Lipids Year in Review™ 2022

Making Education Easy 2022

In this issue:

Abbreviations used in this issue:

ACEI = angiotensin-converting enzyme inhibitor; **ACS** = acute coronary syndrome; **aOR** = adjusted odds ratio; **ARB** = angiotensin receptor blockers; **ASCVD** = atherosclerotic cardiovascular disease; **ATP** = adenosine triphosphate; **CAD** = coronary artery disease; **CABG** = coronary artery bypass graft; **CI** = confidence interval; **CKD** = chronic kidney disease; **COVID-19** = coronavirus disease 2019; **CRP** = C-reactive protein; **CT** = computed tomography; **CV** = cardiovascular; **CVD** = cardiovascular disease; **DAPT** = dual antiplatelet therapy; **GLP-1RA** = glucagon-like peptide 1 receptor agonists; **GP** = general practitioner; **HDL-C** = high-density lipoprotein cholesterol; **HMG-CoA** = β-hydroxy β-methylglutaryl-coenzyme A; **HR** = hazard ratio; **ICU** = intensive care unit; **LDL-C** = low-density lipoprotein cholesterol; **OR** = odds ratio; **PBS** = Pharmaceutical Benefits Scheme; **PCI** = percutaneous coronary intervention; **PCSK9** = proprotein convertase subtilisin/kexin type 9; **RCT** = randomised controlled trial; **SGLT2I** = sodium-glucose cotransporter 2 inhibitors.

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

We have selected the most significant research in the field of lipids for 2022, condensed into an easy-to-read review for your convenience. Included are a number of studies investigating the effects of lipoprotein(a) levels on various outcomes including the association of lipoprotein(a) with atherosclerotic plaque progression, and a review of the European Atherosclerosis Society consensus statement on lipoprotein(a) in atherosclerotic cardiovascular disease and aortic stenosis. We finish with several studies on statins, with a large Swedish population-based registry study providing further evidence in support of the protective effects of statins against hospitalisation and death in patients who contract COVID.

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
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Lipid lowering effects of the CETP inhibitor obicetrapib in combination with high-intensity statins: A randomized phase 2 trial

Authors: Nicholls SJ et al.

Summary: This 8-week, randomised, double-blind, placebo-controlled trial examined the lipid-lowering effects of obicetrapib in 120 dyslipidaemic patients (median LDL-C 88 mg/dL) receiving background high-intensity statin treatment. Over 8 weeks, obicetrapib 5 mg or 10 mg reduced median LDL-C by up to 51% (primary endpoint; $p < 0.0001$) compared with placebo, decreased apolipoprotein B by up to 30% ($p < 0.0001$), reduced non-HDL-C by up to 44%, and increased HDL-C by up to 165% ($p < 0.0001$).

Comment: In observational studies, high HDL-C has been associated with a lower rate of cardiovascular (CV) events on a population level, so it was thought increasing HDL levels with cholesteryl ester transfer protein (CETP) inhibitors could improve CV outcomes. The agents studied to date have not demonstrated improved CV outcomes, and in fact torcetrapib was associated with an increased risk of stroke and myocardial infarction. It has been postulated that it is the rate of HDL-C efflux rather than the absolute level that is more important, but several other CETP inhibitors, such as evacetrapib and anacetrapib raise HDL-C but also lower LDL-C by 30-35%. Despite this, no improvement in outcomes were demonstrated in the RCTs with these agents. This recent study shows that obicetrapib lowers LDL-C as well as raising HDL-C, but whether this will translate into an improvement in outcomes is dubious given the results of the previous clinical trials.

Reference: Nat Med. 2022;28(8):1672-1678
Abstract

Independent commentary by Associate Professor John Amerena

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.

Association between high-density lipoprotein cholesterol levels and adverse cardiovascular outcomes in high-risk populations

Authors: Liu C et al.

