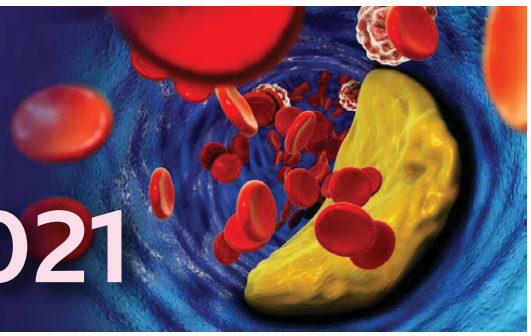
Lipids Year in Review™ 2021



Making Education Easy 2021

In this issue:

Abbreviations used in this issue:

ACL = adenosine triphosphate citrate lyase; **ACS** = acute coronary syndrome; **ASCVD** = atherosclerotic cardiovascular disease; **ESUS** = embolic stroke of undetermined source; **HDL** = high-density lipoprotein; **HR** = hazard ratio; **LDL** = low-density lipoprotein; **Lp(a)** = lipoprotein(a); **MACE** = major adverse cardiovascular events; **MI** = myocardial infarction; **PCSK9** = proprotein convertase subtilisin/kexin type 9

Claim CPD/CME points Click here for more info.

Welcome to this Year in Review of lipid-related research.

We have selected the most significant research in the field of lipids for 2021, condensed into an easy-to-read review for your convenience. The included research covers new treatments such as evinacumab (a monoclonal antibody against angiopoietin-like protein 3) and bempedoic acid (first-in-class ACL inhibitor), as well as secondary analyses of the FOURIER trial and the ODYSSEY Outcomes trial, and a possible explanation for the contrasting results of the REDUCE-IT and STRENGTH trials.

We hope you find this review interesting, and look forward to receiving any comments and feedback you may have.

Kind Regards,

Associate Professor John Amerena

john.amerena@researchreview.com.au

Evinacumab in patients with refractory hypercholesterolemia

Authors: Rosenson RS et al.

Summary: This phase 2 trial investigated the efficacy and safety of the human monoclonal antibody evinacumab in patients with refractory hypercholesterolaemia. 272 patients with LDL cholesterol ≥70 mg/dL with atherosclerosis or 100 mg/dL without atherosclerosis were randomised in a double-blind design to receive subcutaneous evinacumab (450mg weekly, 300mg weekly, or 300mg fortnightly), intravenous evinacumab (5 mg/kg or 15 mg/kg every 4 weeks) or placebo. At week 16, the differences in the least-squares mean change from baseline in LDL cholesterol level between the subcutaneous evinacumab groups (450mg weekly, 300mg weekly, and 300mg every 2 weeks) and the placebo group were –56.0, –52.9, and –38.5 percentage points, respectively (all $p<0.001$), and between the intravenous evinacumab groups (5 mg/kg and 15 mg/kg) and the placebo group were –24.2 and –50.5 percentage points, respectively (both $p<0.001$). Serious adverse events occurred in 3–16% of patients in the trial groups during the treatment period.

Comment: Angiopoietin-like protein 3 (ANGPTL3) is one of a family of proteins that regulate the major components of lipid profile: LDL cholesterol, HDL cholesterol, and triglycerides. It does this by inhibiting lipoprotein lipase which hydrolyses the triglycerides carried in triglyceride-rich lipoproteins in the circulation, and by inhibiting endothelial lipase to modulate HDL cholesterol metabolism, but the mechanism by which ANGPTL3 regulates LDL cholesterol remains unclear. Inhibition of this protein thus has become a promising therapeutic target. This study with the monoclonal antibody evinacumab that inhibits ANGPTL3 confirms the efficacy and safety profile of this strategy, but we will have to await outcome trials before it will come into clinical practice. If it does get into the clinical arena, it will be interesting to see where it fits in, as the PCSK9 inhibitors, other monoclonal antibodies, and inclisiran (a simRNA inhibitor of PCSK9) are likely to be available.

Reference: N Engl J Med 2020;383:2307-19
Abstract

Efficacy and safety of PCSK9 inhibition with evolocumab in reducing cardiovascular events in patients with metabolic syndrome receiving statin therapy

Authors: Deedwania P et al.

