Cardiology Research Review™

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Issue 137 - 2021

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Abbreviations used in this issue:

ACS = acute coronary syndrome; **AF** = atrial fibrillation; **ASCVD** = atherosclerotic cardiovascular disease; **BP** = blood pressure; **CAD** = coronary artery disease; **COVID-19** = coronavirus disease 2019; **HR** = hazard ratio; **LDL** = low-density lipoprotein; **MI** = myocardial infarction; **PCSK9** = proprotein subtilisin/kexin type 9.

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Welcome to the latest issue of Cardiology Research Review.

In this issue, a subanalysis of the LoDoCo2 trial shows that the cardiovascular benefits of low-dose colchicine in patients with stable CAD are unaffected by history of ACS, a US study finds that more intensive efforts are needed to achieve optimal cholesterol management in patients with ASCVD, and a study in Scotland shows the importance of achieving lipid-lowering and statin adherence targets after MI. An analysis of UK Biobank data reports that increased coffee consumption might actually reduce the risk of arrhythmia, an Israeli study finds a very low risk of myocarditis after receipt of the Pfizer-BioNTech vaccine, and an Australian study revisits the use of multidrug polypills for the treatment of hypertension.

We hope you find these and the other selected studies interesting, and welcome your feedback.

Kind Regards,

Associate Professor John Amerena
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Colchicine in patients with chronic coronary disease in relation to prior acute coronary syndrome

Authors: Opstal TSJ et al.

Summary: Low-dose colchicine has been shown to reduce the risk of cardiovascular events in patients with stable CAD. This analysis of the LoDoCo2 trial investigated whether the beneficial effects of colchicine are related to the time of onset of treatment after ACS. 5522 patients with chronic CAD were randomised to receive colchicine 0.5mg once daily or placebo. The primary composite end-point (cardiovascular death, spontaneous MI, ischaemic stroke, or ischaemia-driven coronary revascularisation) was compared between patients with no prior ACS, recent (6–24 months) ACS, remote (2–7 years) ACS, or very remote (>7 years) ACS. The risk of the primary end-point was found to be independent of prior ACS status. Colchicine consistently reduced the primary end-point in patients with no prior ACS (HR 0.81, 95% CI 0.52–1.27), recent ACS (HR 0.75, 95% CI 0.51–1.10), remote ACS (HR 0.55, 95% CI 0.37–0.82), and very remote ACS (HR 0.70, 95% CI 0.51–0.96).

Comment: The LoDoCo2, COLCOT and COPS studies have all demonstrated the benefits of low-dose colchicine in patients with stable CAD but this therapy has still not become common practice in most parts of the world, and has not been incorporated into guidelines yet. This subanalysis of LoDoCo2 shows that a history of ACS does not influence the benefit of colchicine in patients with coronary disease, and interestingly shows that patients who have had a remote ACS derive as much benefit as those with recent ACS. The lack of temporal association with benefit was also seen in the COMPASS study with low-dose rivaroxaban, where the benefits were the same whenever the index event occurred. These studies demonstrate that these secondary preventative therapies should be considered in all patients with a history of ACS irrespective of when it occurred.

Reference: J Am Coll Cardiol 2021;78(9):859-66
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 had treatment escalation over a 2-year period after diagnosis was made, while receiving ongoing medical care. Whether this is also due to lack of awareness of targets, 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.

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

Associations of statin adherence and lipid targets with adverse outcomes in myocardial infarction survivors

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). These associations were not affected by adjustment for confounders.

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 the inability to get to lipid targets in patients post MI, as there was an increased rate of all-cause and cardiovascular mortality in these patients, 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 PSCK9 use in patients with recurrent ACS or multivascular disease in Australia 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

Coffee consumption and incident tachyarrhythmias

Authors: Kim E-J et al.