Summary: This prospective, multicentre, cohort study used data from the UK Biobank (n = 14,478; mean age 62.1 years; 76.4% male) and the US Emory Cardiovascular Biobank (n = 5467; mean age 63.8 years; 66.4% male), to examine the relationship between very high HDL-C levels (>80 mg/dL) and mortality in patients with coronary artery disease. Over a median of 8.9 years' follow-up in the UK and 6.7 years in the US, there was a U-shaped association with outcomes; risk was higher in patients with low and very high HDL-C levels versus midrange values. Very high HDL-C levels were associated with an increased risk of all-cause mortality (HR 1.96; 95% CI 1.42-2.71; p < 0.001) and CV mortality (HR 1.71; 95% CI 1.09-2.68; p = 0.02) versus HDL-C levels of 40-60 mg/dL, and these associations persisted after adjustment for HDL-C genetic risk scores. Sensitivity analyses suggested that risk of all-cause mortality with very high HDL-C levels was elevated among men (HR 2.63; 95% CI 1.75-3.95; p < 0.001) but not women (HR 1.39; 95% CI 0.82-2.35).

Comment: It has been thought from epidemiological and observational studies that having high HDL-C levels is cardioprotective. More recent studies in the general population however have suggested that high HDL-C is associated with an increased risk of CV disease, particularly in those patients with underlying coronary disease. This article looking at data from the UK and Emory biobanks has suggested that patients with very high HDL-C had a worse outcome and increased risk of CV and all-cause death compared to patients with a lower HDL-C, even when adjusted for confounders. This raises the possibility that there is a U-curved relationship between CV and all-cause mortality and HDL-C levels, but the reasons for this are unclear, especially as the association was independent of common polymorphisms associated with high levels of HDL-C.

Reference: JAMA Cardiol. 2022;7(7):672-680
Abstract

Association of coronary plaque with low-density lipoprotein cholesterol levels and rates of cardiovascular disease events among symptomatic adults

Authors: Mortensen MB et al.

Summary: This cohort study used data from the Western Denmark Heart Registry to assess the prevalence of noncalcified and calcified plaques in 23,143 symptomatic adults (median age 58 years; 55.6% female) undergoing coronary computed tomographic (CT) angiography and the association with CV events across a range of LDL-C levels (<77, 77-112, 113-154, 155-189, and ≥190 mg/dL). Over a median follow-up of 4.2 years, there were a total of 1029 atherosclerotic CV disease (ASCVD) events and deaths. Across all LDL-C strata, absence of coronary artery calcium (CAC) ranged from 46.2% of patients with LDL-C levels of ≥190 mg/dL to 54.9% with LDL-C levels of 77-112 mg/dL and was not associated with detectable plaque in most patients (22.8% with LDL-C levels of ≥190 mg/dL; 11.4% with LDL-C levels <77 mg/dL). Absence of CAC was associated with low rates of ASCVD and death (6.3 per 1000 person-years; 95% CI 5.6-7.0), with increasing rates associated with CAC scores of 1-99 (11.1 per 1000 person-years; 95% CI 10.0-12.5) and CAC scores of ≥100 (21.9 per 1000 person-years; 95% CI 19.9-24.4). For a CAC score of 0, the event rate in the overall population was 6.3 per 1000 person-years (95% CI 5.6-7.0) versus 6.9 per 1000 person-years (95% CI 4.0-11.9) for those with LDL-C levels of ≥190 mg/dL.

Comment: Coronary calcium scoring is commonly used as a means of quantifying CV risk. The higher the calcium score the greater risk of a CV event and an elevated CAC score is often used to justify aggressive lipid-lowering therapy, even in patients whose LDL-C is not markedly elevated. However, there is no evidence at present that this approach is beneficial. This interesting study suggests that in patients who have elevated LDL-C and are traditionally thought to be high risk, that the absence of calcification and plaque on CT coronary angiography confers a lower risk of ASCVD events in the future. If these results can be reproduced it suggests that using CT coronary angiography may help better define risk in patients with elevated LDL-C, which perhaps could indicate less aggressive treatment is required.

Reference: JAMA Netw Open 2022;5(2):e2148139
Abstract

Association of low-density lipoprotein cholesterol levels during statin treatment with cardiovascular and renal outcomes in patients with moderate chronic kidney disease

Authors: Yen C-L et al.

