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Abbreviations used in this issue

AVNRT = atrioventricular nodal re-entrant tachycardia
BP = blood pressure
HR = hazard ratio
MI = myocardial infarction
NSAID = nonsteroidal anti-inflammatory drug
OR = odds ratio
PCI = percutaneous coronary intervention

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ACNC Australasian Cardiovascular Nursing College

NZMA New Zealand Medical Association

Welcome to the latest issue of Cardiology Research Review.

In this issue we report a meta-analysis of the risk of MI in people taking NSAIDs, an observational study of the prevalence of subclinical leaflet thrombosis after implantation of bioprosthetic aortic valves, and evidence of a nocebo response in patients taking statins. An analysis of data from the ONTARGET and TRANSCEND trials and a meta-analysis of randomised controlled trials add to the continuing debate about appropriate on-treatment BP targets, and catheter ablation is shown to be the treatment of choice for symptomatic AVNRT.

We hope you enjoy these and the other selected studies, and look forward to any feedback you might have.

Kind regards,

Professor Alexander Sasse
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Risk of acute myocardial infarction with NSAIDs in real world use

Authors: Bally M et al.

Summary: This systematic review and meta-analysis investigated the risk of acute MI in patients taking oral NSAIDs. A search of Canadian and European healthcare databases identified a cohort of 446,763 individuals (61,460 with acute MI) that were suitable for inclusion. Taking any dose of NSAIDs for 1 week, 1 month, or >1 month was associated with an increased risk of MI. With use for up to 1 week, the probability of increased MI risk (OR >1.0) was 92% for celecoxib, 97% for ibuprofen, and 99% for diclofenac, naproxen, and rofecoxib. Corresponding odds ratios were 1.24 for celecoxib, 1.48 for ibuprofen, 1.50 for diclofenac, 1.53 for naproxen, and 1.58 for rofecoxib. Higher doses of NSAIDs were associated with a greater risk of MI. When used for >1 month, risks did not appear to exceed those associated with shorter durations.

Comment: Commonly patients with cardiovascular disease will be – due to demographics – burdened with joint and arthritis problems. So what about NSAIDs to keep them mobile and allow them to exercise? The risk of MI starts right after the first exposure, and longer treatment as well as a higher dosage seem to be associated with greater probabilities of increased risk of MI. This appears to be a class effect, as use of all studied NSAIDs was associated with an increased risk of acute MI. This largest study of its kind can give us some guidance on what to avoid, unfortunately it does not solve the dilemma of keeping our patients moving as well.

Reference: BMJ 2017;357:j1909
Abstract

Independent commentary by Professor Alexander Sasse.

Professor Alexander Sasse is Consultant Cardiologist, Director of Cardiac Imaging and Head of the Cardiology Department at Wellington Hospital. His clinical interests include the various modalities of cardiac imaging, structural heart disease, general cardiology and the prevention of stroke. He went to medical school and did his training in Germany (Bonn/Aachen) and has been a Cardiologist since 2004. In 2007 he came to Wellington and has been there ever since. His appointments include being a senior lecturer at Wellington School of Medicine (University of Otago) since 2007, and adjunct Professor at the School of Biological Sciences (Victoria University) Wellington since 2012. He is currently treasurer and central NZ regional representative of the NZ CSANZ committee.

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Subclinical leaflet thrombosis in surgical and transcatheter bioprosthetic aortic valves

Authors: Chakravarty T et al., on behalf of the RESOLVE and SAVORY Investigators

Summary: This observational study examined the prevalence of subclinical leaflet thrombosis after transcatheter or surgical aortic valve replacement. Data were analysed for 890 patients in the RESOLVE and SAVORY registries who had interpretable computed tomography (CT) scans at varying intervals after receiving a bioprosthetic aortic valve. Overall, 12% of patients had subclinical leaflet thrombosis (4% had thrombosis of a surgical valve and 13% had thrombosis of a transcatheter valve; p=0.001). Subclinical leaflet thrombosis was less frequent among patients receiving anticoagulants than among those receiving dual antiplatelet therapy (4% vs 15%; p<0.0001). Thrombosis resolved in all patients receiving anticoagulants, but persisted in nearly all (91%) patients not receiving anticoagulants (p<0.0001). Subclinical leaflet thrombosis was associated with increased rates of transient ischaemic attacks (TIAs).

