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Welcome to the latest issue of Cardiology Research Review.

This month we report that patients with prosthetic heart valves are at risk for streptococcal endocarditis after invasive dental procedures, low education is a causal risk factor for coronary heart disease, and the Healthy Heart Score seems to be reasonably predictive of the development of long-term atherosclerotic vascular disease. The combination of a low-dose statin with a nutraceutical is a viable therapeutic option in patients with high-dose statin intolerance, the PCSK9 inhibitor alirocumab is more effective add-on therapy than ezetimibe in patients taking maximally tolerated statin doses, and gene therapy shows promise in patients with refractory angina.

We hope you find these and the other selected studies interesting, and look forward to receiving any feedback you may have.

Kind Regards,

Associate Professor John Amerena
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Dental procedures, antibiotic prophylaxis, and endocarditis among people with prosthetic heart valves

Authors: Tubiana S et al.

Summary: This French study evaluated the association between invasive dental procedures and infective endocarditis due to oral streptococci in patients with prosthetic heart valves. 138,876 adults with a prosthetic heart valve were included, of whom 69,903 (49.9%) underwent at least one dental procedure. Only half of the patients undergoing an invasive procedure received antibiotic prophylaxis. During a median follow-up of 1.7 years, 267 people developed infective endocarditis associated with oral streptococci (incidence rate 93.7 per 100,000 person-years). Compared with non-exposure periods, there was no increase in the rate of oral streptococcal infective endocarditis in the 3 months after an invasive dental procedure, and after an invasive dental procedure without antibiotic prophylaxis. In a case crossover analysis, exposure to invasive dental procedures was more frequent during case periods than during matched control periods (5.1% vs 3.2%; p<0.03).

Comment: There has been great controversy over the use of prophylactic antibiotics in patients with valvular heart disease who are undergoing dental procedures. The current recommendations are that if patients have native valvular heart disease antibiotic prophylaxis is not required but if they have prosthetic heart valves they are at high risk and the administration of peri-procedural antibiotics is recommended. Although the first recommendation has not been widely adopted in Australia, the second has, so it is surprising that in this French study only 50% of patients who had prosthetic heart valves received peri-procedural antibiotic prophylaxis. This study suggests that invasive dental procedures without prophylactic antibiotics in patients with prosthetic heart valves increase the risk of developing streptococcal endocarditis, and thus reinforces the current guidelines.

Reference: BMJ 2017;358:j3576
Abstract

Education and coronary heart disease

Authors: Tillmann T et al.

Summary: This mendelian randomisation study determined whether educational attainment is a causal risk factor in the development of coronary heart disease. Researchers obtained genetic data from two large consortia, CARDioGRAMplusC4D and SSGAC, comprising 112 studies (n=543,733) from predominantly high-income countries. Findings from the mendelian randomisation analyses were then compared with results from traditional observational studies. Genetic predisposition towards 3.6 years of additional education was found to be associated with a one-third lower risk of coronary heart disease (odds ratio, 0.67), and was also associated with less smoking, lower body mass index, and a favourable blood lipid profile.

Comment: This study nicely demonstrates what we often see in clinical practice: patients from lower socio-economic and lower educational backgrounds have increased incidence of cardiovascular disease compared to their counterparts in higher social strata who are better educated. The reason for this is almost certainly lifestyle differences as smoking, obesity, less exercise and higher salt intake are more likely to be prevalent in the less educated lower socio-economic groups. This is important from a public health perspective because, if health education is delivered to all students from an early age, these groups in particular may make better lifestyle choices that will result in less development of cardiovascular disease over time.

Reference: BMJ 2017;358:j3542
Abstract
**Application of a lifestyle-based tool to estimate premature cardiovascular disease events in young adults**

**Authors:** Gooding H et al.

**Summary:** This analysis of the CARDIA study evaluated the use of the Healthy Heart Score (HHS) for estimating premature atherosclerotic cardiovascular disease (ASCVD) events. 4893 adults aged 18–30 years underwent measurement of lifestyle factors in 1985–1986 and were followed up for a median 27.1 years. The HHS included age, smoking status, body mass index, alcohol intake, exercise, and a healthy diet score. 163 premature ASCVD events occurred during follow-up. The HHS showed moderate discrimination for assessing the 25-year risk of ASCVD (death from coronary heart disease, nonfatal MI, and fatal or nonfatal ischaemic stroke). It performed better in men than in women, in white than in black participants, and in those with versus without clinical risk factors at baseline.