Summary: This Chinese study assessed data from the Chang Gung Research Database to examine CV and renal outcomes in 8500 patients with stage 3 chronic kidney disease across different LDL-C strata receiving statins. Patients with LDL-C levels of 70-100 mg/dL had lower overall risks of major adverse cardiac and cerebrovascular events than those with levels ≥100 mg/dL (6.8% vs 8.8%; HR 0.76; 95% CI 0.64-0.91), along with lower risk of intracerebral haemorrhage (0.23% vs 0.51%; HR 0.44; 95% CI, 0.25-0.77), and reduced risk of new-onset end-stage renal disease (ESRD) requiring chronic dialysis (7.6% vs 9.1%; subdistribution HR 0.82; 95% CI 0.73-0.91]). LDL-C <70 mg/dL provided a marginally lower risk of major adverse cardiac and cerebrovascular events (7.3% vs 8.8%; HR 0.82; 95% CI 0.65-1.02) and a reduced risk of new-onset ESRD requiring chronic dialysis (7.1% vs 9.1%; HR 0.76; 95% CI 0.67-0.85).

Comment: The benefits of statins in patients with chronic renal dysfunction have been debated as the outcome trials of lipid lowering with statins in patients with severe dysfunction have not been able to demonstrate any improvement in outcome. This study looked at less severe degrees of renal dysfunction (stage 3) and examined the effects of statin therapy on CV and renal events in this population. It found that lowering LDL-C to <1.8 mmol/L (<70 mg/dL) produced lower CV outcomes and less progression to end-stage renal failure. It would therefore suggest that intensive lipid-lowering in patients with stage 3 kidney disease is worthwhile, but it is still debatable as to whether there is any benefit in patients with end-stage renal disease.

Reference: J Am Heart Assoc. 2022;11(19):e027516
Abstract

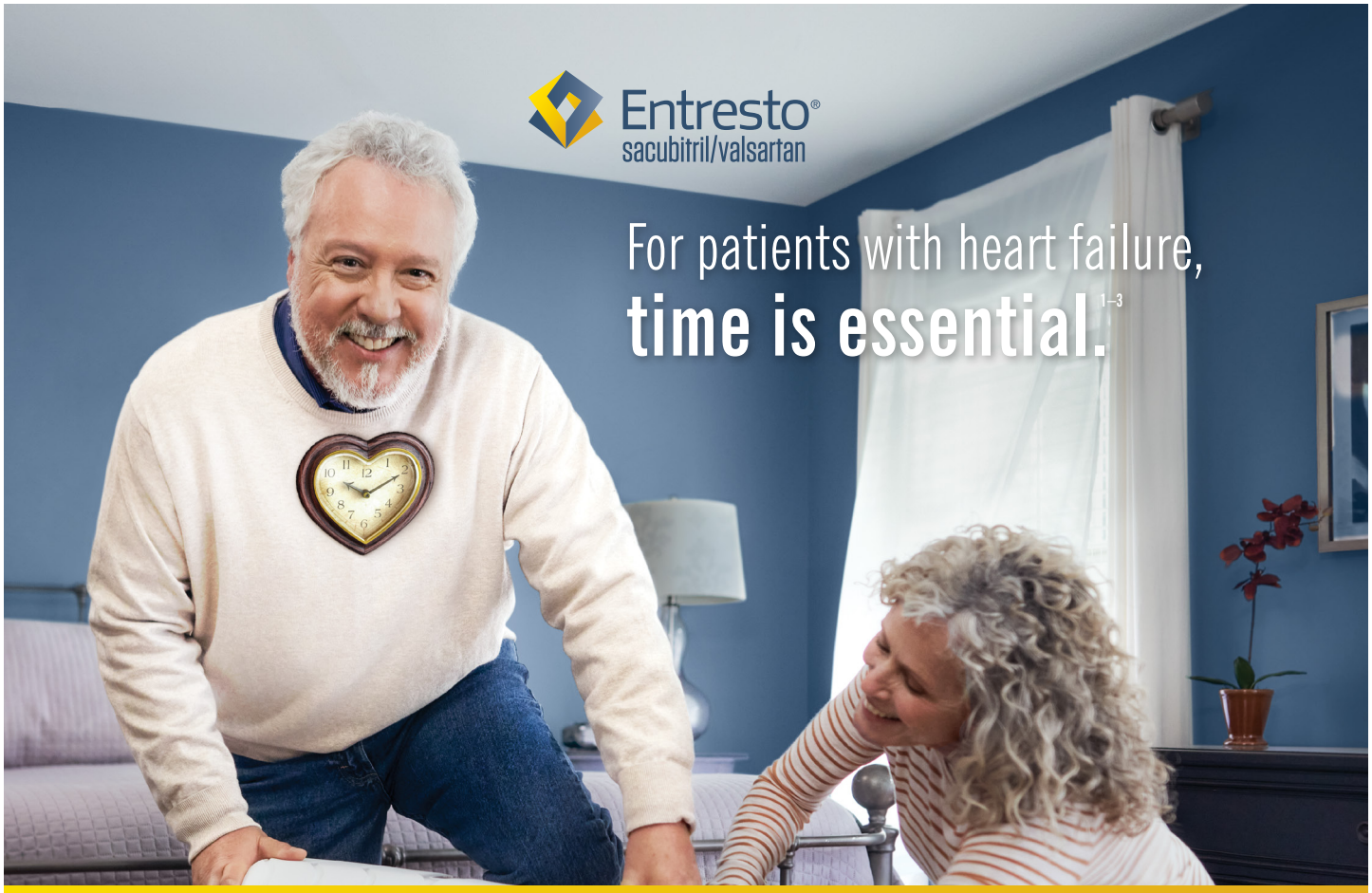
How do lipoprotein(a) concentrations affect clinical outcomes for patients with stable coronary artery disease who underwent different dual antiplatelet therapy after percutaneous coronary intervention?

