New frontiers in the management of dyslipidaemia

Proprotein convertase subtilisin/kexin 9 inhibitors and small interfering ribonucleic acid

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RECENT ADVANCES in the development of proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors and small interfering ribonucleic acid (siRNA) have changed the landscape of pharmacotherapy for dyslipidaemia. Here, we provide a summary of the evidence supporting the use of PCSK9 inhibitors and siRNA, with relevant recommendations from consensus guidelines.

Statins have long been the mainstay of treatment for dyslipidaemia. However, the achievement of treatment goals is poor, with one study of high-risk patients on statins suggesting that only 20–26% and 67–77% of individuals achieve target low-density lipoprotein cholesterol (LDL-C) levels below 1.8 or 2.6 mmol/L, respectively.[1] Possible contributing factors include adverse effects and poor daily compliance. PCSK9 inhibitors (evolocumab and alirocumab) and siRNA directed against PCSK9 (inclisiran) provide an opportunity to reach target LDL-C levels using an alternative mechanism of action to statins, with improved compliance due to the potential of long-duration semi-annual dosing: evolocumab is given subcutaneously either fortnightly (140 mg) or monthly (420 mg);[2,3] alirocumab is given subcutaneously initially either fortnightly (75 mg) or monthly (300 mg);[4,5] and inclisiran (284 mg) is given subcutaneously on Day 0, at 3 months and then every 6 months.[6,7] Adverse effects of all three drugs are listed in Table 1.

The mechanism of action of PCSK9 inhibitors is as follows. The PCSK9 protein binds to the LDL-C receptor on the hepatocyte, targeting it for degradation, resulting in reduced LDL-C clearance. The PCSK9 inhibitors, evolocumab and alirocumab, which are monoclonal antibodies, reduce the activity of PCSK9, resulting in the lowering of cholesterol.[2–5,8] Another method of targeting PCSK9 is siRNA, which binds to the RNA-induced silencing complex to cleave mRNA encoding for PCSK9, subsequently resulting in reduced hepatic production of PCSK9.[6,7]

There is evidence for the LDL-C-lowering effects of PCSK9 inhibitors and siRNA from different trials. The Open Label Study of Long Term Evaluation Against LDL-C Trial (OSLER)-1 and OSLER-2 showed that in patients with elevated LDL-C, with or without lipid therapy, evolocumab can reduce LDL-C by 61% and 1.9 mmol/L (mean) at 12 weeks, with 74% of patients reaching target LDL-C (<1.8 mmol/L), compared with only 4% on placebo.[2] Similarly, the efficacy of alirocumab was demonstrated in the Long-term Safety and Tolerability of Alirocumab (SAR236553/REGN727) Versus Placebo on Top of Lipid-Modifying Therapy in High Cardiovascular Risk Patients With Hypercholesterolemia (ODYSSEY Long Term) trial, with LDL-C being reduced by 62% and 1.9 mmol/L (mean) at 24 weeks, with 79% of patients reaching target LDL-C (<1.8 mmol/L), compared with only 8% on placebo.[4]

Despite improvements in LDL-C, it is important to demonstrate translation to cardiac outcomes. The Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk (FOURIER) trial of evolocumab in patients with atherosclerotic cardiovascular disease (ASCVD) with elevated LDL-C or high-density lipoprotein cholesterol on maximally tolerated statins showed a 15% risk reduction for a composite of cardiac outcomes (cardiovascular death, myocardial infarction, stroke, hospitalisation for unstable angina, or coronary revascularisation) and a 20% risk reduction for a composite of cardiac death, myocardial infarction and stroke.[3] ODYSSEY Outcomes trial

of alirocumab as secondary prevention for recently hospitalised patients with acute coronary syndrome and elevated lipids despite maximally tolerated statins showed a 15% risk reduction in death from any cause and a similar reduction in the composite primary end point, which included coronary heart disease, non-fatal myocardial infarction and stroke.[5] The results from these landmark trials led to updates in worldwide consensus guidelines, as discussed below.[9,10] Subsequent justification of the use of PCSK9 inhibitors for cardiac outcomes was shown in a 2019 meta-analysis of 54 trials with 97,910 patients, which identified a 16% risk reduction in major adverse cardiac events, a 17% risk reduction in non-fatal myocardial infarction and 25% risk reduction in stroke.[8]

