LDL-C levels, despite use of maximal statin doses and ezetimibe, might derive a potentially greater clinical benefit with PCSK9 inhibition. This is further supported by the findings of SPIRE-2.^{33,34}

Patients with the highest cardiovascular risk, regardless of LDL-C levels, should also be considered for therapy. Subgroup analyses of FOURIER provide some insight into groups with elevated levels of modifiable risk, with an apparent association with lower numbers needed to treat.^{28–32}

A take-home message from each of these studies has been the tolerability of achieving lower LDL-C levels than currently advocated by treatment guidelines. In the large outcomes trials, no adverse effect was observed in relation to achieving low lipid levels. This should give clinicians increasing reassurance of the importance of targeting lower LDL-C levels in patients deemed to be at a high risk of having a cardiovascular event. As these agents are increasingly used in clinical trials, particularly in older patients than typically enrolled in the outcome trials, it will be important to continue to evaluate their safety in a real world setting.

An important factor underscoring how to optimally integrate these agents into clinical practice will be their cost effectiveness. A high

cost of production, combined with more modest event reductions than originally predicted and a lack of mortality benefit all suggest that PCSK9 inhibitors are unlikely to be used empirically.³⁸ In fact, modelling performed to date suggests that a more convincing case would be made for broader use if the annual cost per patient were to be reduced to approximately US\$2,500, well below current prices.³⁹ As a result, identification of groups that are at particularly high risk, as outlined above, in addition to demonstration of cost effectiveness in these groups are urgently required in order to determine how to most effectively use these agents in clinical practice. This appears to be the position of contemporary clinical statements, including the European Society of Cardiology/European Atherosclerosis Society and the UK's National Institute for Health and Care Excellence, which advocate for the use of these agents in very high-risk patients whose LDL-C remains unacceptably high despite use of maximally tolerated statin therapy, with or without concomitant ezetimibe.^{40–42} Such information will be pivotal in terms of the ability to inform updates to treatment guidelines with regard to effective lipid lowering interventions in cardiovascular prevention.

Future Steps

ODYSSEY outcomes and further subgroup analyses, in combination with appropriate cost effectiveness data, are essential in further determining the optimal clinical use of these agents. Alternative approaches to targeting PCSK9 are receiving attention in clinical development. RNA inhibition using inclisiran aims to impair hepatocellular synthesis of PCSK9. While the degree of PCSK9 inhibition and LDL-C lowering

is slightly less than that observed with monoclonal antibodies, the durability of these effects is considerably longer.⁴³ In general, this agent appears to be well tolerated. This provides the potential for administration three or four times a year. This may present a more cost-effective approach to PCSK9 inhibition, although the long-term efficacy and safety will require thorough investigation in larger clinical trials.

The role of PCSK9 inhibition in other atherogenic lipid parameters remains uncertain. While these agents have been demonstrated to lower levels of lipoprotein(a), the relative contribution of this effect to clinical benefit has not been fully elucidated. This may be particularly important in patients with familial hypercholesterolaemia, in whom elevated levels of both LDL-C and lipoprotein(a) often coexist.⁴⁴ The modest impact on triglyceride-rich lipoprotein levels suggests that alternative strategies are more likely to be of benefit in targeting patients whose heightened cardiovascular risk is driven by hypertriglyceridaemia.

Conclusion

In a relatively short period, the science of PCSK9 and its fundamental role in lipid metabolism has been elucidated, in parallel with the development of effective inhibitory agents. This has translated to predictable benefits on cardiovascular risk. Considerable work continues to define how to most cost effectively triage the right patient to treatment with those agents in order to prevent the ongoing pandemic of cardiovascular disease. ■

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