Summary: This prospective cohort study assessed the association between coffee consumption and arrhythmias. Data for 386,258 individuals (mean age 56 years; 52.3% female) were retrieved from the UK Biobank. During a mean follow-up of 4.5 years, 16,979 participants developed an incident arrhythmia. After adjustment for confounding factors, each additional cup of habitual coffee consumed was associated with a 3% lower risk of incident arrhythmia (HR 0.97, 95% CI 0.96–0.98; p<0.001). In analyses of different arrhythmia subtypes, similar significant associations were observed for AF and/or atrial flutter, and supraventricular tachycardia (SVT).

Comment: Coffee is anecdotally thought to be a trigger for arrhythmia as it does cause tachycardia in some patients, but there is very little evidence for this. This prospective study looked at the relationship between coffee consumption and arrhythmia (SVT, AF, atrial flutter, ventricular tachycardia and ectopic activity) and found if anything the opposite was true. Mendelian randomisation did not suggest there were any genetically-mediated differences in coffee metabolism that increased the chances of arrhythmia. So from a clinical perspective, a blanket recommendation to minimise coffee intake cannot be justified and will not reduce the tendency to tachyarrhythmia in predisposed patients, unless there is a clear temporal association with drinking coffee and start of arrhythmia.

Reference: JAMA Intern Med 2021;181(9):1185-93
Abstract

Temporal association between episodes of atrial fibrillation and risk of ischemic stroke

Authors: Singer DE et al.

Summary: This study evaluated the temporal association between AF episodes and ischaemic stroke in patients with a cardiac implantable electronic device (CIED). 891 patients with a CIED who sustained an ischaemic stroke and who had 120 days of continuous remote rhythm monitoring prestroke were included. The effects of AF duration ≥5.5h on any given day in the 1–30 days prestroke (case period) and 91–120 days prestroke (control period) were compared. 52 patients had AF ≥5.5h in the case period and 14 had AF ≥5.5h in the control period (odds ratio 3.71, 95% CI 2.06–6.70). The greatest stroke risk was seen in the first 5 days after an AF episode ≥5.5h (odds ratio 5.00, 95% CI 2.62–9.55), and an AF episode >23h on any given day was associated with the clearest increase in stroke risk (odds ratio 5.00, 95% CI 2.08–12.01).

Comment: The threshold for recommending anticoagulation in patients with AF and high CHADSVASc score is contentious, especially when the AF is detected on interrogation of CIEDs such as permanent pacemakers or implantable cardioverter-defibrillators. Current guidelines recommend anticoagulation if episodes are >24h duration and no anticoagulation if episodes are <6h duration, but for episodes between 6 and 24h there is some disagreement. This study suggests that in patients with a CIED and stroke who were monitored continuously before the stroke, an episode of AF >5.5h duration was associated with increased risk of stroke, particularly in the short term. They propose intermittent short-term anticoagulation in these patients when an AF episode >5.5h is detected, but logistically this would be difficult and I would favour long-term anticoagulation in this situation.

Reference: JAMA Cardiol 2021; published online Sep 29
Abstract

Myocarditis after COVID-19 vaccination in a large health care organization

Authors: Witberg G et al.

Summary: This study in Israel investigated the incidence of myocarditis after receipt of at least 1 dose of the Pfizer-BioNTech vaccine for COVID-19. A search of Clalit Health Services databases found that among more than 2.5 million vaccinated individuals aged ≥16 years, 54 cases met the criteria for myocarditis. Most (76%) cases were mild and 22% were intermediate; 1 case was associated with cardiogenic shock. The estimated incidence of myocarditis in individuals who had received at least 1 dose of vaccine was 2.13 cases per 100,000 persons (95% CI 1.56–2.70), and the highest incidence of myocarditis (10.69 cases per 100,000 persons) was reported in males aged 16–29 years.

