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REVIEW

Status of PCSK9 Monoclonal Antibodies in Australia

Daniel J Scherer, MBBS, FRACP [a,b*], Adam J Nelson, MBBS, FRACP [a,b], Richard O'Brien, MBBS, PhD, FRACP [c,d], Karam M. Kostner, MD, PhD, FRACP, FCSANZ [e], David L. Hare, DPM, FRACP [f,g], David M. Colquhoun, MBBS, FRACP [h,i], Philip J. Barter, MBBS, PhD, FRACP [j], Philip Aylward, MA, PhD, FRACP [k], Stephen J. Nicholls, MBBS, PhD, FRACP [l], Gerald F. Watts, DSc, PhD, DM [m,n]

[a]South Australian Health and Medical Research Institute (SAHMRI), Adelaide, SA, Australia
[b]University of Adelaide, Adelaide, SA, Australia
[c]Medicine, Austin Clinical School, University of Melbourne, Melbourne, Vic, Australia
[d]Department of Endocrinology, Austin Health, Melbourne, Vic, Australia
[e]Department of Cardiology, Mater Hospital, University of Queensland, Brisbane, Qld, Australia
[f]Faculty of Medicine, Dentistry and Health Sciences, University of Melbourne, Melbourne, Vic, Australia
[g]Department of Cardiology, Austin Health, Melbourne, Vic, Australia
[h]School of Medicine, University of Queensland, Brisbane, Qld, Australia
[i]Wesley Medical Centre, Wesley Hospital and Greenslopes Private Hospital, Brisbane, Qld, Australia
[j]School of Medical Sciences, University of New South Wales, Sydney, NSW, Australia
[k]Flinders University and Medical Centre, Adelaide, SA, Australia
[l]Department of Medicine, Monash University, Melbourne, Vic, Australia
[m]School of Medicine, Faculty of Medicine and Health Sciences, University of Western Australia, Perth, WA, Australia
[n]Lipid Disorders Clinic, Department of Cardiology, Royal Perth Hospital, Perth, WA, Australia

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Proprotein convertase subtilisin/kexin type 9 (PCSK9) monoclonal antibodies (mAb) have progressed from showing marked low density lipoprotein cholesterol lowering in early phase trials through to reducing cardiovascular events in large clinical outcome trials. Recently in Australia, the indication for evolocumab has been expanded to include both heterozygous and homozygous familial hypercholesterolaemia under the Pharmaceutical Benefits Scheme (PBS). With prices remaining high currently their use in non-familial hypercholesterolaemia in Australia remains by private prescription only at this stage.

This manuscript summarises the major outcomes trials of the PCSK9 mAbs and the secondary analyses that have assessed their benefits in high risk patient groups, and describes the consensus of authors on which patients would most likely benefit from PCSK9 mAb therapy.

Keywords PCSK9 inhibitors • Lipids • Cardiovascular risk • Atherosclerosis

*Corresponding author at: South Australian Health and Medical Research Institute (SAHMRI), PO Box 11060, Adelaide, SA, 5001 Australia.
Tel.: +61-8128-4486., Email: daniel.scherer@sahmri.com

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Introduction

Proprotein convertase subtilisin/kexin type 9 (PCSK9) has been shown to play a pivotal role in the regulation of low density lipoprotein (LDL) receptors. PCSK9 targeted monoclonal antibodies (mAbs) have been developed to bind PCSK9 and negate its effect on degradation of LDL receptors, allowing increased recycling of receptors and subsequently increased clearance of circulating LDL cholesterol (LDL-c) [1].

PCSK9 Inhibitors in Australia

The early program PCSK9 mAb studies have shown a profound LDL-c lowering effect when used alone or in addition to statin therapy [2,3].

There are two PCSK9 mAbs available for use in Australia, alirocumab and evolocumab, and both are registered for use as an adjunct to diet and exercise to reduce LDL-c in adults with one or more of: heterozygous familial hypercholesterolaemia (FH), clinical atherosclerotic cardiovascular disease (ASCVD), or hypercholesterolaemia with high or very high cardiovascular risk. They are indicated for use in combination with a statin, or statin with other lipid-lowering therapies in patients unable to reach LDL-c goals with maximum tolerated dose of a statin, or in combination with other lipid lowering therapies in patients who are statin intolerant or for whom a statin is contraindicated. In addition to these, evolocumab is also indicated in homozygous FH and has more recently had its indication expanded for use in primary hypercholesterolaemia.