Authors: Cui K et al.

Summary: This analysis of data from the prospective Fuwai Percutaneous Coronary Intervention Registry assessed the effect of lipoprotein(a) levels on the efficacy and safety of prolonged dual antiplatelet therapy (DAPT) versus shortened DAPT in 3201 stable coronary artery disease patients with a drug-eluting stent. Over a median follow-up of 2.5 years, DAPT for >1 year reduced the risk of major adverse CV and cerebrovascular events and definite/probable stent thrombosis compared with DAPT ≤1 year in patients with elevated lipoprotein(a). In patients with normal lipoprotein(a) levels, the risks of these events were not different between DAPT >1 year and ≤1 year.

Comment: Despite small benefits of continuing DAPT for >12 months after an acute coronary syndrome (ACS) with or without percutaneous intervention, it is not frequently done due to concern about excessive risk of bleeding. This study looked at the relationship between elevated lipoprotein(a) and the benefits of ongoing DAPT and found that the patients who had elevated lipoprotein(a) had benefit from continuation of DAPT for >12 months after their event, whereas those whose lipoprotein(a) was normal had no benefit, perhaps implying that elevated known CV risk with elevated lipoprotein(a) can be attenuated by prolonged DAPT. Further study needs to be done on this, but this may help select patients who would benefit from ongoing DAPT after ACS. It would be interesting to study whether this strategy would be effective in patients with elevated lipoprotein(a) who have not had an event as a primary prevention strategy, or whether dual pathway inhibition (aspirin and low-dose rivaroxaban) would be even more beneficial in these patients.

Reference: J Am Heart Assoc. 2022;11(9):e023578
Abstract



START ENTRESTO EARLY†: Recommended as a first choice treatment for chronic HFrEF by Australian HF Consensus Statement 2022[4‡]

†In patients on beta-blocker and stabilised on ACEI/ARB. ‡This differs from the PBS criteria, which state that patients must be on a beta-blocker and stabilised on ACEI/ARB before commencing Entresto.

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§Lower risk of CV death or first HF hospitalisation with ENTRESTO® vs ACEI (enalapril; 20% RRR, $p<0.001$)[5]

Overall incidence of AEs with ENTRESTO® was comparable to enalapril:[5]

- Symptomatic hypotension was more common with ENTRESTO® vs enalapril (14.0% vs 9.2%, $p<0.001$)[5]
- Cough (11.3% vs 14.3%), serum creatinine ≥25 ug/mL (3.3% vs 4.5%) and serum potassium >6.0 mmol/L (4.3% vs 5.6%) were less frequent with ENTRESTO® vs enalapril ($p<0.05$ for all)[5]

PBS Information: Authority required (STREAMLINED) for chronic heart failure. Patients must be NYHA Class II–IV, have LVEF ≤40% and be receiving optimal standard chronic heart failure treatment. Refer to PBS Schedule for full Authority Information.

PBS streamlined authority code: 6915 chronic heart failure

For healthcare professionals only. Before prescribing, please review full Product Information available here.