**Comment:** The Australian cardiovascular disease risk calculator is often used to evaluate the absolute risk of patients with risk factors developing cardiovascular disease over time. It is not particularly useful in patients without risk factors and this study has evaluated a lifestyle-based score to try and address this gap. The HHS includes factors such as smoking status, body mass index, alcohol intake, exercise and diet and seems to have a reasonable predictive value for the development of long-term atherosclerotic vascular disease. As with the cardiovascular risk calculator this information could be used to motivate patients to change their lifestyle with the hope of avoiding future cardiovascular events.

**Reference:** JAMA Intern Med 2017;177(9):1354-60

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**Effects of once-weekly exenatide on cardiovascular outcomes in type 2 diabetes**

**Authors:** Holman R et al., for the EXSCEL Study Group

**Summary:** The EXSCEL study investigated the cardiovascular effects of adding once-weekly exenatide to usual care in patients with type 2 diabetes. 14,752 patients with type 2 diabetes (73.1% also had cardiovascular disease) were randomised to receive subcutaneous injections of extended-release exenatide 2mg or matching placebo once weekly. The primary composite outcome was death from cardiovascular causes, nonfatal MI, or nonfatal stroke. During a median 3.2 years of follow-up, a primary composite outcome event occurred in 11.4% of patients in the exenatide group and 12.2% of patients in the placebo group. The intention-to-treat analysis indicated that exenatide was noninferior to placebo with respect to safety (p<0.001 for noninferiority) but was not superior to placebo with respect to efficacy (p=0.06 for superiority).

**Comment:** The LEADER study of liraglutide in patients with type 2 diabetes and established cardiovascular disease showed a beneficial effect with a reduction in cardiovascular events and mortality. This agent is available in Australia but not funded through the Pharmaceutical Benefits Scheme as yet, and does not have an indication for cardioprotection. It was therefore of great interest to see the results of the EXSCEL trial using once-weekly exenatide in a similar population. Unfortunately the primary outcome was not met as there was no reduction in combined end-point of nonfatal MI, nonfatal stroke or cardiovascular death in the patients in the active treatment group, although there was a significant reduction in all-cause mortality which was a secondary end-point. There was a significant treatment discontinuation which may have been due to the difficulty in using the device to administer exenatide. At present all we can say is that once-weekly exenatide is noninferior to placebo in reduction of cardiovascular events in patients with type 2 diabetes and cardiovascular disease as the anticipated benefits were not able to be demonstrated.


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Oxygen therapy in suspected acute myocardial infarction

Authors: Hofmann R et al., for the DETO2X-SWEDEHEART Investigators

Summary: The DETO2X-AMI trial examined the use of routine oxygen therapy in patients with suspected acute MI. 6629 patients with suspected MI and an oxygen saturation >90% were randomised to receive either supplemental oxygen (6 L/min for 6–12 hours, delivered via an open face mask) or ambient air. The median duration of oxygen therapy was 11.6h, and the median oxygen saturation at the end of the treatment period was 99% in patients assigned to oxygen and 97% in patients assigned to ambient air. Hypoxaemia developed in 1.9% and 7.7% of patients in the respective groups. The primary end-point of death from any cause within 1 year after randomisation occurred in 5.0% of patients assigned to oxygen and 5.1% of patients assigned to ambient air (p=NS). 3.8% and 3.3% of patients in the respective groups were rehospitalised with MI within 1 year (p=NS).

Comment: Supplemental oxygen in the context of acute coronary syndromes has been standard practice for many years. A small study in Australia suggested that this may increase the risk of recurrent ischaemic events and mortality over time, and postulated that high oxygen concentration could induce vaasospasm. This Swedish study did not show any benefit of supplemental oxygen over placebo in patients who had an acute coronary syndrome and whose oxygen saturation was greater than 90%, and there was no difference in recurrent ischaemic events, hospitalisation or death at 1 year. Thus, these two studies do not support the routine use of oxygen in patients with acute coronary syndrome whose oxygen saturation is above 90% but it should still be used in patients who are hypoxic on presentation.