Summary: This secondary analysis of the FOURIER trial investigated outcomes associated with evolocumab in patients with and without metabolic syndrome (MetS). In the FOURIER trial, patients with stable ASCVD who were taking a statin were randomised to receive add-on evolocumab or placebo for a median of 2.2 years. Of 27,342 patients (mean age 63 years; 75.4% male) included in this analysis, patients with MetS at baseline were at higher risk for cardiovascular events (cardiovascular death, MI, stroke, hospitalisation for unstable angina, or coronary revascularisation) during follow-up than patients without MetS (adjusted HR 1.31, 95% CI 1.18–1.46; p<0.001). Evolocumab reduced the risk of cardiovascular events compared with placebo in patients with MetS (HR 0.83, 95% CI 0.76–0.91) more so than in patients without MetS (HR 0.89, 95% CI 0.79–1.01; p for interaction=0.39, ns). The drug reduced LDL cholesterol levels similarly in each patient group, and did not increase the risk of new-onset diabetes or other major safety outcomes.

Comment: In the FOURIER study, evolocumab was the first of the PCSK9 inhibitors to demonstrate that reducing LDL to very low levels improved cardiovascular outcomes and was well tolerated in patients with stable cardiovascular disease. This subgroup analysis of patients with MetS in FOURIER showed that having MetS increased the risk of a cardiovascular event by 30% compared to patients without MetS, and that the benefits of aggressive lipid lowering were nonsignificantly greater in patients with MetS. There was no increase in new-onset diabetes, suggesting that the small increase in development of diabetes with statins is not due to low LDL levels. Thus, we should pay more attention to the presence of MetS in our patients with cardiovascular disease, and be even more aggressive with lipid management.

Reference: JAMA Cardiol 2021;6(2):139-47
Abstract

Lipoprotein(a) and benefit of PCSK9 inhibition in patients with nominally controlled LDL cholesterol

Authors: Schwartz GG et al.

Summary: This *post hoc* analysis of the ODYSSEY Outcomes trial evaluated the use of alirocumab in patients with nominally controlled LDL cholesterol, and determined the influence of Lp(a) levels. 23.0% of 18,924 patients in the ODYSSEY Outcomes trial who were taking statins had LDL cholesterol levels near 70 mg/dL (median 69.4 mg/dL) at the time of randomisation to alirocumab or placebo. In this subgroup, MACE rates were 4.2 and 3.1 per 100 patient-years, respectively, among placebo recipients with baseline Lp(a) levels greater than the median (13.7 mg/dL) or less than or equal to the median. Corresponding adjusted treatment HRs were 0.68 (95% CI 0.52–0.90) and 1.11 (95% CI 0.83–1.49), respectively (p for interaction = 0.017). In the higher LDL cholesterol subgroup, MACE rates were 4.7 and 3.8 per 100 patient-years among placebo recipients with baseline Lp(a) >13.7 mg/dL or ≤13.7 mg/dL, respectively; corresponding adjusted treatment HRs were 0.82 (95% CI 0.72–0.92) and 0.89 (95% CI 0.75–1.06; p for interaction = 0.43, ns).

Comment: This interesting subanalysis of the ODYSSEY study using the PCSK9 inhibitor alirocumab showed that when LDL was low at baseline, further reduction was only beneficial if Lp(a) was elevated. PCSK9 inhibitors lower Lp(a) by an unclear mechanism, and these findings support the concept that residual risk in patients with ASCVD and well controlled lipids could be modulated via Lp(a) reduction. It would have been nice to see that the improvement in outcomes was associated with the reduction in Lp(a) but I suspect post-treatment Lp(a) levels were not collected. Large outcome studies with specific therapies to lower Lp(a) are about to begin so we will await the results of these with interest, to prove that Lp(a) is a worthy therapeutic target.

Reference: J Am Coll Cardiol 2021;78(5):421-33
Abstract

Lipid lowering with bempedoic acid added to a proprotein convertase subtilisin/kexin type 9 inhibitor therapy: A randomized, controlled trial

Authors: Rubino J et al.