References: 1. Atherton JJ et al. Heart Lung Circ 2018; 27: 1123–1208. **2.** Gheorghiade et al. Am J Cardiol 2005; 96: 11G–17G. **3.** Solomon SD et al. JACC Heart Fail 2016; 4: 816–822. **4.** Sindone AP et al. Med J Aust 2022; 217: 212–7. **5.** McMurray JJ et al. N Engl J Med 2014; 371: 993–1004. **6.** ENTRESTO approved Product Information.

Abbreviations: ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; CV, cardiovascular; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; RRR, relative risk reduction.

NOVARTIS

Efficacy and safety of bempedoic acid in patients not receiving statins in phase 3 clinical trials

Authors: Laufs U et al.

Summary: This was a pooled analysis of data from four 12-52-week placebo-controlled phase III bempedoic acid studies in patients not taking concomitant statins and a phase III study of bempedoic acid plus ezetimibe fixed-dose combination. At week 12, bempedoic acid (n = 394) lowered LDL-C levels 26.5% (95% CI 29.7-23.2; p < 0.001) more than placebo (n = 192), while fixed-dose bempedoic acid plus ezetimibe lowered LDL-C by 39.2% (95% CI 51.7-26.7%; p < 0.001). Muscle-related disorders occurred at a rate of 26.4 per 100 person-years with bempedoic acid and 28.6 per 100 person-years with placebo.

Comment: Bempedoic acid is an agent which blocks cholesterol synthesis by inhibiting ATP citrate lyase upstream from HMG-CoA reductase which is inhibited by statins. The advantage of this agent over statins is that ATP citrate lyase is not present in skeletal muscle, so it has been postulated there is less risk of muscle side effects with this agent compared with statins. This agent is currently being tested in large clinical outcome trials, but this study would suggest that there is a meaningful reduction in LDL-C using this agent in statin-intolerant patients with a decrease of around 26% when used alone, but this increased to 39% when it was combined with ezetimibe. The rates of muscle-related adverse effects were similar between bempedoic acid and the placebo group. This agent is promising and although perhaps not as potent as statins in lowering LDL-C, when combined with ezetimibe there is a reduction which hopefully will translate into an improvement in CV outcomes in patients with CV disease who cannot tolerate statin therapy.

Reference: J Clin Lipidol. 2022;16(3):286-297
Abstract

Attainment of low-density lipoprotein cholesterol goals in patients treated with combination therapy: A retrospective cohort study in primary care

Authors: Marquina C et al.

Summary: This retrospective cohort study assessed LDL-C levels and LDL-C goal attainment in 9173 patients (mean age 65.8 years; 60.1% male; 56.7% ≥1 CV risk factor) treated with combination lipid-lowering therapy (statins plus non-statins) by GPs across Australia between 2013-2019. Median on-treatment LDL-C was 2.1 mmol/L and 45.4% of the cohort met LDL-C goals; fixed-dose statins plus ezetimibe had the highest LDL-C goal achievement rate (49.8%). Multivariate analyses identified factors associated with LDL-C goal achievement that included male sex (OR 1.4; 95% CI 1.3-1.6; p < 0.001), age >80 years (OR 4.2; 95% CI 1.5-6.6; p = 0.006), and a history of type 2 diabetes (OR 1.7; 95% CI 1.5-1.9; p < 0.001) and coronary heart disease (OR 1.4; 95% CI 1.2-1.6; p < 0.001).

Comment: Over time, target lipid levels for primary and secondary prevention have become progressively lower due to accumulating data that the lower the LDL-C the better the outcome, especially in secondary prevention. This has resulted in higher doses of statins being recommended, and combination therapy with ezetimibe encouraged to attain target levels. This study shows that despite these medications being widely available and subsidised through the PBS, many patients in Australia did not reach their nominated targets. Whether this is due to lack of knowledge of contemporary guidelines by practitioners, or reluctance to use high-dose statins due to actual or imagined fear of producing adverse effects, or poor compliance by patients is not known, but there will be some patients on high-dose statin and ezetimibe who cannot achieve target levels and would be good candidates for PCSK9 inhibitors. The criteria for reimbursement for these agents through the PBS has recently been relaxed, and GPs will now be able to initiate therapy with them, which may help improve control of lipids, especially in the highest-risk patients.