Abstract

Antinflammatory therapy with canakinumab for atherosclerotic disease

Authors: Ridker P et al., for the CANTOS Trial Group

Summary: The CANTOS trial evaluated the use of the anti-inflammatory monoclonal antibody canakinumab in patients with atherosclerosis. 10,061 patients with previous MI and a high-sensitivity C-reactive protein (hs-CRP) level ≥2 mg/L were randomised to receive placebo or 1 of 3 canakinumab doses (100mg, 150mg, and 500mg) subcutaneously every 3 months. The primary efficacy end-point was nonfatal MI, nonfatal stroke, or cardiovascular death. At a median follow-up of 3.7 years, the incidence rate for the primary end-point (per 100 person-years) was 4.50 in the placebo group compared with 4.11, 3.86 and 3.90 in the canakinumab 50mg, 150mg, and 500mg groups, respectively. Hazard ratios compared with placebo in patients who had an acute coronary syndrome and whose oxygen saturation was greater than 90%, and there was no difference in recurrent ischaemic events, hospitalisation or death at 1 year. Thus, these two studies do not support the routine use of oxygen in patients with acute coronary syndrome whose oxygen saturation is above 90% but it should still be used in patients who are hypoxic on presentation.

Comment: Antinflammatory therapy with canakinumab for atherosclerotic disease has been standard practice for many years. A small study in Australia suggested that this may increase the risk of recurrent ischaemic events and mortality over time, and postulated that high oxygen concentration could induce vaasospasm. This Swedish study did not show any benefit of supplemental oxygen over placebo in patients who had an acute coronary syndrome and whose oxygen saturation was greater than 90%, and there was no difference in recurrent ischaemic events, hospitalisation or death at 1 year. Thus, these two studies do not support the routine use of oxygen in patients with acute coronary syndrome whose oxygen saturation is above 90% but it should still be used in patients who are hypoxic on presentation.

Abstract

Comparison of low-dose statin versus low-dose statin + Armolipid Plus in high-intensity statin-intolerant patients with a previous coronary event and percutaneous coronary intervention (ADHERENCE Trial)

Authors: Marazzi G et al.

Summary: The ADHERENCE trial investigated the efficacy and tolerability of low-dose statin therapy plus the nutraceutical Armolipid Plus in high-risk patients. 100 patients with coronary artery disease who had undergone percutaneous coronary intervention in the preceding 12 months, were high-dose statin intolerant, and did not achieve ≥50% reduction in LDL cholesterol with low-dose statin alone were randomised to continue with the low-dose statin alone or have Armolipid Plus® added. After 3 months, patients in the low-dose statin + Armolipid Plus® group had a significant reduction in LDL cholesterol and total cholesterol (p<0.0001), and 70% of them achieved the therapeutic target (LDL cholesterol <70 mg/dL). None of the patients taking low-dose statin alone reached the therapeutic target. Three patients in each group withdrew because of myalgia.

Comment: Many patients are unable to take high-dose statins due to perceived or real adverse effects, predominantly myalgia/myositis or arthralgia, and thus are unable to achieve target levels. This is especially important after acute coronary syndrome, as a lower LDL is associated with a decrease in recurrent events. Ezetrol® can be used in this context, but this study shows that a “natural” red yeast rice extract can lower lipids significantly and is well tolerated. This type of agent is available in Australia as Lipoplex®, but is not funded through the Pharmaceutical Benefits Scheme. It needs to be prescribed however, as the Therapeutic Goods Administration deems it to be a lipid-lowering agent.

Reference: Am J Cardiol 2017;120(6):893-97
Abstract

Efficacy and safety of alirocumab versus ezetimibe over 2 years (from ODYSSEY COMBO II)

Authors: El Shahowy M et al.