Comment: There has been a lot of publicity about the risk of developing myopericarditis after mRNA vaccination for COVID. This Israeli study examined >2.5 million individuals who had at least 1 dose of the Pfizer vaccine and found an incidence of 2.13 cases per 100,000. Almost all cases were mild-moderate, with a minority having left ventricular dysfunction that recovered over time in most. The risk/benefit of vaccination in this age group is clearly in favour of receiving it, with a very low risk and tremendous benefit from both an individual and public health perspective.

Reference: New Engl J Med 2021; published online Oct 6
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).
Full biography here.

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CHF patients aged ≥ 70 years deserve an age-proven β-blocker[1,2]

NEBILET reduced the risk of all-cause mortality or cardiovascular hospitalisation in a broad range of CHF patients aged ≥ 70 years*[1,2]

*vs placebo P = 0.039; patients ≥ 70 years regardless of age, gender or left ventricular ejection fraction

NEBILET: Age proven in CHF patients aged ≥ 70 years[1,2]

CHF = Chronic Heart Failure

PBS Information: Restricted benefit. Moderate to severe heart failure. Refer to PBS Schedule for full restricted benefit information.

Please review full Product Information before prescribing. The Product Information can be accessed at www.menarini.com.au/pi

NEBILET (nebivolol hydrochloride) tablets 1.25mg, 5mg, 10mg. Indication(s): Essential hypertension. Stable chronic heart failure (CHF) as an adjunct to standard therapies in patients 70 years or older. **Dose and Method of Administration:** Once daily dosing, can be given with or without meals, consistent approach is recommended. Indication 1 - Hypertension: 5 mg daily. Renal insufficiency: recommended starting dose is 2.5 mg daily, can be increased to 5 mg if needed. Patients > 65 years: recommended starting dose is 2.5 mg daily, can be increased to 5 mg if needed. Patients > 75 years: caution must be exercised and these patients should be monitored closely. Indication 2 - CHF: The initial up titration should be done gradually at 1-2 weekly intervals based on patient tolerability, starting at 1.25 mg once daily, increased to 2.5 mg, then to 5 mg and then to 10 mg once daily. Initiation of therapy and every dose increase should be done under close medical supervision for at least 2 hours. No dose adjustment is required in patients with mild to moderate renal insufficiency. Use in patients with severe renal insufficiency (serum creatinine ≥ 250 micromol/L) is not recommended. **Contraindications:** Hypersensitivity to the active or any of the excipients; liver insufficiency or liver function impairment; acute heart failure; cardiogenic shock or episodes of heart failure decompensation requiring IV inotropic therapy; sick sinus syndrome, including sino-atrial block; second and third degree heart block (without a pacemaker); history of bronchospasm (e.g. including COPD) and/or asthma; untreated phaeochromocytoma; metabolic acidosis; bradycardia (HR < 60 bpm prior to starting therapy); hypotension (systolic BP < 100 mmHg); severe peripheral circulatory disturbances. **Precautions:** Avoid abrupt cessation unless clearly indicated – reduce dosage gradually over 1-2 weeks. If it must be withdrawn abruptly, close observation is required. Anaesthesia; untreated congestive heart failure, unless stabilised; bradycardia; peripheral circulatory disorders (e.g. Raynaud's disease, intermittent claudication); first degree heart block; Prinzmetal's or variant angina; lipid and carbohydrate metabolism – does not affect glucose levels in diabetic patients, but may mask symptoms of hypoglycaemia; hyperthyroidism; COPD; asthma; phaeochromocytoma; various skin rashes; conjunctival xerosis; oculomucocutaneous syndrome; psoriasis; increased sensitivity to allergens and severity of anaphylactic reactions; galactose intolerance, Lapp-lactase deficiency or glucose-galactose malabsorption; hepatic insufficiency or impaired liver functions; severe renal insufficiency; children and adolescents; pregnancy (Cat C); lactation; driving vehicles or operating machines. See approved PI. **Interactions:** Combination not recommended: Class I antiarrhythmics; calcium channel antagonists (verapamil/diltiazem); centrally-acting antihypertensives; other beta-blockers (incl. eye drops). Combination to be used with caution: Class III antiarrhythmics; anaesthetics (volatile); insulin and other oral diabetic medicines; calcium antagonists (dihydropyridine type); catecholamine depleting agents; baclofen; amifostine. For other combinations requiring careful consideration, see approved PI. **Adverse effects:** Headache, dizziness, tiredness, fatigue, paraesthesia, constipation, nausea, diarrhoea, cardiac failure aggravated, bradycardia, hypotension, hypertension, atrial fibrillation, angina pectoris, dyspnoea, oedema, slowed AV conduction/AV-block, bronchospasm. Post-marketing reports of hypersensitivity, angioneurotic oedema, abnormal hepatic function, acute pulmonary oedema, acute renal failure, myocardial infarction, Raynaud's phenomenon, thrombocytopenia. See approved PI. [mPI Version 8.0]