Comment: Advances in imaging, and here particularly CT imaging, have given us insights into prosthetic valves that were previously not available. Four percent of surgically implanted bioprosthetic valves and 13% of transcatheter valves showed signs of valve thrombosis. This was associated with more TIAs. Thrombosis was affected by anticoagulation management and did respond to anticoagulation once diagnosed. It will be interesting to see what the implications of this finding are, possibly more patients on anticoagulation but for how long? Also, this finding should help in the design and development of prosthesis types and ultimately improve outcome.

Reference: Lancet 2017;389(10087):2383-92
Abstract

Adverse events associated with unblinded, but not with blinded, statin therapy in the Anglo-Scandinavian Cardiac Outcomes Trial–Lipid-Lowering Arm (ASCOT-LLA)

Authors: Gupta A et al., on behalf of the ASCOT Investigators

Summary: This study assessed the prevalence of adverse events reported with statin therapy in a randomised double-blind placebo-controlled trial compared with its non-randomised non-blind extension phase. In the ASCOT-LLA, eligible patients were randomly assigned to atorvastatin 10 mg/day or matching placebo in a double-blind design. In a subsequent non-randomised non-blind extension phase, all patients were offered open-label atorvastatin 10 mg/day. 10,180 patients were included in the analysis of the double-blind phase (median follow-up 3.3 years) and 9899 patients were included in the analysis of the open-label phase (median follow-up 2.3 years). During the blinded phase, muscle-related adverse events were reported at a similar rate in atorvastatin and placebo recipients. Reports of sleep disturbance were significantly lower among atorvastatin than placebo recipients. Too few cases of cognitive impairment were reported for a statistically reliable analysis. In contrast, muscle-related adverse events were reported at a significantly higher rate in statin recipients than non-statin recipients during the open-label extension phase.

Comment: This lipids trial using atorvastatin contains valuable results for daily clinical practice. Statins don't have the best reputation, the list of potential side effects is long and complaints from patients are not uncommon. The main outcome of this study is a nocebo effect; side effects were reported when the treatment was open label. When blinded, muscle-related side effects and erectile dysfunction did not differ between placebo and treatment groups. A reassuring result demonstrating that some adverse effects are not causally related to the statins but are more driven by concerns around potential side effects.

Reference: Lancet 2017;389(10088):2473-81
Abstract

Achieved blood pressure and cardiovascular outcomes in high-risk patients: results from ONTARGET and TRANSCEND trials

Authors: Böhm M et al.

Summary: This study investigated the association between different on-treatment BP levels and cardiovascular outcomes in high-risk patients. Previously reported outcomes data from 30,937 high-risk patients in the ONTARGET and TRANSCEND trials (median follow-up 56 months) were reviewed. Mean achieved systolic BP (SBP) was a more accurate predictor of outcomes than baseline or time-updated SBP, and was associated with the lowest risk at approximately 130mm Hg. Risk increased at SBP 110–120mm Hg for the combined outcome (cardiovascular death, MI, stroke, and hospital admission for heart failure), cardiovascular death alone, and all-cause death. Compared with diastolic BP (DBP) 70–80mm Hg, a mean DBP <70mm Hg during treatment was associated with a greater risk of the combined outcome (HR, 1.31), MI (HR, 1.55), hospital admission for heart failure (HR, 1.59) and all-cause death (HR, 1.16). A pretreatment and mean on-treatment DBP of approximately 75mm Hg was associated with the lowest risk.

Comment: Study on BP number 1. How does the level of BP affect outcome? This study looked at a fairly large cohort of patients treated for hypertension. SBP less than 120mm Hg was associated with more cardiovascular outcomes and higher mortality compared to SBP 120–140mm Hg. The lowest risk was found around an achieved SBP of 130mm Hg. A DBP less than 70mm Hg was also associated with greater risk. Aiming for a DBP of 75mm Hg had the lowest risk. The conclusion was that lowering BP is certainly beneficial, but over medicating and BPs that are too low might reverse some of that effect.

Reference: Lancet 2017;389(10085):2226-37
Abstract

Systolic blood pressure reduction and risk of cardiovascular disease and mortality

Authors: Bundy J et al.