Summary: This phase 2 study investigated the safety and efficacy of bempedoic acid when added to background therapy with the PCSK9 inhibitor evolocumab in patients with hypercholesterolaemia. Patients initially underwent a 1.5-month screening/washout period during which they discontinued all lipid-lowering therapies, then a 3-month period during which they initiated background evolocumab therapy, and then a 2-month treatment period during which they were randomised to receive add-on bempedoic acid 180mg or placebo once daily. 57 patients completed the study. Mean baseline LDL cholesterol after 3 months of evolocumab background therapy was 103.1 mg/dL. The addition of bempedoic acid to evolocumab therapy significantly lowered LDL cholesterol by 30.3% compared with placebo (p<0.001). Bempedoic acid also significantly decreased apolipoprotein B, non-HDL cholesterol, total cholesterol, and high-sensitivity C-reactive protein (p≤0.029 for all). The safety profile of bempedoic acid was comparable to that of placebo.

Comment: Bempedoic acid is a prodrug that is activated by a hepatic enzyme not present in skeletal muscle. It inhibits ATP-citrate lyase, an enzyme upstream of β-hydroxy β-methylglutaryl-coenzyme A reductase in the cholesterol biosynthesis pathway (*J Am Heart Assoc* 2019;8(7):e011662). It is available overseas as a stand-alone therapy and in combination with ezetimibe. This study shows that it is effective in lowering LDL by around 30% when added to a PCSK9 inhibitor, and that it is well tolerated. If it becomes available in Australia, it will be a useful additive therapy, particularly in patients with familial hypercholesterolaemia to attain even lower LDL levels and in statin-intolerant patients.

Reference: J Clin Lipidol 2021;15(4):P593-601
Abstract

Adherence to lipid-lowering treatment by single-pill combination of statin and ezetimibe

Authors: Rea F et al.

Summary: This large cohort study in Italy investigated whether adherence to statin + ezetimibe therapy is improved by administration of the 2 drugs in a single-pill combination. 256,012 patients (aged 40–80 years) from the Lombardy Region who were newly treated with a statin in 2011–2013 were followed until 2018 to identify those who needed add-on ezetimibe. 5351 patients who started a single-pill combination of statin + ezetimibe were propensity score matched with 2881 patients who started a 2-pill combination. Adherence to drug therapy at 1 year was measured as the proportion of days covered (PDC). Patients who had a PDC >75% were defined as highly adherent to drug therapy, while those with PDC <25% were defined as poorly adherent. Compared to patients prescribed a 2-pill combination, those prescribed a single-pill combination had an 87% greater likelihood of being highly adherent to treatment and a 79% lower likelihood of being poorly adherent. The risk of cardiovascular outcomes decreased by 55% in patients with high versus poor adherence.

Comment: This study looked at adherence, compliance and outcomes in patients on lipid-lowering therapy who were taking a combination lipid-lowering pill instead of the 2 separate components, in this case simvastatin and ezetimibe. Not surprisingly, all these parameters were better in the patients on a single pill, although the study was not powered for outcomes. These fixed-dose pills are available in Australia in many dose combinations and this study suggests they should be preferentially used, to improve compliance and attainment of target lipids, but also to reduce the pill burden and cost for patients.

Reference: Adv Ther 2021;38(10):5270-85
Abstract

RESEARCH REVIEW™
Australia's Leader in Specialist Publications

A possible explanation for the contrasting results of REDUCE-IT vs. STRENGTH: Cohort study mimicking trial designs

Authors: Doi T et al.

Summary: The Copenhagen General Population Study (CGPS) tested the hypothesis that the contrasting results in the REDUCE-IT and STRENGTH trials for the effect of high-dose, purified omega-3 fatty acids on the prevention of ASCVD can be explained by differences in the active oils (eicosapentaenoic acid (EPA) versus EPA + docosahexaenoic acid) and comparator oils (mineral versus corn) that were used. The CGPS (n=106,088) used the same inclusion criteria as REDUCE-IT and STRENGTH, and follow-up was the same as the median durations of REDUCE-IT (4.9 years) and STRENGTH (3.5 years). The ASCVD HR for active oil vs comparator oil was 0.88 (95% CI 0.84–0.93) in the CGPS mimicking REDUCE-IT compared with 0.75 (95% CI 0.68–0.83) in REDUCE-IT. Corresponding HRs were 0.96 (95% CI 0.93–0.99) in the CGPS mimicking STRENGTH compared to 0.99 (95% CI 0.90–1.09) in STRENGTH.