Initially in Australia, subsidisation of PCSK9 mAbs was restricted to the use of evolocumab in patients with homozygous FH, dependent on meeting multiple other criteria. The indications for subsidisation have recently been expanded to include heterozygous FH patients also. While potent LDL-c lowering by PCSK9 mAbs has been shown in the early trials, more recent studies have significantly advanced the understanding of their efficacy on harder outcomes with intravascular imaging and large outcomes study findings presented in the last year. We present a summary of the recent trials and updated international guidelines, including the recently presented full update of the American College of Cardiology (ACC) and American Heart Association (AHA) clinical practice guidelines on the management of blood cholesterol [4], that have incorporated PCSK9 mAbs. We also provide an expert consensus opinion of a group of Australian lipid specialists on the patients most likely to derive benefit from PCSK9 mAbs in Australia.

PCSK9 is a proprotein convertase enzyme predominantly expressed in the liver and small intestine. Initially synthesised as a zymogen before undergoing autocatalytic cleaving to become active, it then facilitates the degradation of LDL receptors by channelling them towards the lysosomal degradation pathway rather than recycling to the cell surface when they are endocytosed within hepatic cells. PCSK9 mAbs directly bind PCSK9 to prevent them binding to LDL receptors [1].

The Global Assessment of Plaque Regression With a PCSK9 Antibody as Measured by Intravascular Ultrasound (GLAGOV)

The GLAGOV trial was the first large intravascular imaging trial of the PCSK9 mAbs to be published [5]. The trial assessed the impact of evolocumab on plaque burden and composition as measured by intravascular ultrasound (IVUS). This randomised, double-blind, placebo-controlled study included 968 patients with symptomatic coronary artery disease and other high-risk features. The primary endpoint was the nominal change in percentage atheroma volume (PAV). The study population consisted of patients with angiographic ASCVD, between 20–50% severity, demonstrated at the time of clinically indicated coronary angiography. Patients were required to have an LDL-c level $\geq$2 mmol/L or between 1.55–2 mmol/L and accompanied by other high cardiovascular risk factors, on maximally tolerated doses of a statin. IVUS was performed at baseline and at 78-week follow-up.

The addition of evolocumab to statin therapy achieved LDL-c lowering to a mean of 0.95 mmol/L. The GLAGOV trial confirmed an ongoing linear relationship between LDL-c lowering and plaque regression with evolocumab leading to a decrease in PAV of 0.95% ($p < 0.001$ compared with baseline; between group difference: 1.0% [95% CI, -1.8 to -0.64%]; $p < 0.001$). The secondary endpoint of total atheroma volume reduction was also significant in the evolocumab treated arm and patients treated with evolocumab were more likely to experience plaque regression than the placebo arm (64.3% vs 47.3%, $p < 0.001$).

Evolocumab and Clinical Outcomes in Patients With Cardiovascular Disease (FOURIER)

The Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER) trial was the first large cardiovascular outcomes trial published [6]. It was a multi-centre, double blind, randomised control trial designed to investigate the effect of evolocumab in addition to statin therapy on cardiovascular events. 27,564 patients were enrolled across 49 countries. The primary endpoint was a composite of cardiovascular death, myocardial infarction, stroke, hospitalisation for unstable angina, or coronary revascularisation. The study population was made up of patients with clinically evident atherosclerotic cardiovascular disease (ASCVD) and an LDL-c >1.8 mmol/L. In addition to this, patients required additional characteristics that placed them at high cardiovascular risk. Patients were randomised 1:1 to evolocumab either 140 mg every 2 weeks or 420 mg monthly, or matched placebo.