Reference: Clin Lipidol. 2022;16(4):498-507
Abstract

Lipoprotein(a) in atherosclerotic cardiovascular disease and aortic stenosis: A European Atherosclerosis Society consensus statement

Authors: Kronenberg F et al.

Summary: This consensus statement from the European Atherosclerosis Society provides updated evidence for the role of lipoprotein(a) in ASCVD and aortic valve stenosis, suggests clinical guidance for testing and treating elevated lipoprotein(a), and assesses its inclusion in global risk estimation. Elevated lipoprotein(a) is a risk factor even at very low LDL-C levels and high lipoprotein(a) levels are associated with aortic valve microcalcification and macrocalcification. Lipoprotein(a) does not appear to be a risk factor for venous thrombosis and impaired fibrinolysis, while very low lipoprotein(a) levels may be associated with increased risk of diabetes. Lipoprotein(a) has pro-inflammatory and pro-atherosclerotic effects that may be related to oxidised phospholipids carried by lipoprotein(a). The guidelines recommend testing lipoprotein(a) at least once in adults with cascade testing having value in familial hypercholesterolaemia, or with family or personal history of (very) high lipoprotein(a) or premature ASCVD. Early intensive risk factor management is recommended, targeted according to global CV risk and lipoprotein(a) level. Consideration should be given to lipoprotein apheresis in patients with very high lipoprotein(a) levels and progressive CV disease despite optimal management of risk factors.

Comment: We know that elevated lipoprotein(a) is associated with an increased risk of CV events, even in patients who have low LDL-C. We know that in all the major trials of statins there is a 30-40% reduction in events, but there is still a large residual risk. Lipoprotein(a) has been postulated to be a factor in recurrent events in patients whose lipids are well controlled, as well as inflammation. We also know that elevated lipoprotein(a) is associated with microcalcification of the aortic valve leading to stenosis. This position statement acknowledges this and recommends that lipoprotein(a) be measured at least once in all patients to identify a high-risk group. Whether lowering lipoprotein(a) decreases CV events in primary or secondary prevention has yet to be demonstrated, but large outcome trials are currently underway to determine if this is the case.

Reference: Eur Heart J. 2022;43(39):3925-3946
Abstract

Lipoprotein(a) levels in a global population with established atherosclerotic cardiovascular disease

Authors: Nissen SE et al.

Summary: This multinational, cross-sectional epidemiological study examined patterns of lipoprotein(a) levels in ASCVD populations from 48 countries in North America, Europe, Asia, South America, South Africa, and Australia (n = 48,135; mean age 62.6 years; 25.9% female) and racial, ethnic, regional and gender differences. Median lipoprotein(a) level was 18.0 mg/dL (42.0 nmol/L) with median LDL-C of 77 mg/dL. Lipoprotein(a) levels were higher in women than men (22.8 vs 17.0 mg/dL; p < 0.001), in younger patients than older patients, and were 3-fold higher in black patients than white, Hispanic, or Asian patients. Lipoprotein(a) levels were >50 mg/dL in 27.9% of patients, >70 mg/dL in 20.7% of patients, >90 mg/dL in 12.9% of patients and >150 nmol/L in 26.0% of patients.

Comment: This study complements the recent lipoprotein(a) ESC guidelines as it illustrates that elevated lipoprotein(a) is an under-recognised risk factor for CVD, which is seldom measured. Some of this undertesting may be because estimation of lipoprotein(a) is not funded, as is the case in Australia, so there is a significant out of pocket cost to the patient. When there is no way of modifying lipoprotein(a) levels it is difficult to push patients to have this test, but now that agents that significantly reduce lipoprotein(a) are being tested in outcome RCTs, there should be pressure to get the test funded, and for levels to be measured in high-risk patients, especially those who have CV events despite well-controlled traditional risk factors.

Reference: Open Heart 2022;9(2):e002060
Abstract

Use of lipid-, blood pressure-, and glucose-lowering pharmacotherapy in patients with type 2 diabetes and atherosclerotic cardiovascular disease

Authors: Nelson AJ et al.

