Cardiology Research Review™

Making Education Easy

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In this issue:

Abbreviations used in this issue:

ACS = acute coronary syndrome; **AMI** = acute MI; **CABG** = coronary artery bypass graft; **CV** = cardiovascular; **DAPT** = dual antiplatelet therapy; **ICH** = intracranial haemorrhage; **MI** = myocardial infarction.

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Welcome to the latest issue of Cardiology Research Review.

This month we present a review of previously unpublished data from the Minnesota Coronary Experiment that re-evaluates the traditional diet-heart hypothesis. This is followed by evidence that using adrenaline promptly after a failed cardioversion in cardiac arrest is ill advised (and not recommended by the American Heart Association), and we compare the use of restrictive and liberal transfusion strategies in patients with cardiovascular disease. The PCSK9 inhibitor evolocumab proves to be more effective and better tolerated than ezetimibe in patients with muscle-related statin intolerance, and the mitogen-activated protein (MAP) kinase inhibitor losmapimod disappoints in patients with AMI.

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

john.amerena@researchreview.com.au

Re-evaluation of the traditional diet-heart hypothesis

Authors: Ramsden C et al.

Summary: This analysis of recovered data from the Minnesota Coronary Experiment (MCE) re-evaluated the traditional diet-heart hypothesis. The MCE (1968–73) was a randomised controlled trial that tested whether replacing saturated fat with vegetable oil rich in linoleic acid reduced coronary heart disease and death by lowering serum cholesterol. Data were obtained from unpublished documents with completed analyses for the randomised cohort (n=9423); longitudinal serum cholesterol levels for 2355 participants exposed to the study diets for ≥1 year; and 149 autopsy files. The intervention group had a significant reduction in serum cholesterol levels compared with controls (–13.8% vs –1.0%; p<0.001). Kaplan Meier graphs showed no mortality benefit for the intervention group in the full randomised cohort or for any prespecified subgroup. Adjusted Cox regression models showed a 22% higher risk of death for each 30 mg/dL decrease in serum cholesterol levels (p<0.001). There was no evidence of benefit in the intervention group for coronary atherosclerosis or MI.

Comment: This study of previously unpublished data again brings into question the benefits of dietary intervention to reduce cholesterol. There is, however, irrefutable evidence that statins improve outcomes in primary and secondary prevention, which raises the possibility that it is the statin itself, as well as cholesterol lowering, that reduces events, especially given the difficulty in demonstrating benefit with lipid lowering with non-statin agents, apart from the small benefits seen with ezetimibe in IMPROVE-IT.

Reference: BMJ 2016;353:i1246

Abstract

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

Early administration of epinephrine (adrenaline) in patients with cardiac arrest with initial shockable rhythm in hospital

Authors: Andersen L et al.

Summary: This registry study investigated the impact of giving adrenaline in the first 2 minutes after defibrillation to patients who have a cardiac arrest in hospital. Data for 2978 patients who had a cardiac arrest in hospital who were registered in the Get With The Guidelines-Resuscitation registry were analysed. 51% of patients received adrenaline within 2 minutes after the first defibrillation, contrary to current American Heart Association guidelines. Administration of adrenaline within 2 minutes after the first defibrillation was associated with decreased odds of survival to hospital discharge (odds ratio 0.70; p<0.001), as well as decreased odds of return of spontaneous circulation (0.71; p<0.001) and survival to hospital discharge with a good functional outcome (0.69; p<0.001).

Comment: Although it intuitively seems reasonable to give intravenous adrenaline promptly after a failed cardioversion in cardiac arrest, especially if there is hypotension, this study shows that this worsens outcomes if the patient has a potentially shockable rhythm. It seems that repeat cardioversion to try and restore rhythm and output is preferable to early adrenaline administration, which should be delayed and used later if there is pulseless electrical activity, no cardiac rhythm or ongoing hypotension.

Reference: BMJ 2016;353:i1577
Abstract

Effect of restrictive versus liberal transfusion strategies on outcomes in patients with cardiovascular disease in a non-cardiac surgery setting

Authors: Docherty A et al.

Summary: This systematic review and meta-analysis compared outcomes after restrictive versus liberal blood transfusion strategies in patients with CV disease in a non-cardiac surgery setting. Eleven trials that enrolled 3033 patients with CV disease were included in the meta-analysis. 1514 patients received restrictive transfusion and 1519 received liberal transfusion. The pooled risk ratio for the association between transfusion thresholds and 30-day mortality was 1.15 (p=NS), with little heterogeneity. The risk of ACS was increased in patients managed with restrictive versus liberal transfusion (risk ratio 1.78, p=0.01).

Comment: We know that transfusion in the context of ACS is associated with more recurrent ischaemia and poor outcomes. Transfusion is usually required due to bleeding in this context and usually necessitates discontinuation of antiplatelet and antithrombotic treatment. It has been hard to separate out the relative contributions of bleeding itself, treatment discontinuation, transfusion, and ischaemia due to anaemia, to the worse outcomes, but this study suggests that the latter is important and that more liberal transfusion may mitigate some of the risk.