Comment: There has been great consternation as to the reasons why high-dose omega-3 fatty acids were beneficial in the REDUCE-IT trial but not the STRENGTH study, despite similar changes in lipids and C-reactive protein. The compounds used were different (EPA versus EPA + docosahexaenoic acid) but the comparators were also different (mineral versus corn oil). This analysis looked at event rates in the comparator groups in these trials compared to similar patients in the CGPS and showed that there was a potential negative impact of mineral oil on outcomes, thus accentuating the benefits of EPA and partially explaining the discordant results. Although Steve Nissen (chair of the STRENGTH's executive committee) has called for a head-to-head study to determine if there are real differences between these formulations, this is unlikely to occur.

Reference: Eur Heart J 2021; published online Aug 29
Abstract

Association of statin treatment with progression of coronary atherosclerotic plaque composition

Authors: van Rosendael AR et al.

Summary: This cohort study evaluated the effect of statin treatment on progression of coronary atherosclerotic plaque composition. 857 patients in 7 countries who underwent serial coronary computed tomography angiography (CCTA) 2 or more years apart and had quantitative measurements of coronary plaques throughout the entire coronary artery tree were included. Six plaque composition types were defined on a voxel-level basis according to the plaque attenuation (expressed in Hounsfield units): low attenuation (–30 to 75HU), fibro-fatty (76–130HU), fibrous (131–350HU), low-density calcium (351–700HU), high-density calcium (701–1000HU), and 1K (>1000 HU). In total, 2458 coronary lesions in 857 patients were evaluated. Untreated coronary lesions increased in volume over time for all 6 compositional types. Statin therapy was associated with volume decreases in low-attenuation plaque (p=0.001), and fibro-fatty plaque (p<0.001), and greater progression of high-density calcium plaque (p<0.001), and 1K plaque (p<0.001). When analyses were restricted to lesions without low-attenuation plaque or fibro-fatty plaque at baseline, statin therapy was not associated with a change in overall calcified plaque volume, but was associated with a transformation toward more dense calcium.

Comment: A high coronary calcium score is associated with an increased risk of future cardiac events in the general population (*J Am Coll Cardiol* 2018;72(4):434-47), and I am often asked by patients if lowering their cholesterol will reduce coronary calcification. This study looked at patients who had serial CCTA and coronary calcium score and showed that lowering LDL with statins improves plaque characteristics and volume, but paradoxically increases calcium density in the plaque, potentially making them more stable and less inflammatory. Patients therefore need to be reassured that although statins are likely to increase coronary calcification, this is probably a good thing, as it may indicate transformation of plaques to more stability, and less risk of cardiovascular events.

Reference: JAMA Cardiol 2021;6(11):1257-66
Abstract

Statin treatment and outcomes after embolic stroke of undetermined source

Authors: Sagris D et al.

Summary: This study used data from the Athens Stroke Registry to investigate the effect of statins on stroke recurrence, MACE and mortality in patients with ESUS. Among 264 ESUS patients who were discharged and followed up for 4 years, 33.7% were treated with a statin at discharge. Multivariate analysis showed that statin treatment at discharge was an independent predictor of lower rates of stroke recurrence (adjusted HR 0.48, 95% CI 0.26–0.91), MACE (adjusted HR 0.48, 95% CI 0.28–0.82), and death (adjusted HR 0.50, 95% CI 0.27–0.93).

Comment: Lipid lowering with statins is standard guideline-directed therapy after ischaemic stroke, based on the results of the SPARCL study. ESUS represents around 17% of all stroke numbers and there are no evidence-based strategies to prevent stroke recurrence in this population (*J Am Coll Cardiol* 2020;75(3):333-40). Two studies looking at rivaroxaban (NAVIGATE ESUS) and dabigatran (RE-SPECT ESUS) in patients with ESUS who had not had atrial fibrillation detected did not show any benefit with anticoagulation. This small study showed that statin usage after ESUS improved not only stroke recurrence, but reduced MACE and mortality. Although it was a relatively small study, the results are suggestive enough to recommend statins be used in this population, and that the target LDL should probably be the same as for patients who have had ACS (<1.8 mmol/L).