The Trial to Evaluate the Effect of Inclisiran Treatment on LDL-C in Subjects With Heterozygous Familial Hypercholesterolemia (ORION)-9, ORION-10 and ORION-11 explored the efficacy of inclisiran in patients on maximally tolerated statins with familial hypercholesterolaemia, ASCVD risk equivalent and ASCVD.[6,7] These trials showed that inclisiran can reduce LDL-C by 48–52%, with an absolute reduction of 1.3–1.8 mmol/L at 510 days. A higher proportion of patients on inclisiran than on placebo were able to achieve target LDL-C levels <1.8 mmol/L (41–74% vs 1–15%).[6,7] The reduction in LDL-C is encouraging, and the potential of six-monthly dosing suggests inclisiran has the potential to improve adherence and outcomes compared with statins. Cardiac outcomes from inclisiran are currently being studied.

The American College of Cardiology/American Heart Association Task Force and European Society of Cardiology/European Atherosclerotic Society have released guidelines regarding the use of PCSK9 inhibitors (Table 2).[9,10] Indications include familial hypercholesterolaemia, severe hypercholesterolaemia and statin intolerance, the prevention of secondary ASCVD and patients on maximally tolerated statin and ezetimibe not meeting target LDL-C levels.

PCSK9 inhibitors and siRNA targeting PCSK9 are therapeutic options that represent a significant opportunity to meet target LDL-C goals within the population. The alternative mechanism of action to statins allows for combination therapy, and fortnightly to six-monthly dosing could significantly improve compliance rates. At the time of writing, evolocumab, alirocumab and inclisiran are all approved by the Therapeutic Goods Administration for use in Australia, with evolocumab and alirocumab subsidised under the Pharmaceutical Benefits Scheme if initiated by a non-general practitioner (GP) specialist with continuing scripts provided by GPs. The role of these new agents and their overall place in the therapeutic options for dyslipidaemia management will further evolve when these agents become mainstream.

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Table 1. Summary of proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors and small interfering RNA targeting PCSK for dyslipidaemia

Drug class	Drug name (Brand)	Mechanism of action	Dosing (route)	Adverse effects
PCSK9 inhibitor	Evolocumab (Repatha; Amgen, Thousand Oaks, CA, USA)	PCSK9 inhibitors are monoclonal antibodies that inhibit the activity of the PCSK9 protein and increase LDL-C clearance The PCSK9 protein binds to the LDL-C receptor on the hepatocyte, targeting it for degradation, resulting in reduced LDL-C clearance	140 mg fortnightly or 420 mg monthly (subcutaneously)	Arthralgia, headache, neurocognitive events and injection site reactions[2] Similar to placebo, except for increased injection site reactions[3]
	Alirocumab (Praluent; Regeneron Pharmaceuticals, Tarrytown, NY, USA)		75 mg fortnightly or 300 mg monthly (subcutaneously)	Myalgia, neurocognitive disorders, ophthalmic events and injection site reactions[4] Similar to placebo, except for increased injection site reactions[5]
siRNA against PCSK9	Inclisiran (Leqvio; Novartis Pharmaceuticals, East Hanover, NJ, USA)	The siRNA binds to the RNA-induced silencing complex to cleave mRNA encoding for PCSK9, resulting in the reduced hepatic production of PCSK9 protein	284 mg on Day 0, at 3 months and then every 6 months (subcutaneously)	Similar to placebo, except for increased injection site reactions (majority mild to moderate)[6,7]

LDL-C, low-density lipoprotein cholesterol; siRNA, small interfering RNA.

Table 2. Consensus guidelines for indications for proprotein convertase subtilisin/kexin type 9 inhibitors in the management of dyslipidaemia