References: 1. NEBILET® Approved Product Information, 13 November 2020.
2. Flather MD *et al. Eur Heart J* 2005; 26: 215–25.

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Prevalence and prognostic implications of diabetes with cardiomyopathy in community-dwelling adults

Authors: Segar MW et al.

Summary: This study evaluated the prevalence and prognostic implications of diabetic cardiomyopathy among community-dwelling individuals. 10,208 adults without prevalent cardiovascular disease or heart failure who were participating in 3 cohort studies (ARIC, CHS, and CRIC) were included. Diabetic cardiomyopathy was defined using 3 different criteria: ≥1 echocardiographic abnormality (left atrial enlargement, left ventricle hypertrophy or diastolic dysfunction; least restrictive criteria); ≥2 echocardiographic abnormalities (intermediate restrictive criteria); and elevated N-terminal pro–B-type natriuretic peptide levels (>125 pg/ml in normal/overweight or >100 pg/ml in obese patients) plus ≥2 echocardiographic abnormalities (most restrictive criteria). Among 2900 individuals with diabetes, the prevalence of diabetic cardiomyopathy ranged from 67.0% using the least restrictive criteria to 11.7% using the most restrictive criteria. Risk factors for diabetic cardiomyopathy included higher fasting glucose, increased body mass index, and older age, as well as worse kidney function. The 5-year incidence of heart failure among patients with diabetic cardiomyopathy ranged from 8.4% to 12.8% using the least and most restrictive definitions, respectively.

Comment: This analysis looked at 2900 patients with type 2 diabetes and no apparent ASCVD from several large studies, and found that whatever criteria was used to label the patient having diabetic cardiomyopathy there was a risk of developing heart failure of around 10% over 5 years, and that the risk was roughly double that of the nondiabetic population. The sodium-glucose cotransporter-2 (SGLT2) inhibitors have been shown to reduce heart failure in diabetics (and in non-diabetics). Given the high mortality in patients who develop heart failure (50% in 5 years) and its burden on the patient and the health care system, SGLT2 inhibitors should be strongly considered in the management of patients with type 2 diabetes, especially in the larger, older patients who have renal dysfunction, as these were the risk factors identified for the development of diabetic cardiomyopathy.

Reference: J Am Coll Cardiol 2021;78(16):1587-98
Abstract

Adding a new medication versus maximizing dose to intensify hypertension treatment in older adults

Authors: Aubert CE et al.

Summary: This retrospective observational study within the Veterans' Health Administration compared the use of adding a new medication versus maximising dose to intensify BP-lowering treatment in older patients with hypertension. 178,562 veterans aged ≥65 years with systolic BP ≥130mm Hg who were taking at least 1 antihypertensive medication at less than the maximum dose were included. 25.5% of patients had intensification by adding a new medication and 74.5% had intensification by maximising dose. Compared with maximising dose, adding a new medication was associated with less intensification sustainability but a slightly larger reduction in mean systolic BP.