Summary: This US multicentre cohort study used aggregated data from the National Patient-Centered Clinical Research Network to assess CV preventive therapies in a population (n = 324,706; mean age 68.1 years; 55.6% male; 18.2% Black, 12.8% Latinx) with diabetes and ASCVD. Overall, 58.6% of patients were prescribed a statin, but only 26.8% were prescribed a high-intensity statin; 45.5% received an ACEI or ARB, 3.9% a GLP-1RA, and 2.8% an SGLT2I. Overall, 4.6% of patients were prescribed all three classes of therapies, while 42.6% were prescribed none. Patients receiving a high-intensity statin were more likely to be men, have coronary atherosclerotic disease, and more likely to have seen a cardiologist.

Comment: We know that type 2 diabetes is a strong CV risk factor and that most of the morbidity and mortality in type 2 diabetes is from CV disease, not the complications of diabetes itself. Numerous RCTs have shown LDL-C reduction with a statin improves outcomes in primary and secondary prevention in patients with type 2 diabetes. This study looking at US patients with type 2 diabetes who had established ASCVD, showed that even though these patients are at very high risk, only 59% were on a statin, and only 27% were on a high intensity dose. Whether this is due to financial considerations, or treatment inertia by physicians or a lack of awareness of the compelling data showing outcomes are better in type 2 diabetes with aggressive lipid lowering is unclear, but hopefully Australian numbers would be better, especially as statins are subsidised here.

Reference: JAMA Netw Open 2022;5(2):e2148030
Abstract

Attainment of lipid targets following coronary artery bypass graft surgery: Can we do better?

Authors: Lan NSR et al.

Summary: This Australian single-centre retrospective study assessed the proportion of coronary artery bypass graft (CABG) patients (n = 484; mean age 62.7 years; 80.1% male) who attained LDL-C and non-HDL-C targets during post-operative lipid management (96.9% statins, 90.6% high-intensity; 12.8% ezetimibe). At a median post-operative follow-up of 483 days, LDL-C levels <1.4 mmol/L were attained by 24.4% of patients and <1.8 mmol/L by 47.7% of patients; non-HDL-C levels <2.2 mmol/L were achieved by 28.9% of patients and <2.6 mmol/L by 49.0% of patients.

Comment: This Australian study looked at attainment of lipid targets in patients who underwent CABG between 2015 and 2020. It found that despite these patients being at high risk, many did not achieve the aggressive LDL-C targets that are recommended despite high-dose statins. It is disappointing that the use of ezetimibe was so low (13%) but it is understandable why PCSK9 use was so low, as they were not subsidised for these type of patients at that stage. This is soon to change, however, and we will hopefully see greater use of these potent lipid-lowering agents in these high-risk patients whose LDL-C remains >1.8 mmol/L despite maximally tolerated statin and ezetimibe.

Reference: J Lipid Atheroscler. 2022;11(2):187-196
Abstract

Association of lipoprotein(a) with atherosclerotic plaque progression

Authors: Kaiser Y et al.

Summary: This study examined the association between lipoprotein(a) and adverse plaque progression in 191 patients (median 65.9 years of age; 80% male) with median lipoprotein(a) levels of 100 mg/dL (high lipoprotein(a) group) and 10 mg/dL (low lipoprotein(a) group) with advanced stable coronary artery disease undergoing coronary CT angiography at baseline and 12 months. Patients with high lipoprotein(a) levels had accelerated progression of low-attenuation plaque (necrotic core) versus those with low lipoprotein(a) levels (26.2 mm^3 vs -0.7 mm^3; p = 0.020). Multivariate analysis confirmed a relationship between lipoprotein(a) and low-attenuation plaque volume progression; a 10.5% increase for each 50 mg/dL increase in lipoprotein(a) level (95% CI 0.7-20.3). Total, calcific, and non-calcific plaque volume progression did not differ between groups.

Comment: We know that there is an association between increased levels of lipoprotein(a) and CV disease and events, as well as aortic valve calcification. This study assessed plaque characteristics in patients with advanced coronary artery disease using coronary CT angiography and found that elevated lipoprotein(a) was associated with accelerated progression of plaques with vulnerable features, thus providing a biologically plausible mechanism for the increased risk with elevated lipoprotein(a). Imaging studies using more sophisticated techniques such as optical coherence tomography or intravascular ultrasound are sure to be done with the new agents that lower lipoprotein(a) to try and demonstrate a reduction in progression or a change in plaque characteristics with aggressive lowering of lipoprotein(a), but event driven RCTs will need to be positive before these agents will be used in clinical practice.