Reference: Intern Emerg Med 2021;16(5):1261-6
Abstract

Use of lipid-lowering therapies over 2 years in GOULD, a registry of patients with atherosclerotic cardiovascular disease in the US

Authors: Cannon CP et al., for the GOULD Investigators

Summary: This prospective observational registry study investigated lipid-lowering treatment patterns in patients with ASCVD in the US over a 2-year period. 5006 patients with ASCVD were grouped into 1 of 3 cohorts: patients taking a PCSK9 inhibitor; patients who were not taking a PCSK9 inhibitor and had LDL cholesterol ≥100 mg/dL; and patients who were not taking a PCSK9 inhibitor and had LDL cholesterol 70–99 mg/dL. Patients had medical record reviews and telephone interviews every 6 months for 2 years. Overall, only 17.1% of patients had lipid-lowering therapy intensification during the 2-year follow-up period. In the cohort with LDL cholesterol ≥100 mg/dL, 22.4% had lipid-lowering therapy intensification (statins were intensified in 6.4%, ezetimibe added in 6.8%, and a PCSK9 inhibitor added in 6.3%). In the cohort with LDL cholesterol 70–99 mg/dL, 14.4% had lipid-lowering therapy intensification (statins were intensified in 6.3%, ezetimibe added in 4.5%, and a PCSK9 inhibitor added in 2.2%). In patients taking a PCSK9 inhibitor at baseline, 91.7% were still taking a PCSK9 inhibitor at 2 years.

Comment: This US study yet again shows that there is considerable clinical inertia in management of lipids in patients with ASCVD, despite the availability of statins and PCSK9 inhibitors. Fewer than 20% of patients with established cardiovascular disease had treatment escalation over a 2-year period after diagnosis was made, while receiving ongoing specialist medical care. This is also an issue in Australia and whether this is due to lack of awareness of targets and the benefits of aggressive lipid lowering, or fear of producing adverse effects with treatment intensification is not clear, but there is significant room for improvement in trying to attain lipid targets in these high-risk patients to reduce recurrent events and cardiovascular mortality.

Reference: JAMA Cardiol 2021;6(9):1060-8
Abstract

Associations of statin adherence and lipid targets with adverse outcomes in myocardial infarction survivors: A retrospective cohort study

Authors: Brown R et al.

Summary: This retrospective cohort study used data from the National Health Service Greater Glasgow and Clyde Data Safe Haven to examine statin adherence and lipid target achievement in MI survivors. 11,031 patients who had a non-fatal MI hospital admission were included. Over 4.5 years of follow-up, 76% of patients achieved target LDL cholesterol levels (≤1.8 mmol/L), and 84.5% had mean statin adherence ≥50%. In adjusted models, patients with adherence <50% had an increased risk of not meeting target LDL cholesterol levels (odds ratio 2.03, 95% CI 1.78–2.31; p<0.0001). In univariable models, not meeting LDL cholesterol targets was associated with increased risks of all-cause mortality (HR 1.27, 95% CI 1.16–1.39; p<0.0001) and cardiovascular disease mortality (HR 1.29, 95% CI 1.11–1.51; p=0.0013). Statin adherence <50% was also associated with increased risks of all-cause mortality (HR 1.58, 95% CI 1.44–1.74; p<0.0001) and cardiovascular disease mortality (HR 1.60, 95% CI 1.36–1.88; p<0.0001).

Comment: The previous study showed that most patients with ASCVD do not have increased lipid-lowering therapy over time to try to attain target LDL levels. This study shows the consequences of this inability to get to lipid targets in patients post MI, as there was an increased rate of all-cause and cardiovascular mortality in those patients who did not get to target, whether it was due to noncompliance or treatment inertia. It reinforces the current guidelines for aggressive LDL reduction in patients with ACS, which recommend LDL <1.8 mmol/L, but many think the level should be even lower at <1.4 mmol/L based on the IMPROVE-IT and PCSK9 trials. Now that there has been a relaxation of the criteria for PCSK9 inhibitor use in patients with recurrent ACS or multivascular disease in Australia (see PBS guidelines) we should be considering their use in patients not at target on maximally-tolerated doses of statin and ezetimibe.

Reference: BMJ Open 2021;11:e054893
Abstract

Lowering cholesterol, blood pressure, or both to prevent cardiovascular events: Results of 8.7 years of follow-up of Heart Outcomes Evaluation Prevention (HOPE)-3 study participants

Authors: Bosch J et al.