Approximately 70% of patients were on high intensity statin therapy but use of ezetimibe was infrequent. The median follow-up of patients in the trial was 26 months. Patients treated with evolocumab achieved a mean 59% reduction in LDL-c at 48 weeks in comparison to statin therapy alone and had a significantly reduced risk of the primary composite endpoint, 9.8% vs 11.3% (HR, 0.85; 95% CI, 0.79–0.92; $p < 0.001$). There was also a statistically significant reduction in the harder secondary endpoint of cardiovascular death, myocardial infarction, or stroke, 5.9% vs 7.4% (HR, 0.80; 95% CI, 0.73–0.88; $p < 0.001$). There was, however, no reduction in cardiovascular mortality. The magnitude of the reduction in primary endpoint with evolocumab appeared to increase over time from 12% in the first year to 19% beyond this. When looking specifically at those who achieved ultralow LDL-c levels (2% of patients achieved LDL-c <0.26 mmol/L at 4 weeks) events progressively declined with decreasing achieved LDL-c, suggesting no signal for a therapeutic plateau with lipid lowering and outcomes. In FOURIER there was a 1.3% absolute risk reduction in the key secondary endpoint at 48 months, translating into a number needed to treat (NNT) of 77 to prevent one event over 2 years.

ODYSSEY Outcomes

ODYSSEY outcomes was a multi-centre, double blind, randomised control trial designed to investigate the effect of alirocumab in addition to statin therapy on cardiovascular events [7]. 18,924 patients were enrolled across 57 countries. The primary endpoint was a composite of cardiovascular death, myocardial infarction, stroke, hospitalisation for unstable angina, or coronary revascularisation. The study population was made up of patients with recent acute coronary syndromes, occurring within the previous 1–12 months, with LDL-c > 1.8 mmol/L on maximum tolerated dose of statins. Patients were randomised 1:1 to either 2-weekly alirocumab or placebo. The mean age of patients enrolled was 58 years. Alirocumab dosing was targeted to on treatment LDL-c, aiming for an LDL-c of 0.65–1.3 mmol/L, uptitrated from 75–150 mg every 2 weeks in patients with LDL-C ≥1.3 mmol/L to reach the target range. In a different approach to FOURIER, ODYSSEY outcomes attempted to avoid extremely low LDL-c levels by treating to a target range, including the use of dose reductions of alirocumab in on treatment patients whom LDL-c level dropped below 0.65 mmol/L. This was facilitated with blinded swapping to placebo in patients whom on treatment LDL-c dropped below 0.4 mmol/L, which occurred in 7.7% of patients in the trial.

ODYSSEY Outcomes had a mean follow-up of 48 months, ranging from 2 to 5 years. Patients treated with alirocumab achieved a mean reduction in LDL-c of 54%, down to 1.38 mmol/L. Alirocumab significantly reduced the risk of the primary composite endpoint, 9.5% vs. 11.1% (HR, 0.85; 95% CI 0.78–0.93, $p = 0.0003$). There was also a statistically significant reduction in the harder secondary endpoint of cardiovascular death, myocardial infarction, or stroke, 10.3% vs. 11.9% ($p = 0.0003$). In the secondary endpoint analyses there was a nominally significant p-value for the all-cause mortality difference between alirocumab and placebo, 3.5% vs. 4.1% ($p = 0.026$), this was, however, low in the hierarchical order of secondary analyses and occurred after earlier secondary endpoints were found to not be statistically significant, including no identified reduction in chronic heart disease (CHD) death, 2.2% vs. 2.3% ($p = 0.38$). In ODYSSEY Outcomes there was a 1.6% absolute risk reduction over the 48-month trial, translating into a NNT of 64 to prevent one event over 4 years.

Studies of PCSK9 Inhibition and the Reduction in Vascular Events (SPIRE)

The SPIRE 1 and SPIRE 2 trials were multi-centre, double blind, randomised control trials designed to investigate the effect of a third PCSK9 mAb, bococizumab, in addition to statin therapy on cardiovascular events [8]. They used a composite primary endpoint including cardiovascular death, non-fatal myocardial infarction (MI), non-fatal stroke, and hospitalisation for unstable angina needing urgent revascularisation. The study population was made up of patients at high risk for cardiovascular events, including secondary prevention patients, patients with diabetes, chronic kidney disease, or peripheral vascular disease, and high risk primary prevention patients, including those with FH or an LDL-c >5 mmol/L. SPIRE 1 included patients with a baseline LDL-c >1.8 mmol/L on statin therapy and SPIRE 2 included patients with a baseline LDL-c >2.6 mmol/L on statin therapy. Patients were randomised 1:1 to 150 mg of bococizumab subcutaneously fortnightly or placebo.