Reference: BMJ 2016;352:i1351
Abstract

Efficacy and tolerability of evolocumab vs ezetimibe in patients with muscle-related statin intolerance

Authors: Nissen S et al.

Summary: This analysis of the GAUSS-3 randomised clinical trial compared the lipid-lowering efficacies of 2 nonstatin therapies, ezetimibe and evolocumab, in patients with muscle-related statin intolerance. 511 adults with uncontrolled low-density lipoprotein cholesterol (LDL-C) levels and a history of statin intolerance were randomised to ezetimibe or evolocumab for 24 weeks. Mean percentage change in LDL-C from baseline after 24 weeks was –16.7% with ezetimibe and–52.8% with evolocumab (p<0.001). Muscle symptoms were reported in 28.8% of ezetimibe recipients and 20.7% of evolocumab recipients (p=NS). Treatment was stopped because of muscle symptoms in 6.8% and 0.7% of patients in the respective groups.

Comment: This study shows that the PCSK9 inhibitor evolocumab was well tolerated and very effective in lowering cholesterol in patients with statin-induced myalgia/myopathy. The definition of statin intolerance is problematic, and one wonders if statin-sparing strategies such as using ezetimibe were used in these "intolerant" patients. CV outcomes studies are currently underway with the PCSK9 inhibitors but with the prohibitive cost of these agents (>$1000 per month) their use in "statin intolerant" patients is unlikely to be funded in the near future.

Reference: JAMA 2016;315(15):1580-90
Abstract

Effect of losmapimod on cardiovascular outcomes in patients hospitalized with acute myocardial infarction

Authors: O'Donoghue M et al.

Summary: This study investigated the efficacy and safety of the p38 mitogen-activated protein (MAP) kinase inhibitor losmapimod on CV outcomes in patients hospitalised with AMI. Patients were randomised to either twice-daily losmapimod 7.5mg (n=1738) or matching placebo (n=1765) on a background of guideline-recommended therapy for 12 weeks, with an additional 12-week follow-up. The primary end-point (a composite of CV death, MI, or severe recurrent ischaemia requiring urgent coronary revascularisation) occurred by 12 weeks in 7.0% of placebo recipients and 8.1% of losmapimod recipients (hazard ratio, 1.16; p=NS). Serious adverse events occurred in 14.2% and 16.0% of patients in the respective groups.

Comment: Although MAP kinase inhibition should reduce ischaemic events by reducing inflammation and improving plaque stability, no benefit or harm was seen in the initial LATITUDE study using losmapimod in patients with ACS. This compound joins a growing list of agents that theoretically should be beneficial in patients with coronary disease, such as cholesterylester transfer protein (CETP) inhibitors and vorapaxar, but clinical trials have not shown event rate reduction and they thus have not been used in clinical practice.

Reference: JAMA 2016;315(15):1591-9
Abstract

Mechanisms of stent thrombosis analysed by optical coherence tomography

Authors: Souteyrand G et al., on behalf of the PESTO Investigators

Summary: This study used optical coherence tomography (OCT) to evaluate the characteristics of stent thrombosis. 120 patients with stent thrombosis underwent OCT after initial intervention to the culprit lesion. 39% of patients had a bare metal stents, 59% had a drug-eluting stent, and 2% had a bioresorbable vascular scaffold. OCT identified an underlying morphological abnormality in 97% of cases, including struts malapposition (34%), neoatherosclerotic lesions (22%), major stent underexpansion (11%), coronary evagination (8%), isolated uncovered struts (8%), edge-related disease progression (8%), and neointimal hyperplasia (4%). Ruptured neoatherosclerotic lesions were more frequent with bare-metal stents than with drug-eluting stents (36% vs 14%; p=0.005), whereas coronary evaginations were more frequent with drug-eluting stents than with bare-metal stents (12% vs 2%; p=0.04).

Comment: It appears that the vast majority of stent thrombosis is associated with structural or mechanical abnormalities after stent insertion, so it may be prudent to use intravascular ultrasound more regularly during percutaneous coronary intervention to detect malapposition or under expansion that are potentially fixable at the time of the index procedure. Stent thrombosis is often fatal or causes a large infarct, and although it is very uncommon, anything that can be done to reduce its incidence should be embraced.

Reference: Eur Heart J 2016; published online Jan 12
Abstract

Ischaemic risk and efficacy of ticagrelor in relation to time from P2Y12 inhibitor withdrawal in patients with prior myocardial infarction

Authors: Bonaca M et al.

Summary: This subanalysis of the PEGASUS-TIMI 54 trial investigated the efficacy of ticagrelor in relation to time from P2Y12 inhibitor withdrawal in patients with prior MI. Patients were grouped according to time from last P2Y12 inhibitor (≤30, >30–360, and >360 days). The risk of major adverse cardiovascular events (MACE) and the efficacy of ticagrelor were compared across categories. In the placebo arm, patients who more recently stopped P2Y12 inhibitor therapy had a greater number of risk factors but still had a higher adjusted risk of MACE than those who stopped >1 year prior (p-trend = 0.0097). The benefit of ticagrelor depended on the time from last P2Y12 inhibitor dose, with hazard ratios for ticagrelor vs placebo of 0.73, 0.86, and 1.01, respectively, by time category (p-trend <0.001). The benefit seen with ticagrelor in the shortest time category was similar regardless of time from MI.