Summary: This follow-up of HOPE-3 study participants investigated whether the benefits observed with rosuvastatin during the active treatment phase of the study were sustained, enhanced, or attenuated during subsequent long-term observation. After the randomised treatment period (5.6 years), participants were invited to participate in a further 3.1 years of observation (total 8.7 years). Co-primary outcomes were the composite of MI, stroke, or cardiovascular death (MACE-1), and MACE-1 plus resuscitated cardiac arrest, heart failure, or coronary revascularisation (MACE-2). 9326 (78%) of 11,994 surviving HOPE-3 participants enrolled in the extended follow-up, during which time those who were initially randomised to rosuvastatin had a 20% additional reduction in MACE-1 (HR 0.80, 95% CI 0.64–0.99) and a 17% additional reduction in MACE-2 (HR 0.83, 95% CI 0.68–1.01) compared with placebo. During the total 8.7 years of follow up, there was a 21% reduction in both MACE-1 (HR 0.79, 95% CI 0.69–0.90; p=0.0005) and MACE-2 (HR 0.79, 95% CI 0.69–0.89; p=0.0002) in rosuvastatin recipients versus placebo. There was no benefit of BP lowering during either the active treatment period or the post-trial observation period.

Comment: The UKPDS study showed a beneficial legacy effect of intensive in-study diabetic control many years after the study was finished. In the HOPE-3 study, a similar legacy effect was seen over 3 years in patients who had received rosuvastatin 10mg during the trial, with a further 20% reduction in major cardiovascular events compared to those who received placebo. This may be due to lipid lowering reducing development of atherosclerosis and promoting plaque stability over the 5.6 years of the study, with these salutary effects persisting years after study medication was discontinued.

Reference: Eur Heart J 2021;42(31):2995-3007
Abstract

Lipoprotein(a) is associated with large artery atherosclerosis stroke aetiology and stroke recurrence among patients below the age of 60 years: Results from the BIOSIGNAL study

Authors: Arnold M et al.

Summary: The BIOSIGNAL cohort study evaluated the association of Lp(a) with large artery atherosclerosis (LAA) stroke and risk of recurrent cerebrovascular events in patients with acute ischaemic stroke (AIS). Lp(a) levels were measured within 24h after symptom onset in 1733 AIS patients. Primary outcomes were LAA stroke aetiology and recurrent cerebrovascular events within 1 year. Lp(a) levels were found to be independently associated with LAA stroke aetiology (adjusted odds ratio 1.48, 95% CI 1.14–1.90, per unit $\log_{10}$Lp(a) increase). The adjusted odds ratio for LAA stroke in patients aged <60 years was 3.64 (95% CI 1.76–7.52) per unit $\log_{10}$Lp(a) increase. Lp(a) levels ≥100 nmol/L were associated with an increased risk for recurrent cerebrovascular events among patients who were either <60 years (adjusted HR 2.40, 95% CI 1.05–5.47), had evident LAA stroke aetiology (adjusted HR 2.18, 95% CI 1.08–4.40), or had no known atrial fibrillation (adjusted HR 1.60, 95% CI 1.03–2.48).

Comment: Elevated Lp(a) is associated with an increased risk of developing ASCVD, and in particular coronary artery disease, which has been the most studied in this area. It has also been postulated to be responsible for the residual risk in patients who have recurrent events after ACS despite having lipids at target levels. This study shows that elevated Lp(a) is also strongly associated with large artery stroke (presumably mostly carotid arterial). Whether lowering elevated Lp(a) after ACS and/or stroke reduces recurrent events has not been proven yet, but now therapies that reduce Lp(a) levels are being tested in outcome trials and may well reach clinical practice if the studies are positive, and the agents not too expensive.

Reference: Eur Heart J 2021;42(22):2186-96
Abstract

Independent commentary by
Associate Professor John Amerena,
FRACP, FACC, FCSANZ, Dept. of Clinical and Biomedical Science, University of Melbourne (Geelong).