Both SPIRE trials were stopped prematurely by the sponsor in November 2016. Patients in the earlier SPIRE program lipid lowering studies (n = 4,449) had been found to develop antidrug antibodies (ADA) to bococizumab, developing in almost half of treated patients (48%), and neutralising antibodies present in just under one third of treated patients (29%). These antibodies were found to associate with substantive attenuation of LDL-c lowering effect over time. Unlike the other two available mAbs that are fully human mAbs, bococizumab is a humanised murine mAb that still contains approximately 3% of the murine sequence at the antigen-binding region of the antibody.

At the time of stopping the trials SPIRE 1 had a median follow-up period of 7 months and SPIRE 2 had a median follow-up period of 12 months. Enrolment had almost met pre-planned targets for both trials. Given the similarity of the trials other than baseline LDL-c level, SPIRE 1 and 2 subjects were combined for analysis. In the combined SPIRE 1 and 2 analysis there was a mean 52% reduction in LDL-c in the bococizumab treated group, a statistically significant 59 percentage points lower than the placebo group. This attenuated

over time however, dropping to a 41.8% reduction at 52 weeks and a 38.3% in those followed up to 104 weeks. There was a concentration dependent response between antidrug antibodies to the degree of attenuation of the LDL-c lowering effect over time [9].

While the SPIRE 1 cohort, with a lower baseline LDL-c level and shorter duration of follow-up, did not show a significant difference in the primary endpoint, the higher risk SPIRE 2 group cohort did show a statistically significant 21% reduction in the primary endpoint major adverse cardiac events (MACE) events, (HR 0.79, 95% CI, 0.65–0.97; p = 0.02). In secondary analyses, the benefits of bococizumab appeared most significant in patients that achieved lower LDL-c levels and those that received treatment for a longer duration.

Cost/Benefit in Australia

The currently available PCSK9 inhibitors are both mAbs, which are expensive to produce. A cost-benefit analysis of PCSK9 mAbs would be simple if these agents were inexpensive as they have demonstrable ability to potently reduce LDL-c and also reduce CV events in a broad range of patients with residual risk. As it presently stands, however, at a current cost to the payer of A$7,000 and A$8,000 per year, administration to all patients likely to benefit from their prescription in Australia would be financially prohibitive. With the numbers needed to treat (NNT = 74 for the lower risk FOURIER population, and NNT = 62 for the higher risk ODYSSEY population) the cost of each event prevented is likely to be high. Cost effectiveness analysis specifically for the Australian market using the findings from FOURIER have estimated the incremental cost effectiveness ratio (ICER) of each quality-adjusted life year (QALY) saved to be greater than A$300,000 based on the current pricing [10]. While there is no explicit ICER threshold for the Pharmaceutical Benefits Advisory Committee (PBAC), this falls well above the range of A$45,000 to A$60,000 per additional QALY gained that is felt to be the acceptable threshold [11]. Early modelling studies in the United States found ICER ranging from US$141,700 to US$450,000 per QALY, the majority falling in the ''low value" assessment (>US$150,000 per QALY added) [4]. The ODYSSEY Outcomes trial expanded on the modelling assessments by undertaking trial based economic analysis of alirocumab using the actual event rates they experienced within the trial [12]. Performed with US cost rates they found that, to reach an intermediate value ICER of US $100,000 per QALY using the overall intention to treat (ITT) population, alirocumab would need to be reduced to an annual cost of US$6,319. To get down to US$50,000 per QALY, a figure closer to the assumed PBAC threshold, the annual cost needed to be reduced to US$3,293 in the ITT population or US$6,910 in only patients with baseline LDL-c >2.6 mmol/L.

Expansion of the indication for use in Australia beyond FH alone will require a substantial reduction in unit cost, likely achieved by larger industry rebates and tiered pricing structures that protect for volume [13,14]. Even with a more competitive per-patient cost, higher risk groups, such as the higher baseline LDL-C group, will need to be identified as those with greater absolute risk will benefit most and have more favourable ICER. Furthermore, if small molecule (non-monoclonal) PCSK9 inhibitors in development are able to show similar efficacy in cardiovascular event reduction with RNA inhibitory approaches [15], their less expensive production cost may challenge the place of the PCSK9 mAbs.