Summary: This systematic review and meta-analysis assessed the association of achieved SBP levels with the risk of cardiovascular disease and all-cause mortality in hypertensive adults treated with antihypertensive therapy. A search of Medline and Embase identified 42 trials (n=144,220) suitable for inclusion. In general, there were linear associations between mean achieved SBP and risk of cardiovascular disease and mortality, with the lowest risk at 120–124mm Hg. Randomised groups with a mean achieved SBP of 120–124mm Hg had hazard ratios for major cardiovascular disease of 0.71, 0.58, 0.46 and 0.36 compared with SBP 130–134mm Hg, SBP 140–144mm Hg, SBP 150–154mm Hg, and SBP ≥160mm Hg, respectively, and corresponding hazard ratios for all-cause mortality of 0.73, 0.59, 0.51 and 0.47, respectively. These findings support more intensive control of SBP among adults with hypertension.

Comment: Study on BP number 2. This time a meta-analysis of 144,220 patients. It found the lowest risk at a SBP between 120 and 124mm Hg both for cardiovascular disease as well as mortality. The conclusion was that further reducing SBP to levels below recommended targets improves outcomes. While this might well be statistically proven the results from the previous study still remind us to be cautious about treating BP overly aggressively. Also, the effect of patient age would require more attention. Lowering BP is certainly good, and persistence pays off. But challenges remain with obtaining reliable measurements and avoiding overtreatment as well.

Reference: JAMA Cardiol 2017;2(7):775-81
Abstract

Catheter ablation vs. antiarrhythmic drug therapy in patients with symptomatic atrioventricular nodal re-entrant tachycardia

Authors: Katritsis D et al.

Summary: This study compared the use of catheter ablation and antiarrhythmic drug therapy in patients with symptomatic AVNRT. 61 patients with at least one symptomatic episode of tachycardia per month and an electrophysiologic diagnosis of AVNRT were randomised to receive catheter ablation or long term bisoprolol (5mg once daily) and/or diltiazem (120–300mg once daily). All patients were shown how to treat subsequent tachycardia episodes with autonomic manoeuvres or a 'pill in the pocket' approach. During a 5-year follow-up period, 29 patients in the ablation group remained free of arrhythmia or conduction disturbances, whereas 21 patients in the drug therapy group required hospital admission for cardioversion.

Comment: This small but randomised controlled study compared medical management to invasive management of AVNRT. The threshold was patients having one or more symptomatic episodes per month (on average the patients had between 2 and 3). The authors are clear in their interpretation: antiarrhythmic medical management is felt to be generally ineffective. Complication rates from ablation are in steady decline and did not play a role in their collective of patients. They conclude that catheter ablation is the treatment of choice for symptomatic patients with AVNRT.

Reference: Europace 2017;19(4):602-06
Abstract

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Comparative effectiveness of routine invasive coronary angiography for managing unstable angina

Authors: Vogrin S et al.

Summary: This longitudinal Australian study assessed the effect of routine invasive coronary angiography on mortality in patients with unstable angina. 33,901 patients who were hospitalised with unstable angina in 2001–2011 were assessed for 12-month mortality. Routine invasive angiography was associated with a 52% decrease in 12-month mortality (HR, 0.48). Revascularisation offered no additional mortality benefit over diagnostic angiography alone. The predicted cumulative probability of death at 12 months was 0.024 for patients receiving angiography within 2 months of their index unstable angina compared with 0.097 for those not receiving it.

Comment: Australian researchers have retrospectively reviewed treatment of acute coronary syndrome (ACS) in a fairly large group of patients. The main results were that invasive angiography reduced mortality by 52% at 12 months. Interestingly, the revascularisation procedure following the angiography did not statistically improve the outcome further. The implications are that access to invasive angiography, then triggering the most appropriate strategy for the individual patient, remains the key confounder. The positive outcome from angiography was sustained if angiography and treatment were done within 2 months of initial presentation. While this supports monitoring access to invasive angiography as a performance indicator (as we currently do in NZ), it might have implications for future ACS treatment pathways.

Reference: Ann Intern Med 2017;166(11):783-91
Abstract

Development and validation of a clinical risk score to predict mortality after percutaneous coronary intervention

Authors: Wall J et al.

Summary: This report described the development and validation of a clinical risk score to predict 30-day mortality after PCI. Data were collected from 6522 patients undergoing PCI at the South Yorkshire Cardiothoracic Centre in Sheffield in 2007–2013. Five risk factors (cardiogenic shock, procedural urgency, history of renal disease, diabetes mellitus, and age) were found to be predictive of 30-day mortality. The risk score was validated internally on a further 3290 patients from the South Yorkshire Cardiothoracic Centre and externally on 3230 patients from Manchester Royal Infirmary. The discrimination of the model was high in the development (C-statistic, 0.82), internal (0.81) and external (0.90) cohorts. There were no significant differences between observed and predicted mortality in any of the groups.