Comment: Current Australian guidelines for the management of hypertension support moderate doses of complementary BP-lowering agents to control hypertension rather than giving the maximum dose of a single agent unless there is a compelling reason to do so, such as poor heart rate and BP control in a patient who has angina and hypertension. By using this strategy, there is better BP control and less potential for adverse effects. This study broadly supports this principle, and although it was a primarily male Veteran population, I feel the results are broadly generalisable, especially as we are unlikely to see any randomised data exploring this, given that most antihypertensive agents are now off patent and the costs of running such a trial would be prohibitively expensive for non-pharma agencies such as the National Health and Medical Research Council.

Reference: Ann Intern Med 2021; published online Oct 5
Abstract

Initial treatment with a single pill containing quadruple combination of quarter doses of blood pressure medicines versus standard dose monotherapy in patients with hypertension (QUARTET)

Authors: Chow CK et al., for the QUARTET Investigators

Summary: The Australian QUARTET trial compared the efficacy of a polypill containing quarter doses of 4 BP-lowering drugs versus standard dose irbesartan monotherapy in patients with hypertension. 591 patients were randomised to receive either the quadpill (containing irbesartan 37.5mg, amlodipine 1.25mg, indapamide 0.625mg, and bisoprolol 2.5mg) or an indistinguishable monotherapy control (irbesartan 150mg) once daily for 12 weeks. Additional medications could be added in both groups if needed, starting with amlodipine 5mg. Mean systolic BP was 6.9mm Hg lower in the intervention group than the control group at 12 weeks ($p<0.0001$), and rates of BP control (<140/90mm Hg) were better (76% vs 58%; $p<0.0001$) despite fewer patients in the quadpill group taking additional BP-lowering medications (15% vs 40%). The number of adverse event-related treatment withdrawals at 12 weeks did not differ significantly between groups (4.0% vs 2.4%; $p=0.27$). Among 417 patients who continued with their allocated treatment for 1 year, up-titration was more common in the control group but mean systolic BP remained 7.7mm Hg lower in the quadpill group.

Comment: The principle of using moderate doses of complementary agents to control BP has been extended in this proof-of-concept study from the George Institute in Sydney. A combination pill of small doses of 4 BP-lowering agents in 1 pill was shown to be more effective in controlling BP faster, and with better control at 12 months with less pill burden than conventional therapy. Registration studies with the quadpill are underway with larger patient numbers, and hopefully will show the same results as the pilot study, to allow this promising medication to come to market and improve BP control which is still less than ideal in many patients.

Reference: Lancet 2021;398(10305):1043-52
Abstract

Second asymptomatic carotid surgery trial (ACST-2): A randomised comparison of carotid artery stenting versus carotid endarterectomy

Authors: Halliday A et al.

Summary: The ACST-2 trial compared the long-term protective effects of carotid artery stenting (CAS) and carotid endarterectomy (CEA) in asymptomatic patients with severe stenosis. 3625 patients with severe unilateral or bilateral carotid artery stenosis but no recent stroke or transient cerebral ischaemia were randomised to undergo CAS or CEA. Patients were followed up at 1 month and then annually for a mean 5 years. Overall, only 1% of patients had disabling stroke or death procedurally (within 30 days of the intervention) and only 2% had non-disabling procedural stroke. Kaplan-Meier estimates of 5-year non-procedural fatal or disabling stroke were 2.5% in each group, and for any stroke were 5.3% with CAS versus 4.5% with CEA (rate ratio 1.16, 95% CI 0.86–1.57; p=NS).

Comment: This study looked at the safety of open CEA vs stenting in patients with asymptomatic carotid stenosis in whom a procedure was deemed necessary. It is pleasing to know that in experienced competent operators there is no short- or long-term difference in outcomes between stenting and surgery, but the bigger question is whether any intervention is required in asymptomatic patients with carotid disease, particularly when the US Preventive Services Task Force does not recommend screening for carotid disease in asymptomatic patients.

Reference: Lancet 2021;398(10305):1065-73
Abstract