Comment: In the PEGASUS study, most of the benefit of DAPT in patients 1–3 years after MI was in those who had a shorter duration off DAPT, in that the longer the interval between discontinuation of DAPT and its reinstitution, the less the benefit. This is important in clinical practice, as it supports continuation of DAPT 12 months after ACS, especially in high risk patients, but not restarting ticagrelor in patients who have been stable on aspirin alone for a prolonged period of time after their infarct.

Reference: Eur Heart J 2016;37(14):1133-42
Abstract

Ticagrelor and aspirin for the prevention of cardiovascular events after coronary artery bypass graft surgery

Authors: Saw J et al.

Summary: This double-blind study investigated the effects of ticagrelor on graft patency after CABG surgery. Patients were randomised to receive ticagrelor 90mg twice daily or placebo (in addition to aspirin) for 3 months after CABG surgery. The primary outcome was graft occlusion on computed tomography angiography (CTA) performed 3 months after CABG. CTA was performed in 56 patients who completed >1 month of study drug. Graft occlusion occurred in 28.0% of ticagrelor recipients and 48.3% of placebo recipients (p=0.044). Graft occlusion occurred in 10.3% and 18.3% of analysable grafts in the respective groups (p=NS), and graft occlusion or stenosis ≥50% occurred in 11.5% and 26.7% of grafts in the respective groups (p=0.007). Multivariable analysis confirmed that ticagrelor reduced graft occlusion compared with placebo (odds ratio, 0.25; p=0.03).

Comment: Patients who had CABG surgery after ACS in the PLATO study had less all cause and CV mortality if they were randomised to ticagrelor compared with placebo, but it is not clear in how many patients study medication was restarted and when. This study suggests that using DAPT with aspirin and ticagrelor after CABG surgery reduces graft occlusion 3 months after surgery without increasing major bleeding and although the numbers were small, it supports the strategy of using DAPT for at least 12 months after ACS even if the patients undergo surgical revascularisation.

Reference: Heart 2016;102:763-9
Abstract

Risk of death and stroke associated with anticoagulation therapy after mitral valve repair

Authors: Valeur N et al.

Summary: This Danish registry analysis evaluated the risk of stroke and death associated with anticoagulation therapy after mitral valve repair. 2188 patients without prior vitamin K antagonist (VKA) use who did not have stroke or death by day 7 after discharge were included; median follow-up was 4.9 years. 39% of patients were discharged on VKAs and 24% died or had a stroke during follow-up. Compared with patients without post-discharge VKA, patients taking a VKA had a lower risk of death/stroke at 3 months (hazard ratio, 0.28; p=0.002) and 3–6 months (0.85; p=NS). The risk of significant bleeding complications within 3 months did not differ between groups.

Comment: Short term anticoagulation after mitral valve repair is not routine practice in many centres but this meta-analysis suggests that 3 months' anticoagulation with a VKA reduces stroke and death after mitral valve repair with no excess in major bleeding. Although it would be nice to have randomised clinical trial data or a confirmatory study, these results make a strong case for short term anticoagulation after mitral valve repair, but novel oral anticoagulants should not be used in this context, even if the patient has AF, as mitral valve repair is classified as valvular atrial fibrillation in the US guidelines.

Reference: Heart 2016;102:687-93
Abstract

Use of oral anticoagulants for stroke prevention in patients with atrial fibrillation who have a history of intracranial hemorrhage

Authors: Chao T-F et al.

Summary: This study used the National Health Insurance Research Database in Taiwan to investigate the risks and benefits of oral anticoagulants in patients with atrial fibrillation and a history of ICH. 12,917 patients with atrial fibrillation (CHA_2DS_2-VASc score ≥2) and a history of ICH were identified and assigned to 1 of 3 groups: no treatment, antiplatelet therapy, and warfarin. The rate of ICH and ischaemic stroke in untreated patients was 4.2 and 5.8 per 100 person-years, respectively. The annual ICH and ischaemic stroke rates were 5.3% and 5.2%, respectively, in patients taking antiplatelet therapy and 5.9% and 3.4%, respectively, in patients taking warfarin. In the warfarin group, the number needed to treat was lower than the number needed to harm in those with a CHA_2DS_2-VASc score ≥6, but the number needed to treat was higher than the number needed to harm for patients with a CHA_2DS_2-VASc score <6.

Comment: Physicians are reluctant to restart anticoagulation in patients who have had an ICH on warfarin for fear of causing another bleed. This places the patient at risk of ischaemic stroke, however, and getting the risk/benefit equation is always difficult. This study suggests that if the stroke risk is very high (CHA_2DS_2-VASc score ≥6), the net clinical benefit is still in favour of warfarin. Novel oral anticoagulants have a lower risk of ICH than warfarin so could be used in this context, but occlusion of the left atrial appendage would be worthy of consideration, especially with reports emerging of efficacy and safety when they are used for this indication.

Reference: Circulation 2016;133:1540-7
Abstract

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