Which Patients Are Most Likely to Benefit?

High TIMI risk patients

The TIMI investigators performed a post hoc analysis of the FOURIER trial looking at whether high risk cardiovascular features that are used to predict cardiovascular outcomes with a new thrombolysis in myocardial infarction (TIMI) secondary prevention score (TRS 2°P) [16] would also predict post-ACS patients at higher risk for recurrent cardiovascular events who have the greatest potential for benefit from the addition of evolocumab [17].

The risk score uses nine risk factors (age ≥75 years, diabetes mellitus, hypertension, current smoking, peripheral artery disease, prior stroke, prior coronary artery bypass grafting, history of heart failure, and renal dysfunction [estimated glomerular filtration rate <60 mL/min/1.73m^2]) identified as independent predictors of MI. They showed a stepwise relationship between number of risk factors and the risk of cardiovascular (CV) death, MI or stroke. Patients with five or more of these risk factors had more than double the risk of MACE compared with the total cohort risk in FOURIER. In these higher risk patients the ARR for MACE with evolocumab was increased from 1.6% in the total cohort to 3.6%. Treatment of these high risk patients required only 28 patients to be treated to prevent a MACE event over 2 years. In comparison, the low risk patients with one or less of the risk factors in the trial had a 1.2% ARR, and would require 83 patients to be treated to prevent an event.

Previous MI

In post hoc analysis of the FOURIER trial, high risk groups that were more likely to have events were identified including patients with multiple prior MIs, multi-vessel residual coronary artery disease and those with more recent prior MI (<2 years) [18]. These were all found to be independent predictors of cardiovascular outcomes. Evolocumab elicited a greater risk reduction in each of these high risk groups with ARRs of 2.9%, 2.6%, and 3.4% respectively. When combined, having any of these high risk features resulted in an ARR with evolocumab of 2.5% in the key secondary endpoint event rate. Treatment of these high risk patients would

require 27–30 patients to be treated to prevent one cardiovascular event over 3 years.

While cumulative incidence analysis is used for clinical trial outcome measures, it is not a true example of the actual event risk we see in the clinic. Time to first event is key to trial endpoints but clinically we are interested in subsequent events and cost effectiveness analysis needs to consider this. This was assessed in a post hoc analysis of FOURIER where evolocumab was shown to prevent 29 first primary endpoint events for every 1,000 patients treated, but when subsequent events were included the total number of events prevented for every 1,000 patients treated when looking at subsequent events was 75.

Diabetes

Forty per cent (40%) of the 27,564 patients in the FOURIER trial had diabetes and were looked at as a pre-specified subgroup analysis [19]. Patients with diabetes were more likely to be female, have higher body mass indexes (BMIs), as well as a higher rate of significant comorbidities. Patients with diabetes were at higher risk for cardiovascular events with significantly higher event rates than non-diabetic patients even when adjusted for difference in baseline characteristics (HR 1.26, 95% CI 1.13–1.40, $p < 0.0001$). Evolocumab treatment in patients with diabetes resulted in higher absolute risk reduction in the primary endpoint, lead predominantly by a greater reduction in coronary revascularisation (2.7% reduction in patients with diabetes vs 1.6% reduction in non-diabetic patients). Treatment of these high risk diabetic patients would mean only 37 patients would need to be treated to prevent a cardiovascular event/coronary revascularisation over 3 years in comparison with 63 non-diabetic patients.

Coronary Artery Bypass Grafting

The Improved Reduction of Outcomes: Vytorin Efficacy International (IMPROVE-IT) trial assessed the efficacy of ezetimibe in addition to simvastatin on cardiovascular events compared with simvastatin alone, showing a 2% ARR in the composite endpoint of cardiovascular death, major coronary event, or stroke over 7 years of treatment [20]. 9.3% of patients in IMPROVE-IT had had a prior coronary artery bypass graft (CABG), with these patients being older, more likely to have had a prior MI and greater burden of other comorbidities. Patients with prior CABG had a significantly higher rate of events than those without a history of CABG in the primary endpoint and all secondary endpoints [21]. Ezetimibe and simvastatin treatment in patients with prior CABG resulted in absolute risk reduction of the key three-point secondary endpoint (death from any cause, major coronary event, or stroke) of 8.4%, compared with 0.9% in those without history of CABG. Treatment of these high risk CABG patients showed that only 11 patients were needed to be treated with ezetimibe to prevent a major cardiovascular event over the duration of the 7-year trial in comparison with 111 patients in those without a history of CABG. Analysis has not been performed specifically on the CABG sub-groups of patients that participated in the FOURIER or Odyssey Outcomes trials at this stage but are a high risk group for which this is warranted.