Guideline	Year	Recommendations (class of recommendation)
ESC/EAS[10]	2019	Secondary ASCVD prevention (Class I) • Patients with clinical ASCVD judged to be very high risk[A] on maximally tolerated statin therapy and ezetimibe with LDL-C ≥1.4 mmol/L Familial hypercholesterolaemia (Class I) • Patients with familial hypercholesterolaemia judged to be very high risk[B] on maximally tolerated statin therapy and ezetimibe with LDL-C ≥1.4mmol/L Severe hypercholesterolaemia (Class IIb) • For primary prevention, in patients at very high risk but without familial hypercholesterolaemia who are on maximally tolerated statin therapy and ezetimibe, if target LDL-C ≥1.4 mmol/L is not achieved the addition of a PCSK9 inhibitor can be considered Statin intolerant (Class IIb) • If a statin-based regimen is not tolerated at any dosage (even after a rechallenge), the addition of a PCSK9 inhibitor to ezetimibe may be considered
ACC/AHA Task Force[9]	2018	Secondary ACSVD prevention (Class IIa) • In patients with clinical ASCVD judged to be very high risk[C] on maximally tolerated statin therapy and ezetimibe with LDL-C ≥1.8mmol/L or non-HDL-C ≥2.6 mmol/L following discussion about cost, benefit and safety Familial hypercholesterolaemia (Class IIb) • In patients with heterogeneous familial hypercholesterolaemia aged 30–75 years with LDL-C ≥2.6 mmol/L despite maximally tolerated statin therapy and ezetimibe Severe hypercholesterolaemia (Class IIb) • In patients aged 40–75 years with baseline LDL-C ≥5.7 mmol/L with on-treatment LDL-C ≥3.4 mmol/L despite maximally tolerated statin therapy and ezetimibe

[A]Very high risk is defined as atherosclerotic cardiovascular disease (ASCVD; clinical or imaging), a calculated score ≥10% for the 10-year risk of fatal cardiovascular disease, familial hypercholesterolaemia with ASCVD or with another major risk factor, severe chronic kidney disease (estimated glomerular filtration rate [eGFR] <30 mL/min/1.73 m^2), diabetes with target organ damage or three or more major risk factors, or early onset type 1 diabetes of >20 years.

[B]Very high risk is defined as familial hypercholesterolaemia with ASCVD or with another major risk factor.

[C]Very high risk is defined as a history of multiple major ASCVD events (recent acute coronary syndrome in the past 12 months, history of myocardial infarction other than recent acute coronary syndrome, history of ischaemic stroke, symptomatic peripheral arterial disease) or one major event and multiple high-risk conditions (age ≥65 years, heterogeneous familial hypercholesterolaemia, history of prior coronary artery bypass surgery or percutaneous coronary intervention outside of major ASCVD events, diabetes, hypertension, chronic kidney disease [eGFR 15–60 mL/min/1.73m^2], current smoker, persistently elevated low-density lipoprotein cholesterol [LDL-C] ≥2.6 mmol/L despite maximally tolerated statin therapy and ezetimibe or history of congestive heart failure).

ACC, American College of Cardiology; AHA, American Heart Association; Class I, strong recommendation; Class IIa, moderate recommendation; Class IIb, weak recommendation; EAS, European Atherosclerosis Society; ESC, European Society of Cardiology; PCSK9, proprotein convertase subtilisin/kexin type 9.

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References

1. Jones PH, Nair R, Thakker KM. Prevalence of dyslipidemia and lipid goal attainment in statin-treated subjects from 3 data sources: A retrospective analysis. J Am Heart Assoc 2012;1(6):e001800.
2. Sabatine MS, Giugliano RP, Wiviott SD, et al. Efficacy and safety of evolocumab in reducing lipids and cardiovascular events. N Engl J Med 2015;372(16):1500–9.
3. Sabatine MS, Giugliano RP, Keech AC, et al. Evolocumab and clinical outcomes in patients with cardiovascular disease. N Engl J Med 2017;376(18):1713–22.
4. Robinson JG, Farnier M, Krempf M, et al. Efficacy and safety of alirocumab in reducing lipids and cardiovascular events. N Engl J Med 2015;372(16):1489–99.
5. Schwartz GG, Steg PG, Szarek M, et al. Alirocumab and cardiovascular outcomes after acute coronary syndrome. N Engl J Med 2018;379(22):2097–107.
6. Raal FJ, Kallend D, Ray KK, et al. Inclisiran for the treatment of heterozygous familial hypercholesterolemia. N Engl J Med 2020;382(16):1520–30.
7. Ray KK, Wright RS, Kallend D, et al. Two Phase 3 trials of inclisiran in patients with elevated LDL cholesterol. N Engl J Med 2020;382(16):1507–19.
8. Du H, Li X, Su N, et al. Proprotein convertase subtilisin/kexin 9 inhibitors in reducing

cardiovascular outcomes: A systematic review and meta-analysis. Heart 2019;105(15):1149–59.

9. Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: Executive summary: A report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol 2019;73(24):3168–209.
10. Mach F, Baigent C, Catapano AL, et al. 2019 ESC/EAS guidelines for the management of dyslipidaemias: Lipid modification to reduce cardiovascular risk. Eur Heart J 2020;41(1):111–88.

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