Comment: Cardiology is full of scores, readily available on a number of clever phone apps. This score looks at risk prediction for PCI, importantly it is independent of coronary anatomy. In this case cardiogenic shock, diabetes, renal disease, age and urgency were the only five variables. The risk prediction model was tested retrospectively on a prospectively kept database, outcome was 30-day mortality. The most relevant parameters were cardiogenic shock (OR, 7.7), emergency procedure (OR, 8.7) followed by history of renal disease (OR, 3.9). Time will tell what scoring tools are useful in clinical practice, but risk prediction in combination with 'benefit prediction' from frailty scoring might be helpful.

Reference: Open Heart 2017;4:e000576
Abstract

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Prevalence of subclinical coronary artery disease in masters endurance athletes with a low atherosclerotic risk profile

Authors: Merghani A et al.

Summary: This study assessed the prevalence of subclinical coronary artery disease in masters endurance athletes with a low atherosclerotic risk profile. 152 masters athletes (mean age 54.4 years, 70% male, 77% runners) and 92 matched sedentary controls were assessed by echocardiogram, exercise stress test, computed tomography (CT) coronary angiogram, cardiovascular magnetic resonance imaging (MRI), and 24-hour Holter monitoring. 60% of athletes and 63% of controls had a normal coronary artery calcium (CAC) score. Male athletes had a higher prevalence of atherosclerotic plaques of any luminal irregularity compared with their controls (44.3% vs 22.2%; p=0.009), and only male athletes had a CAC ≥300 Agatston units (11.3%) and a luminal stenosis ≥50% (7.5%). Male athletes demonstrated predominantly calcific plaques, whereas controls showed mostly mixed morphology plaques. The number of years of training was the only independent variable associated with increased risk of CAC >70th percentile for age or luminal stenosis ≥50% in male athletes.

Comment: Routine moderate-intensity exercise reduces cardiovascular disease and increases longevity. But is too much exercise a risk for the heart, and does the strain contribute to atherosclerosis? This study of athletes and their coronary arteries suggest that the answer may be a qualified yes. Masters athletes' hearts with on average 31 years of exercise as well as a control group were analysed with CT but also an array of cardiac tests including echo, MRI and cardiopulmonary exercise testing. The majority (60%) of athletes had no coronary calcium. However particularly male athletes had significantly more coronary plaques than their sedentary counterparts. In comparison, athletes had more calcified plaques and less luminal narrowing, features that the authors associate with more stable plaques. It appears that exercise can cause a potentially deleterious effect on coronaries in some. Or is the stable appearance of the plaques part of a protective mechanism against plaque rupture?

Reference: Circulation 2017;136:126-37
Abstract

Neutrophil stunning by metoprolol reduces infarct size

Authors: García-Prieto J et al.

Summary: The beta1-adrenergic-receptor (ADRB1) antagonist metoprolol reduces infarct size in patients with acute MI. Although the prevailing opinion has been that metoprolol acts mainly on cardiomyocytes, this report demonstrated that metoprolol reduces reperfusion injury by targeting the haematopoietic compartment. Metoprolol has been shown to inhibit deleterious neutrophil inflammatory responses both in patients and in animal models of ischaemia-reperfusion. The infarct-limiting effect of metoprolol is abolished in neutrophil-depleted mice and when neutrophils are prevented from interacting with platelets. The beneficial effects of metoprolol are also abolished by genetic ablation of *Adrb1* and are rescued by restitution of *Adrb1* expression only in haematopoietic cells. These results indicate that neutrophil dynamics are the target of the cardioprotective effect of metoprolol against myocardial ischaemic-reperfusion injury.

Comment: Beta-blockers, here metoprolol, are clinically firmly established in the treatment of MI. This paper was able to demonstrate that metoprolol leads to stunning of neutrophils, these neutrophils interact less with platelets and hence less microvascular obstruction is found. In particular, reperfusion is associated with an inflammatory response and reperfusion injury; metoprolol-mediated effects on neutrophils are felt to play an important role in this process as well. A number of other strategies have been tried to limit reperfusion injury and now we come back to a well known and well established drug. Time to look at treatment algorithms and make sure metoprolol is not missed.

Reference: Nat Commun 2017;8:14780
Abstract

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