PAD

Peripheral arterial disease (PAD) is known to associate with high cardiovascular risk with particularly high event rates compared to other stable atherosclerotic disease. The potential for this high risk to be modifiable has been reinforced recently with the impressive outcomes seen in the Cardiovascular Outcomes for People Using Anticoagulation Strategies (COMPASS) PAD trial [22]. In the FOURIER trial, 13.2% of patients had a history of symptomatic PAD at baseline. This was associated with significantly increased event rates compared to patients without PAD, even when adjusted for other baseline comorbidities and patient's characteristics [23]. This translated to higher absolute reductions in relative risk achieved for MACE with evolocumab in PAD patients (key secondary endpoint 3.5% vs 1.6%, $p < 0.001$). Evolocumab also significantly lowered MALE (major adverse limb events), defined as acute limb ischaemia, amputation, or urgent revascularisation, with a combined MACE and MALE endpoint in PAD patients in FOURIER showing an ARR of 6.3%. Treatment of these high risk PAD patients with evolocumab would mean only 29 patients need to be treated to prevent one MI over the duration of the 2.2 year trial in comparison with 67 patients without PAD, or 16 high risk patients would need to be treated to prevent one MACE or MALE event.

High LDL-c on Statin Therapy

The Cholesterol Treatment Trialists have established from meta-analyses of the major statin trials that reduction of LDL-c with statin therapy results in a 22% reduction in cardiovascular events for each 1 mmol/L reduction in LDL-c achieved and that the size of the proportional reduction in major vascular events is directly proportional to the absolute LDL reduction achieved [24]. Patients with persistently elevated LDL-c levels despite treatment with maximal statin doses remain at a higher cardiovascular risk.

This has been confirmed in the PCSK9 mAbs outcomes trials and their pre-specified subgroup analyses based on baseline LDL-c levels. The SPIRE trials showed no benefit in the lower risk SPIRE-1 trial but a statistically significant reduction in MACE primary endpoint in the higher risk group with baseline LDL-c >2.6 mmol/L.

A pre-specified subgroup analysis of the Odyssey Outcomes trial also found the greatest benefit appeared to be obtained in patients with the highest baseline LDL-c levels. In a subsequent post hoc analysis to look closer at patients with baseline LDL-c >2.6 mmol/L, who made up approximately 30% of the study population, they found that the benefits in

MACE in the alirocumab group were mostly driven by this higher risk subgroup (HR 0.76 v HR 0.91, Pinteraction = 0.05). While a greater benefit with higher LDL-c at baseline is intuitive, the lesser benefit at lower baseline may be complicated by higher rate of down titration or cessation of alirocumab.

ACC/AHA Guidelines High Risk ASCVD Groups

The new ACC/AHA blood cholesterol management guidelines divide secondary prevention patients by defining a group that are at very high risk of future ASCVD events compared with those who have stable ASCD [4]. Very high risk patients are defined as those with multiple major ASCVD events or one major ASCVD event combined with multiple risk enhancing conditions. Major ASCVD events include a recent acute coronary syndrome (ACS) occurring within the last 12 months, history of prior myocardial infarction at the time of new ACS, a history of ischaemic stroke, or symptomatic peripheral arterial disease (history of claudication with ABI < 0.85, or previous revascularidation or amputation).

High risk conditions for assessing very high risk ASCVD patients are defined as age $\geq$65 years old, heterozygous FH, a history of prior coronary artery bypass surgery or percutaneous coronary intervention outside of the major ASCVD event(s), diabetes mellitus, hypertension, chronic kidney disease (eGFR 15–59 mL/min/1.73m^2), being a current smoker, having a history of congestive heart failure, or persistently elevated LDL-C ($\geq$2.6 mmol/L) despite maximally tolerated statin therapy and ezetimibe.