Reference: J Am Coll Cardiol. 2022;79(3):223-233
Abstract

Early statin therapy and in-hospital outcomes in acute coronary syndrome patients presenting with advanced Killip class at admission: Findings from the CCC-ACS project

Authors: Song X et al.

Summary: The Improving Care for Cardiovascular Disease in China-ACS project examined outcomes in 12,149 patients with advanced Killip class (III/IV) ACS receiving early statin therapy (89.3% within 24 hours). Multivariate analysis suggested a 69% reduction in mortality in the early statin recipients (aOR 0.31; 95% CI 0.25-0.39) and paralleled a reduction in ischaemic events (aOR 0.50; 95% CI 0.33-0.74). The protective association of early statins on in-hospital mortality was observed even with a low-to-moderate statin dose. The short-term survival benefit of early statins was independent of LDL-C level.

Comment: Statins are routinely prescribed in patients with ACS but often there is a delay in initiation as it is assumed they are being used for long-term benefit rather than having an acute effect. This study shows that early initiation of statins in patients with high Killip class after ACS (<24 hours) improves in hospital mortality, so early administration should become routine. It is tempting to postulate that this acute effect is mediated by improving plaque stability by reducing inflammation within the plaque, as we know that patients who have a reduction in LDL-C and CRP have the best outcomes after ACS, but this is yet to be proven.

Reference: Am J Cardiovasc Drug 2022;22(6):685-694
Abstract

Long-term efficacy and safety of moderate-intensity statin with ezetimibe combination therapy versus high-intensity statin monotherapy in patients with atherosclerotic cardiovascular disease (RACING): A randomised, open-label, non-inferiority trial

Authors: Kim B-K et al.

Summary: This Korean multicentre, randomised, open-label, non-inferiority trial compared moderate-intensity statin with ezetimibe combination therapy (rosuvastatin 10 mg; ezetimibe 10 mg) or high-intensity statin monotherapy (rosuvastatin 20 mg) in 3780 patients with ASCVD. The primary endpoint (3-year composite of death, major events, or non-fatal stroke) occurred in 172 (9.1%) combination therapy and 186 (9.9%) high-intensity statin monotherapy recipients (absolute difference -0.78%; 90% CI -2.39 to 0.83). The proportion of patients with LDL-C cholesterol concentrations <70 mg/dL were lower with combination therapy at 1 (73% vs 55%), 2 (75% vs 60%), and 3 years (72% vs 58%; all $p < 0.0001$). Discontinuation or dose reduction occurred in 88 combination therapy (4.8%) and 150 monotherapy recipients (8.2%; $p < 0.0001$).

Comment: Traditional teaching has been to use the maximally tolerated dose of statin before addition of ezetimibe to achieve target lipid levels. This study explored using moderate intensity statin plus ezetimibe versus high intensity statin and found no difference in CV outcomes but did show more patients achieved target levels of LDL-C and better tolerability. This being the case perhaps we should consider using ezetimibe earlier as a statin sparing agent, especially as there are fixed dose combinations widely available.

Reference: Lancet 2022;400(10349):380-390
Abstract

Protective effects of statins on COVID-19 risk, severity and fatal outcome: A nationwide Swedish cohort study

Authors: Santosa A et al.

Summary: This study used a Swedish population-based register to examine whether statin exposure in the population (n = 572,695) and in COVID-19 patients affected the risk and severity of COVID-19. In the overall population, prior statin treatment (22.3%) appeared to have protective effects for hospitalisation and COVID-19 death. In hospitalised patients, statin use was associated with lower risk of death (HR 0.86; 95% CI 0.79-0.95), but not ICU admission.

Comment: This is one of several reports that show that statins may be protective in patients who contract COVID. There were less hospitalisations in statin users and in patients who were hospitalised there was a lower death rate. This is clearly not due to lowering lipids but suggests pleiotropic effects of statins, such as improving endothelial function, dampening down inflammation and decreasing viral reproduction could be some of the mechanisms of protection. Thus using statins in high-risk populations for COVID complications, such as in the elderly, immunocompromised and with heart failure, should be considered to reduce the morbidity and mortality associated with COVID infection.

Reference: Sci Rep. 2022;12(1):12047
Abstract

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