Associate Professor John Amerena trained in Melbourne before spending four years in the United States at the University of Michigan. Over that period of time he worked in the fields of hypertension and hyperlipidemia, before returning to Australia where he is now a Cardiologist at Barwon Health. He currently has a joint appointment in the Department of Clinical and Biomedical Sciences at the University of Melbourne and the Department of Epidemiology and Preventive Medicine at Monash University. He is the director of the Geelong Cardiology Research Unit, which is currently involved in many phase II-III clinical trials. While still actively researching in hypertension, his focus has changed to research in antithrombotic/antiplatelet therapies, particularly in the context of acute coronary syndromes and atrial fibrillation. Heart failure is also a major interest, and he is also the Director of the Heart Failure Programme at Barwon Health. He is well published in these areas, as well as in many other areas of cardiovascular medicine.

A safety and clinical efficacy analysis of PCSK9 monoclonal antibodies in patients with markedly elevated creatine phosphokinase levels

Authors: Volis I et al.

Summary: This study in Israel investigated the safety and efficacy of PCSK9 inhibitors in patients with markedly elevated creatine phosphokinase (CPK) levels. A comprehensive HMO database was screened for patients treated with PCSK9 inhibitors in 2016–2019 who had elevated CPK levels (>1000 U/L) prior to initiation of therapy; 26 patients were identified. All 26 patients had previously received statins but had discontinued due to adverse events (myalgia and rhabdomyolysis). 11 patients had concomitant secondary factors for CPK elevation. After initiation of treatment with either alirocumab (n=12) or evolocumab (n=14), 24 (92%) patients had a >50% reduction in CPK levels, and 12 (46%) had CPK levels return to normal. 17 patients (65%) achieved an LDL cholesterol level <70 mg/dL, and 12 (46%) reached <55 mg/dL. No serious adverse reactions were documented, and only 2 patients discontinued treatment (for reasons unrelated to muscle symptoms or CPK elevation).

Comment: Perceived statin intolerance is quite common, but there are genuine cases where statins do cause myositis and/or rhabdomyolysis, requiring permanent discontinuation even in high-risk patients. Anecdotally, the PCSK9 inhibitors are often used to lower lipids in patients who have had myalgia and/or rhabdomyolysis with statins, but until now there has been no evidence demonstrating the safety of this approach. This study shows that PCSK9 inhibitors are likely to be effective and well tolerated in this population.

Reference: Am J Blood Res 2021;11(4):399-404
Abstract

Generalizability of the REDUCE-IT trial and cardiovascular outcomes associated with hypertriglyceridemia among patients potentially eligible for icosapent ethyl therapy: An analysis of the REduction of Atherothrombosis for Continued Health (REACH) registry

Authors: Picard F et al.

Summary: This analysis of the REACH Registry evaluated the proportion of patients potentially eligible for enrolment in REDUCE-IT and compared their outcomes to those excluded because of low triglycerides. Among 62,464 patients with either ASCVD or diabetes enrolled in the REACH Registry, 11.3% would have been eligible for inclusion in REDUCE-IT. Compared with patients excluded for low triglyceride level, the adjusted risk of the primary composite outcome (cardiovascular death, non-fatal MI, non-fatal stroke, unstable angina, or coronary revascularisation) was higher in the REDUCE-IT-eligible group (HR 1.06, 95% CI 1.00–1.13; p=0.04). In addition, unstable angina, non-fatal MI, percutaneous coronary intervention and coronary artery bypass grafting were also more frequent in the REDUCE-IT-eligible group (all p<0.001), whereas the adjusted risk of non-fatal stroke was lower (HR 0.64, 95% CI 0.54–0.75; p<0.001).

Comment: The contribution of elevated triglycerides to cardiovascular risk in patients with established ASCVD is often debated. In this analysis of the REACH study, the outcomes of patients who would have been eligible for inclusion in the REDUCE-IT study (elevated triglycerides and either ASCVD or diabetes plus at least 1 risk factor) were evaluated. Around 11% of REACH patients (ASCVD or diabetes) had the REDUCE-IT characteristics and were shown to have an increased risk of MACE, revascularisation and cardiovascular death, but paradoxically less risk of stroke. This indicates to me that elevated triglycerides do influence outcome in patients with ASCVD, and that lowering triglycerides in this context is probably beneficial, although the clinical trial evidence for this is not robust.

Reference: Int J Cardiol 2021;340:96-104
Abstract

NOVARTIS | Reimagining Medicine

This Research Review is sponsored by an independent educational grant from Novartis