Extremely high LDL-c ($\geq$4.9 mmol/L), including FH, are also highlighted in the new guidelines as high risk patients for ASCVD events who do not require ASCVD risk scoring for commencement on lipid lowering therapy.

Who Should Be Treated in Australia?

International Guidelines

International guidelines are now being updated to include PCSK9 mAbs and guide where they should be used in the options of non-statin lipid lowering therapies. The European Atherosclerosis Society (EAS) and European Society of Cardiology (ESC) made a specific guideline update for the use of PCSK9 mAbs in patients with ASCVD or FH in 2017 [25], and in the United States a full update of the ACC/AHA clinical practice guidelines on the management of blood cholesterol from 2013 has just been presented at the American Heart Association scientific sessions 2018 [4].

The EAS/ESC European guidelines favour the use of ezetimibe as the first-line non-statin therapy in all cases. In patients with ASCVD a PCSK9 mAb is suggested for add-on therapy to statin and ezetimibe in patients with additional CV high risk factors, including FH, who have LDL-c >2.6 mmol/L and with LDL-c >3.6 mmol/L in those with no additional CV high risk factors. In FH patients without clinically diagnosed ASCVD a PCSK9 inhibitor is suggested for add-on therapy to statin and ezetimibe in patients with additional CV high risk factors with LDL-c >3.6 mmol/L and with LDL-c >4.5 mmol/L in those with no additional CV high risk factors.

The updated ACC/AHA blood cholesterol guidelines have included PCSK9 mAbs. Similar to the European guidelines ezetimibe is suggested for first choice non-statin lipid lowering therapy in all patients. The addition of a PCSK9 mAb is considered reasonable in secondary prevention ASCVD patients at very high cardiovascular risk whose LDL-C level remains $\geq$1.8 mmol/L on maximally tolerated statin and ezetimibe therapy. In patients with severe hypercholesterolaemia, LDL-c $\geq$4.9 mmol/L, use of PCSK9 mAbs for primary prevention is considered reasonable in patients 30 to 75 years of age with heterozygous FH with an LDL-c $\geq$2.6 mmol/L while taking maximally tolerated statin and ezetimibe therapy, or in patients 40 to 75 years of age with a baseline LDL-c $\geq$5.7 mmol/L in whom LDL-c $\geq$3.4 mmol/L while taking maximally tolerated statin and ezetimibe therapy.

Patients With Familial Hypercholesterolaemia

While an outcomes trial in FH patients would be difficult to execute with adequate power, it follows that this markedly increased risk group are likely to derive most benefit from PCSK9 mAbs. The presence of FH gene mutations have been shown to associate with a significantly increased risk of coronary artery disease for similar levels of LDL-c elevation (OR 3.4–11.6 compared with patients with elevated LDL-c but no mutation, p interaction<0.1) [26,27]. PCSK9 mAbs have been able to achieve significant LDL-c reductions in FH patients, even in those that have not had a significant reduction with high potency statins [28,29]. This has been shown to be effective in both reducing the frequency and need for expensive alternative therapies such as lipoprotein apheresis [30]. This LDL-c lowering efficacy is seen across various FH mutations, including in double heterozygous, compound heterozygous, and homozygous mutations with some residual LDL receptor function [31].

Given the severely increased cardiovascular risk in confirmed homozygous FH we would recommend that all should be treated with maximal available therapies, including PCSK9 mAbs. This comes with the caveat that PCSK9 mAb therapy should only be continued in homozygous FH patients with confirmed LDL-c lowering after commencement to show there is some residual LDL receptor function.

In addition to statin and ezetimibe we would recommend treating heterozygous FH patients with other high risk features (Table 1) with PCSK9 mAbs if their LDL-c on treatment remains >3.3 mmol/L, and >4.5 mmol/L in those without any high risk features.

In patients without a formal diagnosis of FH that have persistently elevated LDL-c >4.5 mmol/L despite use of statins and ezetimibe their baseline LDL-c off treatment is likely

Table 1 Author consensus of high risk patients that should be considered for treatment with PCSK9 monoclonal antibodies in Australia.