Summary: The COMBO II trial compared the efficacy and tolerability of alirocumab and ezetimibe in high-risk patients who had elevated LDL cholesterol despite taking maximal statin doses. 720 patients were randomised in a double-blind, double-dummy design to receive subcutaneous alirocumab 75mg or 150mg every 2 weeks or oral ezetimibe 10mg daily on a background of statin therapy for 2 years. At study end, LDL cholesterol was reduced by 49% in the alirocumab group and 17% in the ezetimibe group (p<0.0001). 73% and 40% of patients in the respective groups achieved LDL cholesterol <70 mg/dL. Overall safety was similar in both groups at 2 years and during the first versus the second year. 26% of alirocumab recipients had 2 consecutive LDL cholesterol levels <25 mg/dL, compared with 0.4% of ezetimibe recipients. Neutralising antibodies were observed in 7 alirocumab recipients and 0 ezetimibe recipients.

Comment: The PCSK9 inhibitors reduce LDL cholesterol markedly, by enabling LDL receptors to be recycled to the cell surface more efficiently. Evolocumab and alirocumab are the 2 agents being studied at present, and after the impressive results of the FOURIER trial with the former, we eagerly await ODYSSEY trial results with the latter in patients with acute coronary syndrome. This COMBO II study demonstrates that alirocumab is much more effective in lowering LDL than ezetimibe and is well tolerated. However, the development of neutralising antibodies is worrisome, as the efficacy of the agent could be compromised if the rate increases with treatment exposure.

Reference: Am J Cardiol 2017;120(6):831-39
Abstract
Adenoviral intramyocardial VEGF-D\textsuperscript{ΔNΔC} gene transfer increases myocardial perfusion reserve in refractory angina patients

Authors: Hartikainen J et al.

Summary: This phase IIa Finnish study evaluated the effects of AdVEGF-D\textsuperscript{ΔNΔC} (AdVEGF-D) gene therapy in patients with refractory angina. 30 patients were randomised to receive AdVEGF-D or placebo (control group); treatment was targeted to hibernating viable myocardium. Myocardial perfusion reserve increased significantly in the treated area in the AdVEGF-D group compared with baseline at 3 and 12 months, whereas it showed no significant change from baseline in controls at either time-point. No major changes were found in clinical chemistry in either group, but anti-adenovirus antibodies increased by 54% from baseline in patients in the AdVEGF-D group. AdVEGF-D patients in the highest lipoprotein(a) tertile at baseline had the best response to therapy.

Comment: If revascularisation cannot be undertaken there are few treatments to improve myocardial blood flow in patients with refractory angina. This study showed that promoting angiogenesis with gene therapy can improve perfusion and symptoms and may provide another option in these patients. More study is needed, but if these agents are safe and have a durable effect they could come into clinical practice, but should also be studied post-MI and in heart failure.

Reference: Eur Heart J 2017;38(33):2547-55

Abstract

New York Heart Association class and the survival benefit from primary prevention implantable cardioverter defibrillators

Authors: Friedman D et al.

Summary: This pooled analysis of 4 randomised controlled trials investigated the survival benefit of primary prevention ICDs in patients with New York Heart Association (NYHA) class II/III heart failure. A patient-level meta-analysis was performed for 2763 patients with NYHA class II/III heart failure who were participating in 4 primary prevention ICD trials (MADIT-I, MADIT-II, DEFINITE, and SCD-HeFT). 68% of patients had NYHA class II heart failure and 32% had NYHA class III heart failure. Bayesian-Weibull survival regression models showed that ICDs reduced mortality overall (hazard ratio [HR], 0.65) and in NYHA class II patients (HR, 0.55), but nonsignificantly reduced mortality in NYHA class III patients (HR, 0.76).

Comment: There is ongoing debate about the benefits of ICD implantation in older patients with non-ischaemic cardiomyopathy, but current guidelines still recommend implantation based on ejection fraction and not the cause of left ventricular dysfunction. We know that sudden cardiac death (SCD) is the most common cause of death in patients with NYHA class II symptoms, and that as symptoms worsen, death from pump failure overtakes SCD, although SCD does occur in advanced heart failure. This study is broadly supportive of this concept, but raises important questions as to how to determine which patients with NYHA class III and IV heart failure would benefit most from ICD implantation.

Reference: Am Heart J 2017;191:21-29

Abstract

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