Primary prevention
Severe hypercholesterolaemia including Familial Hypercholesterolaemia (FH)
•Homozygous FH
– All homozygous FH patients (should have follow -up LDL-c to ensure they have some receptor activity)
• Heterozygous FH with no risk enhancers
– LDL-c > 4.5 mmol/L
• Heterozygous FH with risk enhancers (e.g. Lp(a) > 50 mg/dL, Ca score >100 prior to statin therapy, FHx of CVD, proven atherosclerosis, angina, Aboriginal and Torres Strait Islander Australians)
– LDL-c >3.3 mmol/L
Secondary prevention with risk enhancers
Peripheral Arterial Disease
Stroke
Familial Hypercholesterolaemia
Diabetes
Coronary Artery Bypass Grafting
Presence of multivessel coronary disease
Aboriginal and Torres Strait Islander Australians
Acute Coronary Syndrome
• LDL-c >2.6 mmol/L
Acute Coronary Syndrome with risk enhancers
• LDL-c >1.8 mmol/L
Very high risk patients are defined as those with multiple major ASCVD events or 1 major ASCVD event combined with multiple risk enhancing conditions
*All LDL-c levels indicated are for patients on treatment after 6 weeks of maximally tolerated statin dose followed by the addition of ezetimibe for 6 weeks

Abbreviations: ASCVD, atherosclerotic cardiovascular disease.

to be high enough to qualify as probable FH with Dutch Lipid Clinical Network Score and so we recommend considering them in the same manner as FH patients with respect to primary prevention.

Secondary Prevention

Patients who have persistently elevated LDL-c levels despite statin and ezetimibe treatment remain at higher risk of cardiovascular events. The analyses of the outcomes trials that have assessed baseline LDL-c levels are consistent in finding the majority of benefit is driven by those with LDL-c levels >2.6 mmol/L. While the current PBS criteria for PCSK9 mAb prescribing requires an LDL-c >3.3 mmol/L we recommend this be lowered to >2.6 mmol/L on maximal tolerated statin and ezetimibe in patients with a previous ACS.

Acute coronary syndrome patients at particularly high risk for further cardiovascular events include those with PAD, prior stroke, FH, diabetes, prior CABG, and Aboriginal or Torres Strait Islander heritage. In these patients we recommend PCSK9 inhibitors be made available to those in whom LDL-c remains >1.8 mmol/L on maximal tolerated statin and ezetimibe.

Conclusion

The PCSK9 mAb outcomes trials have confirmed that the profound LDL-c lowering capacity observed in earlier studies translates to a reduction in cardiovascular events. International guidelines have been updated to include PCSK9 mAbs and guide in which patients they would be most appropriately used, however there have been notable deficits in these including children and adolescents with FH and patients with diabetes without ASCVD. Broader access for patients in Australia will not only require a marked reduction in price but also a more targeted approach to groups at highest absolute cardiovascular risk. Analysis of the efficacy in these subgroups demonstrates superior risk reduction, fewer numbers needed to treat, and ought to lead to a more favourable ICER.

Early phase trials of the small interfering RNA Inclisiran have shown impressive serum PCSK9 and LDL-c lowering effects. If further trials are able to show safety and efficacy when combined with high potency statins it will progress to a cardiovascular outcomes trial and provide significant competition in the PCSK9 inhibition market if they show similar efficacy, particularly given its longer duration of action and lower manufacturing costs.

Since the outcomes trials for the PCSK9 mAbs have been completed international guidelines have been updated with ezetimibe consistently seen as the preferred initial non-statin add-on for lipid lowering. Significant reductions in ASCVD events have also been seen with other new therapies in secondary prevention and risk enhanced patients, with elevated triglyceride levels, treated with highly purified omega-3 polyunsaturated fatty acids (PUFAs) [32]. New lipid lowering medication outcomes trials moving forward may have to be designed to show benefits in comparison to more than just high dose statin therapy alone, with combined high dose statin and ezetimibe required as a comparator for high cost medications.

Whether the Pharmaceutical Benefits Advisory Committee will recommend a broader indication for PCSK9 mAbs including non-familial hypercholesterolaemia patients for subsidisation remains to be seen.

Declaration of Interest

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